Approaches to Overcoming Variance Due to Heterogeneity - Case study in a Rare Disease

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IOM Workshop,
Oct 20, 2015

cTAP
The **c**ollaborative **T**rajectory **A**nalysis **P**rogram

1. Why?
2. Hypothesis and Preliminary Results
3. From Consortium to Platform?

The Problem (2010-2015)

TRIAL	PHASE	PATIENTS**	Met Primary endpoint
DEMAND II	Ph 2	53	yes
DEMAND V	Ph 2	51	no
DEMAND III	Ph 3*	186	no
PTC 007	Ph 2*	174	no
DMD-ACT	Ph 3*	228	no
Tadalafil	Ph 3*	331	2016
Pfizer	Ph 2	105	2017

* Pivotal trial

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

Failed Trial – or Failed Drug?

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

Clue #1 – High unexplained variance

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

Summary from Prosensa Investor presentation, 2014

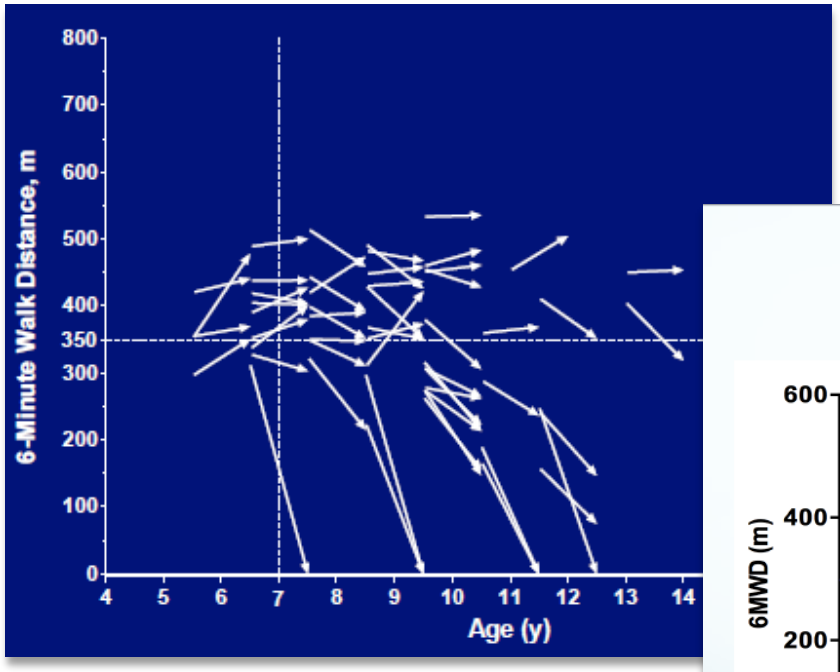
Study	Design	Δ 6MWT (m)	SD (m)	Study (weeks)	n
McDonald 2010*	Natural History	-57	104	52	18
Ataluren 2010*	Placebo arm	-42	90	48	57
Mazzone 2011**	Natural History	-42	74	52	71
Goemans 2012*	Natural History	-38	96	52	19
McDonald 2013**	Natural History	-59	82	48	33
Drisapersen 2014	Placebo Arm	-53	78	48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

Hindsight: poor Signal to noise, underpowered

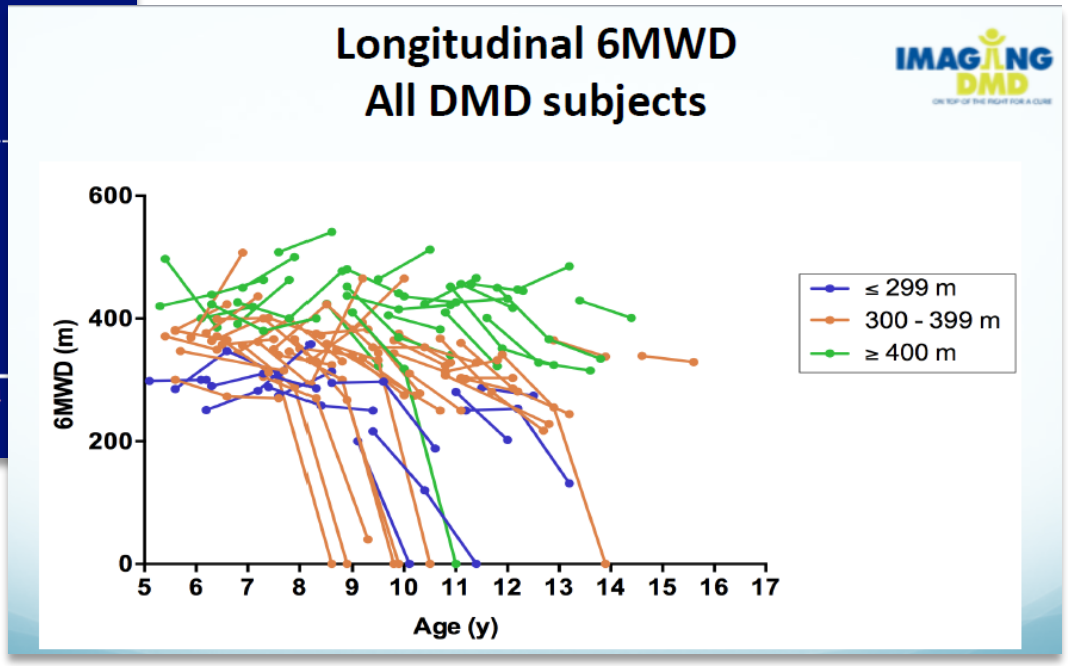
PUBLISHED AFTER TRIALS DESIGNED

Phenotypic Heterogeneity – a major source of variance

Ataluren PIIb placebo arm



Imaging DMD data

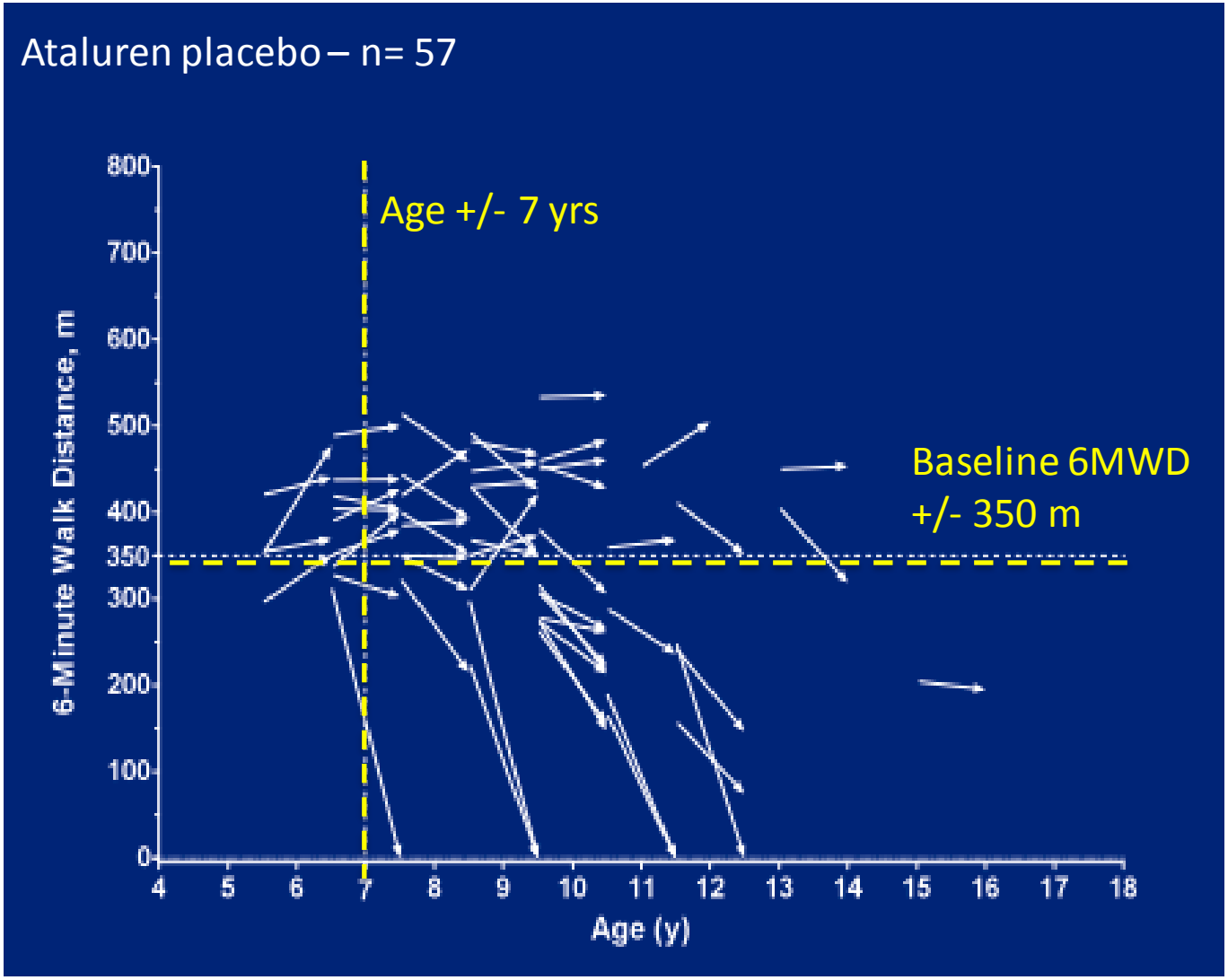


Approaches to overcoming heterogeneity-driven variance in clinical trials

- Account for known prognostic markers
- Improve consistency in measuring outcomes
- Change outcome measure
- Develop biomarkers
- Run a bigger trial

Rarely an option in rare disease!

Proposed Prognostic Factors



Reduction in variance SD: 90m => 82m

Some, but limited benefit

In 1Q 2014….

- > 5 years clinical development
- > 1000 open port biopsies
- # Drug approvals – zero
- Reduction in heterogeneity-based variance ~ 10-15%

What can we learn from other diseases?
Other disciplines?

Idea: Focus on the entire longitudinal trajectory

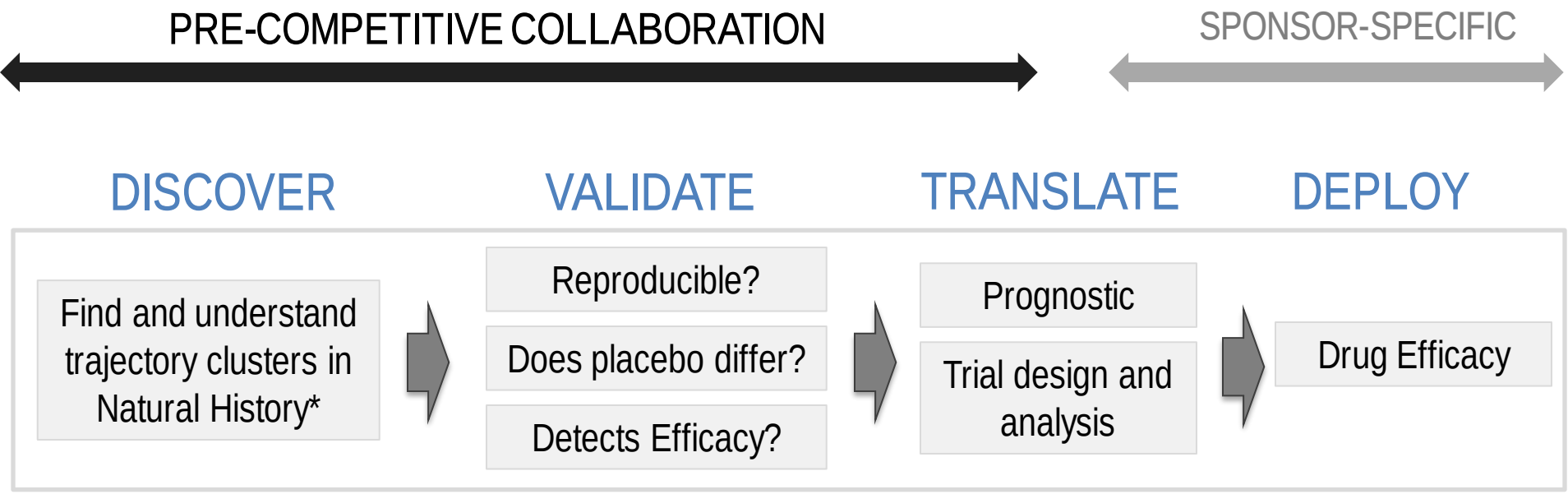
PREMISE

- Each patient has own distinctive longitudinal trajectory of disease progression
- Clinical trials - a window into each patient trajectory
- Natural history - a composite of trajectories

TESTABLE "HYPOTHESIS"

- Cluster heterogeneous longitudinal trajectories of disease progression => reduce variance

Proposed Collaboration Overview



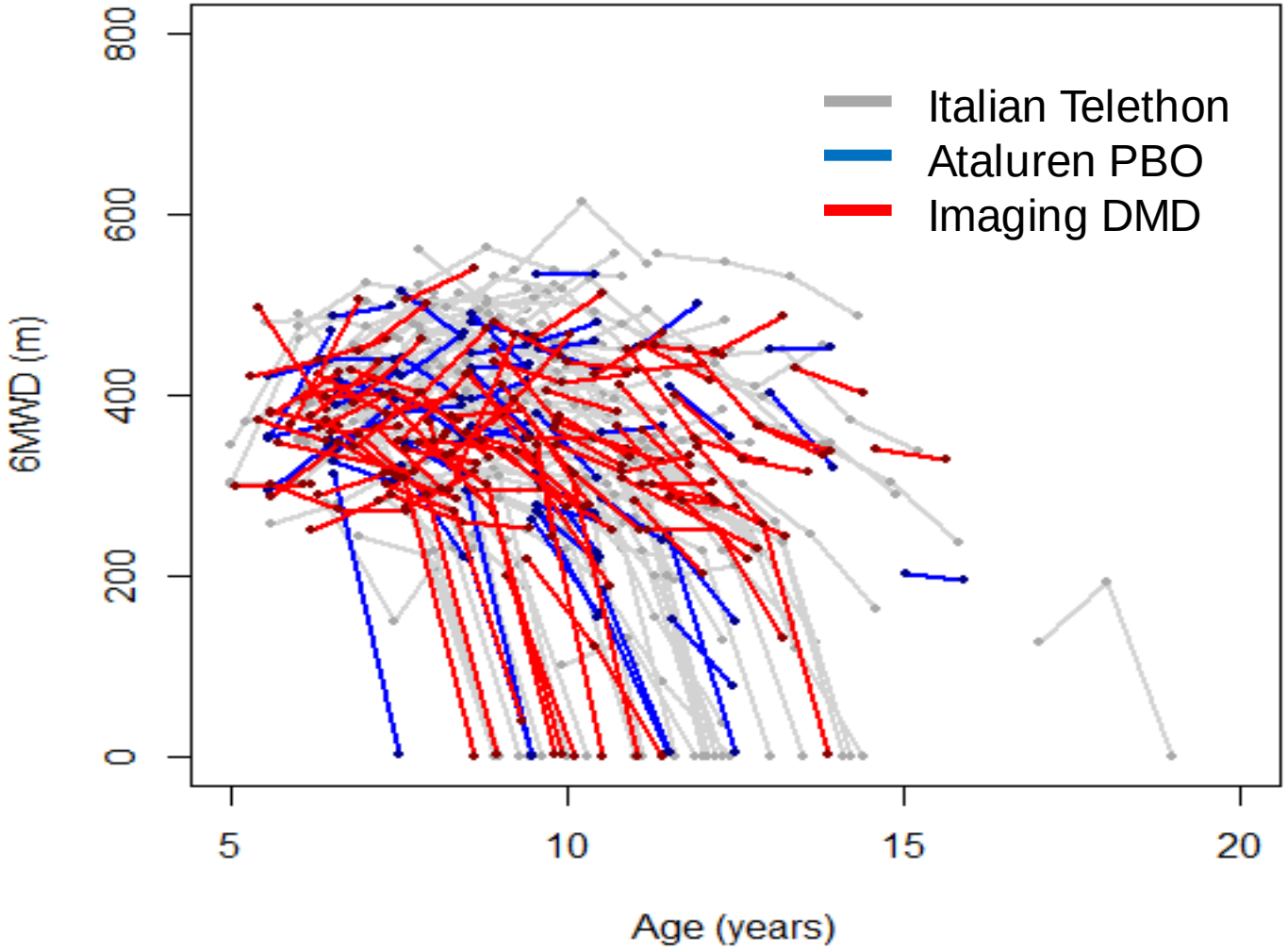
**Latent Class Trajectory Analysis*

Latent Class Trajectory Analysis

- Methodology developed in social sciences and healthcare economics
- Developed to handle variance due to heterogeneity in longitudinal clusters
- Of Growing interest (Pub Med)

See references

Rough Proof of Concept: data digitally traced from published figures



Latent Class Trajectory analysis
Cluster age-based 6MWD trajectories?

Models for 6MWD trajectories to be compared:

A. age + age^2

B. age + age^2 with 2 classes

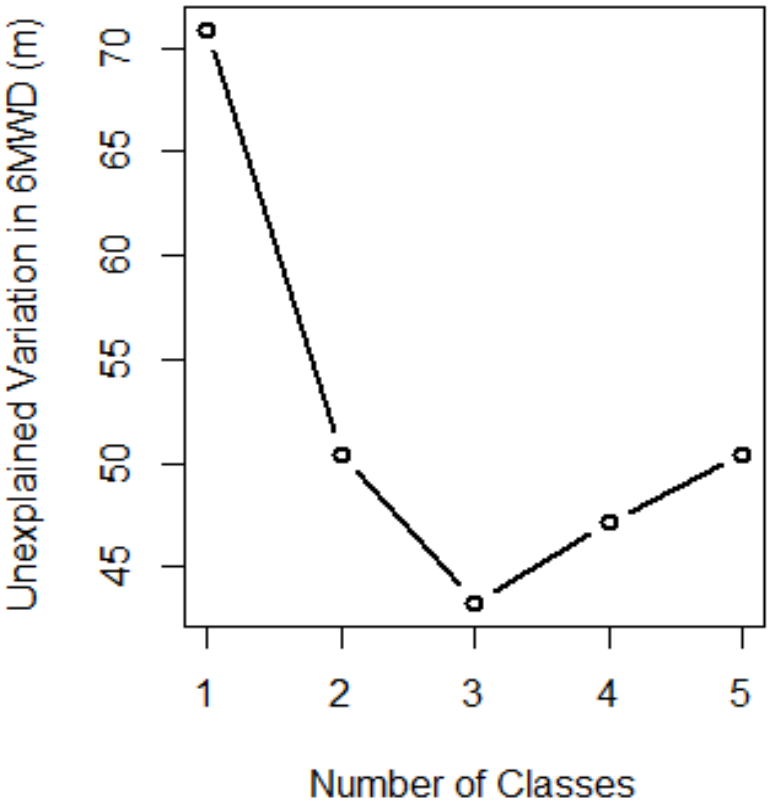
C. age + age^2 with 3 classes

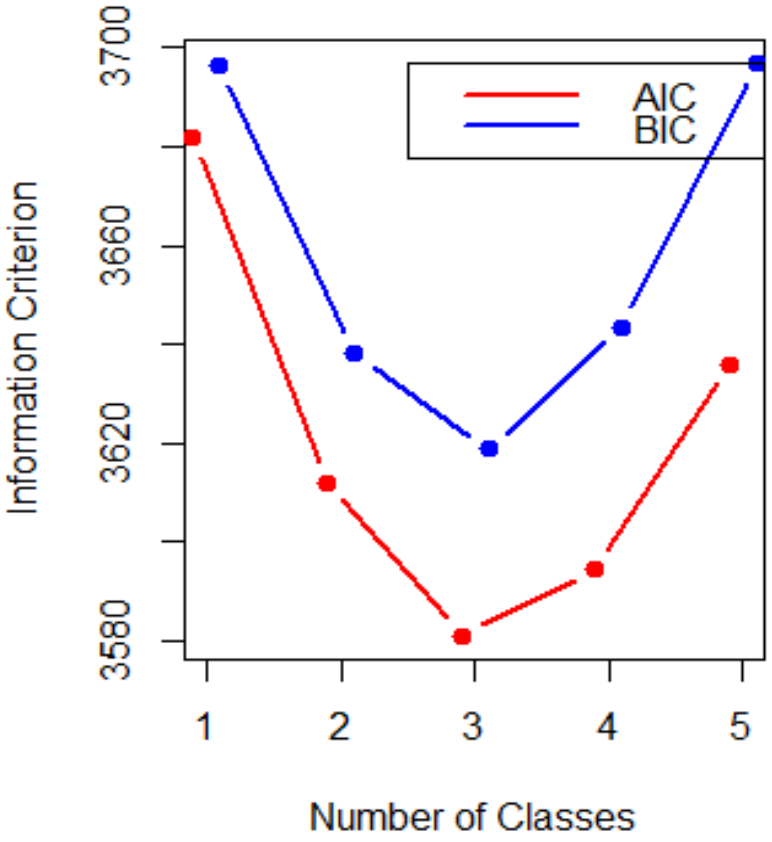
D. age + age^2 with 4 classes

E. age + age^2 with 5 classes

Which model best explains the data?

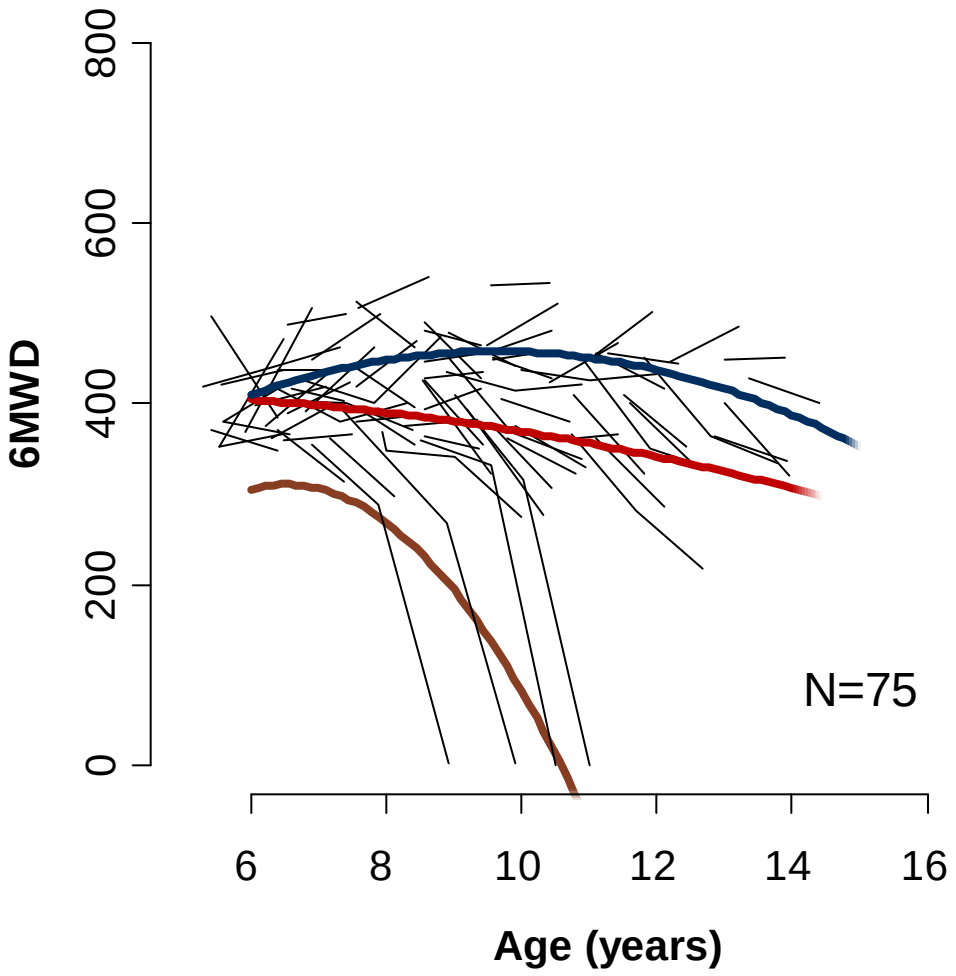
How many clusters?





- 3 classes fit better than 1 or 2
- SD for unexplained variation reduced ***71m → 43 m***

Incorporating more data for boys with baseline 6MWD > 350 m



Additional data extracted from Lee Sweeney et al.

Total N = 75

Three clusters vs. two vs. one:

- **Improved statistical measures of model fit; three clusters was best**
- **Three clusters reduced unexplained variance in 6WMD 71m => 43m**

Take-aways

- There are strong signs of trajectory clustering
- Marked reduction in unaccounted for variance (> 50%)
- Next: Validation in independent, larger samples

cTAP Access to Patient Data
Progress in Year 1

- Data Sources
  - 2 multi-center clinical registries
  - 2 large neuromuscular clinical practices
  - US and EU

- >1260 patients
- > 90% with dystrophin genotype
- >5000 patient-years
- >>35,000 data points

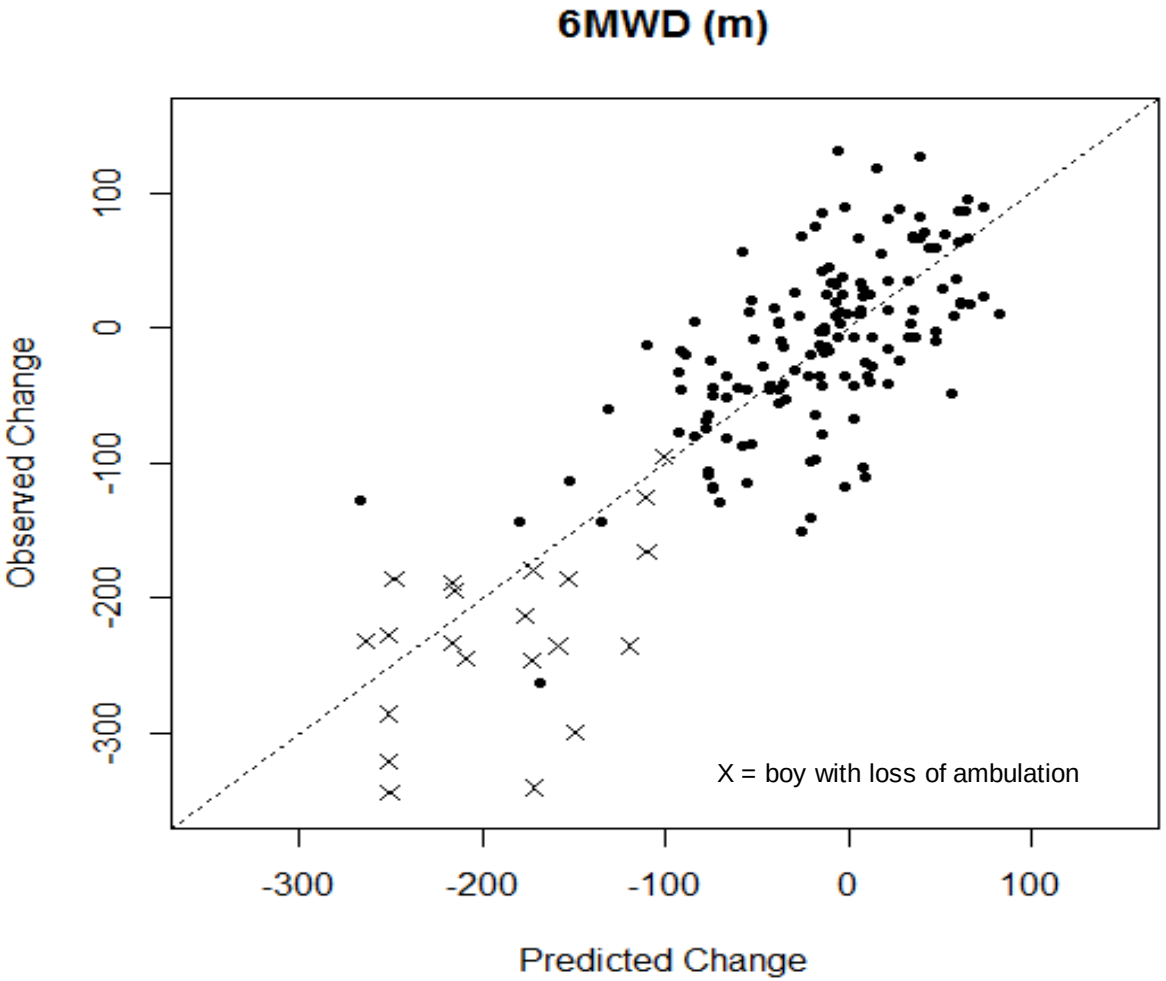
But wait – so much patient data beyond 6MWD

- Ambulatory function
  - NorthStar Ambulatory Assessment (NSAA)
  - 21 parameter assessment
- Timed Functional tests
  - Rise from supine
  - 10 mwr
  - 4 SC
- Non-ambulatory function
  - pulmonary
  - cardiac
  - Bone density

- Patient Reported Outcomes
- History of steroid use
  - Drug, regimen
  - Age at GC start, duration
- Dystrophin genotype
- Age, Height, weight, BMI

Will additional parameters improve prognosis?

Prognostic model Preliminary Results
Observed vs. predicted annualized change in 6MWD



Don't assume traditional methods have been exhausted!

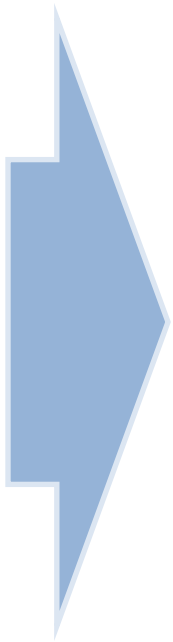
Multiple pivotal trials failed to meet primary endpoint
Impact of reduced variance on power

	Unexplained variation (m)						
Treatment effect (m)	40	50	60	70	80	90	100
20	96%	84%	69%	56%	45%	37%	31%
25	100%	96%	87%	75%	64%	54%	45%
30	100%	99%	96%	89%	79%	69%	60%

Approximate power in a trial of n=110 treated vs. n=110 controls

Reduced variance: 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

Regulatory Science Workshop - Implications

Tension:

Impact/Value of markedly greater power

vs

Regulatory Risk (Guinea-pig(s))

- Any "Non-traditional" statistical approach
- Safe(ish) Zones => Regulated applications
- Leverage beyond Duchenne

cTAP: a collaborative, analytical Platform

Pre-Competitive	OBJECTIVE, INDEPENDENT
De-identified patient data	SHARE DATA EQUALLY
Analyses, at scale	IMPACT- NOW
Financial Resources	FLEXIBLE
All stakeholders	A FIRST IN DMD

More effective drug development => enable drugs to patients sooner

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