The TAP Collaboration

Susan J. Ward, Ph.D.
The TAP Collaboration
and
James Signorovitch, Ph.D.
Vice President, The Analysis Group Inc.

TREAT-NMD
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cTAP
The **c**ollaborative **T**rajectory **A**nalysis **P**rogram in Duchenne Muscular Dystrophy

1. What and Why
2. Aspirations and Challenges
3. Preliminary Results
4. Next

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

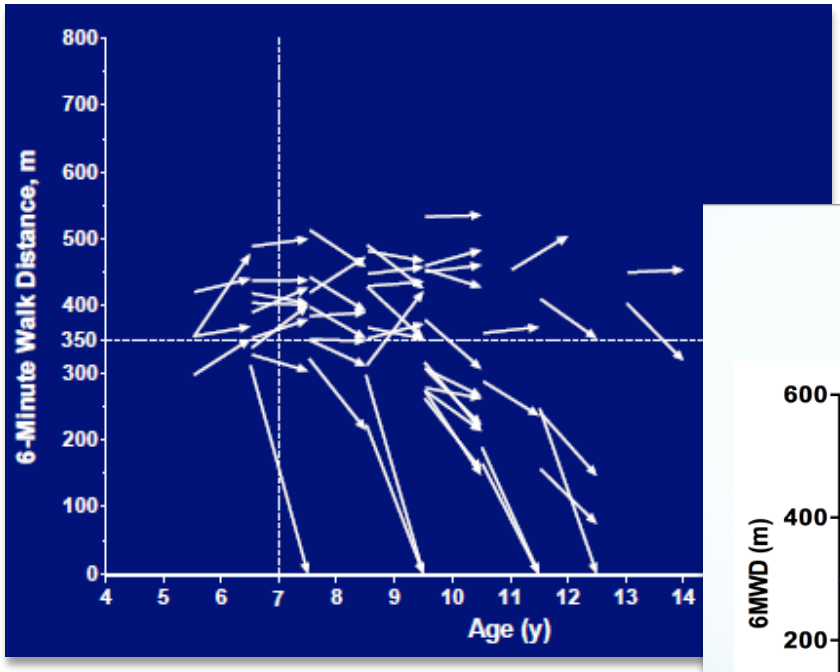
Study	Design	Δ 6MWT (m)	SD (m)	Study (weeks)	n
McDonald 2010*	Natural History	-57	104	52	18
Ataluren 2010*	Placebo arm	-42	90	48	57
Mazzone 2011**	Natural History	-42	74	52	71
Goemans 2012*	Natural History	-38	96	52	19
McDonald 2013**	Natural History	-59	82	48	33
Drisapersen 2014	Placebo Arm	-53	78	48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

Hindsight: poor Signal to noise, underpowered

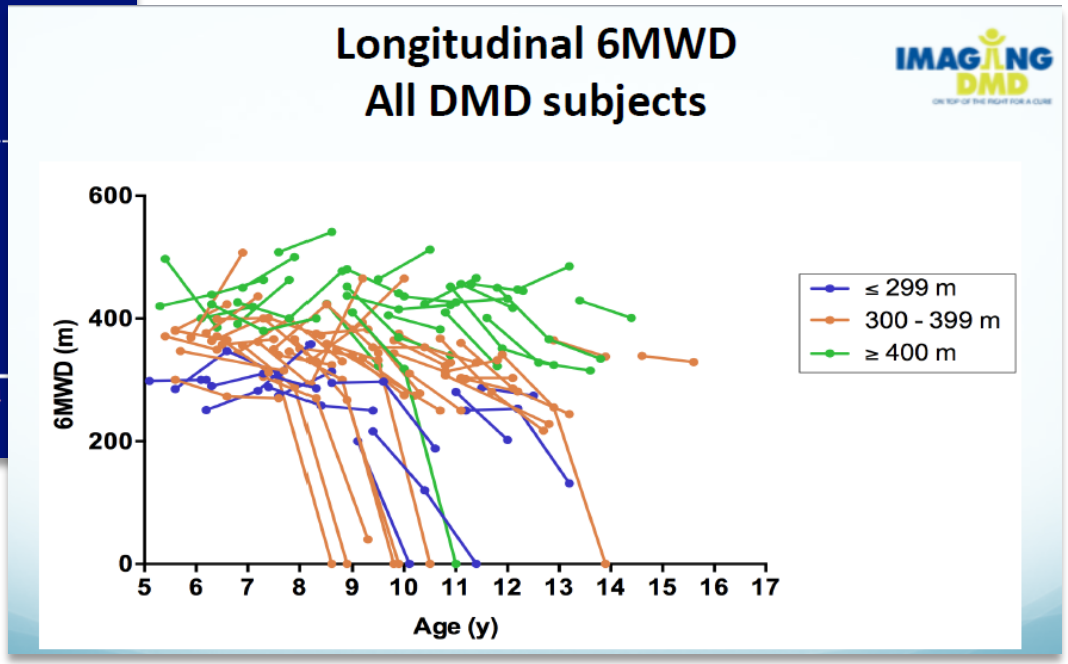
PUBLISHED AFTER TRIALS DESIGNED

Phenotypic Heterogeneity – a major source of variance

Ataluren PIIb placebo arm



Imaging DMD data



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

The Collaborative Trajectory Analysis Project (cTAP)

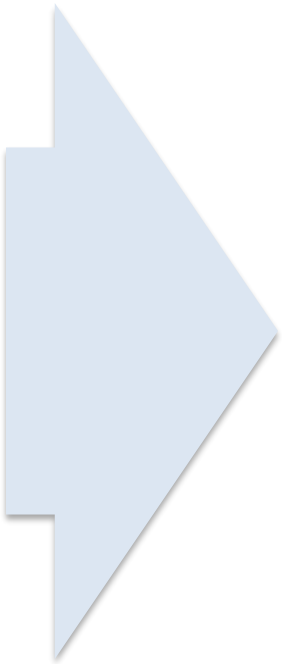
Mission

- Account for phenotypic variation in DMD
- Embrace methods from other diseases, other fields
- Translate into tools for trial design/analysis
- Make insights available to everyone in Duchenne
- Deliver near-term impact

Enable drug developers to bring new therapies to patients, sooner

Founding Collaborators

- Analysis Group
- Cure Duchenne



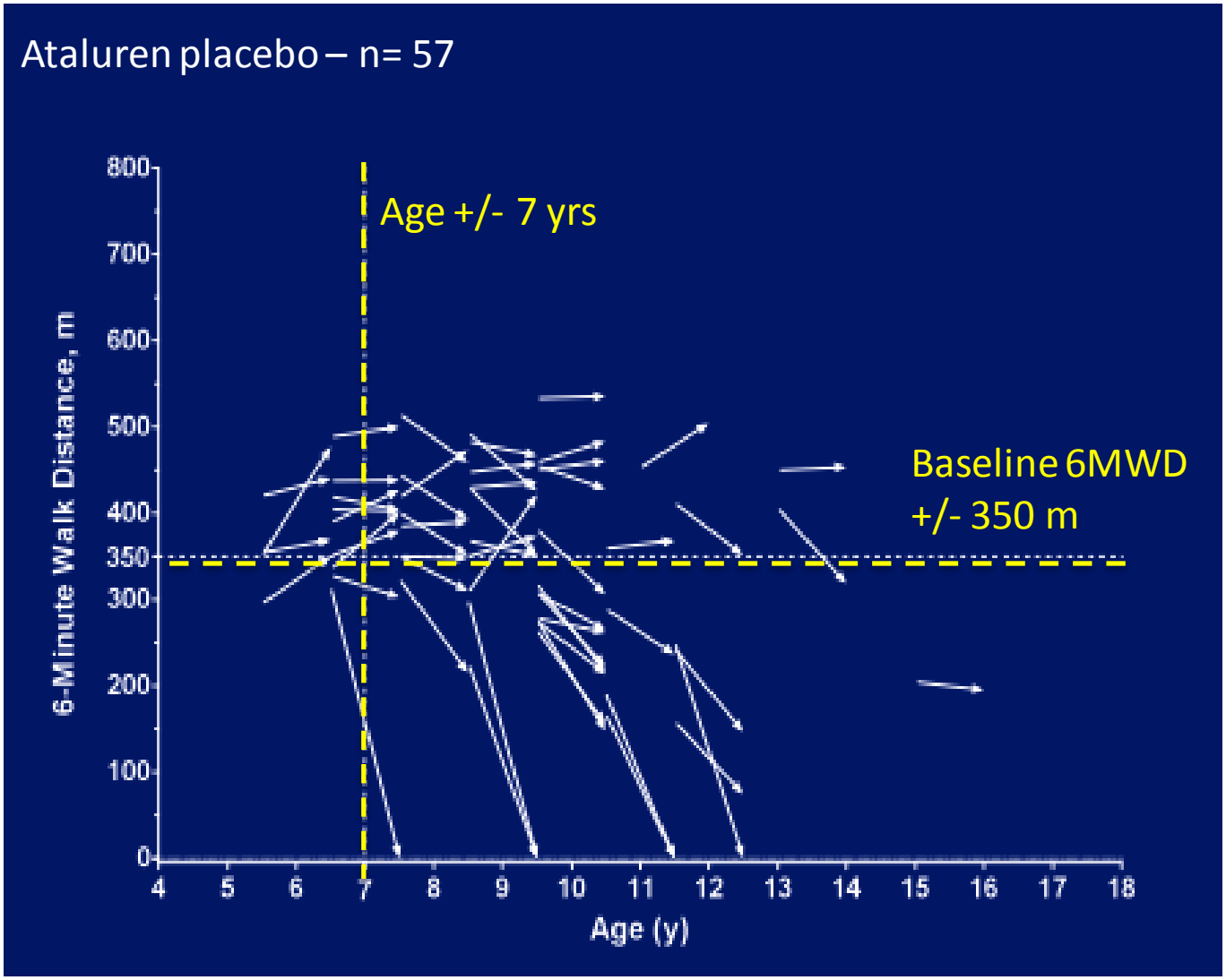
- Eugenio Mercuri and Italian Telethon
- Pfizer
- Prosensa (Biomarin)
- Shire
- PPMD
- Sarepta
- PTC Therapeutics

The Analysis Group Inc.

- Partner: Dr. James Signorovitch, Vice President
- AG has ~600 professionals with advanced degrees: biostatistics, statistics, pharmacology, applied math, economics, health policy
- Analytical and research services for healthcare, other industries
- Extensive scientific publications; client regulatory submissions
- Experienced in collaborative research with Foundations and Registries in Rare Diseases
- Rigorous security compliant with EU data protection, HiPPA; highly sensitive individual patient data handled routinely

http://www.analysisgroup.com/
http://www.analysisgroup.com/health_care_consulting.aspx

Prognostic Factors - Benchmark

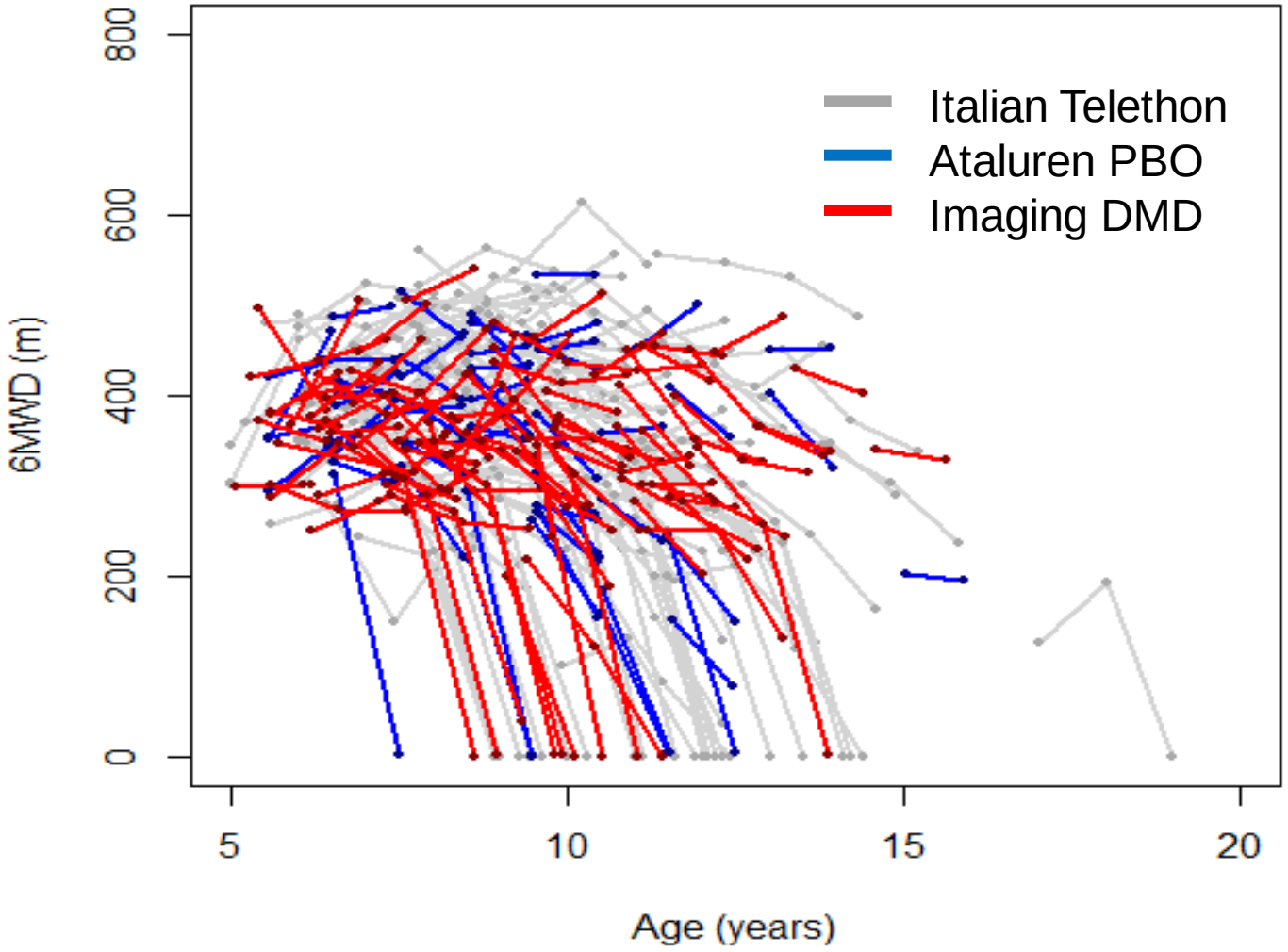


Reduction in variance SD:
97m => 78m
(~ 20%)

Latent Class Trajectory Analysis

- Methodology used in social sciences and healthcare economics
- Developed to handle variance due to heterogeneity in longitudinal trajectories
- Not a currently accepted regulatory path
- Of growing interest understanding outcome

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

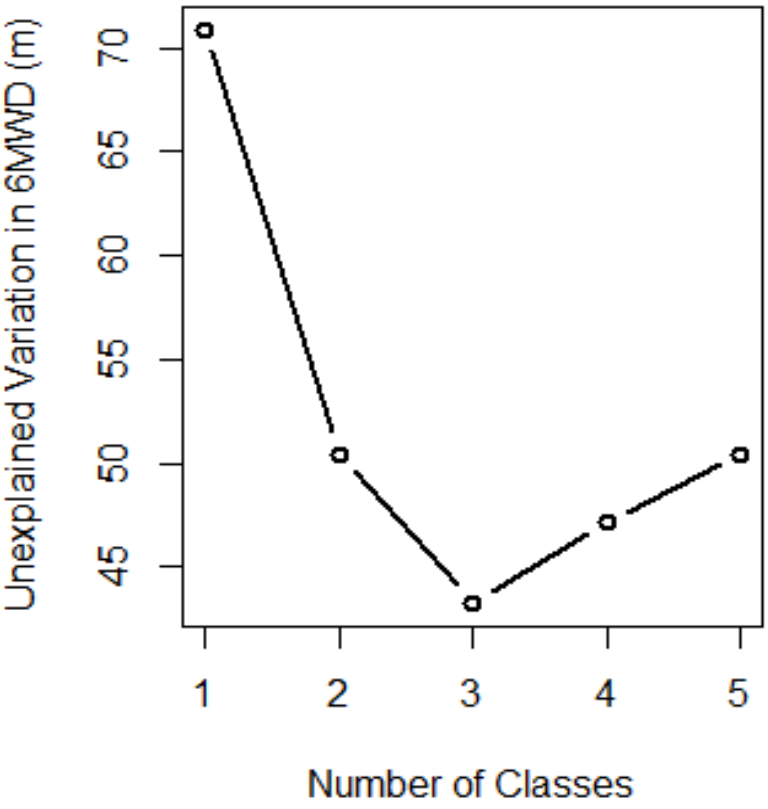
C. age + age^2 with 3 classes

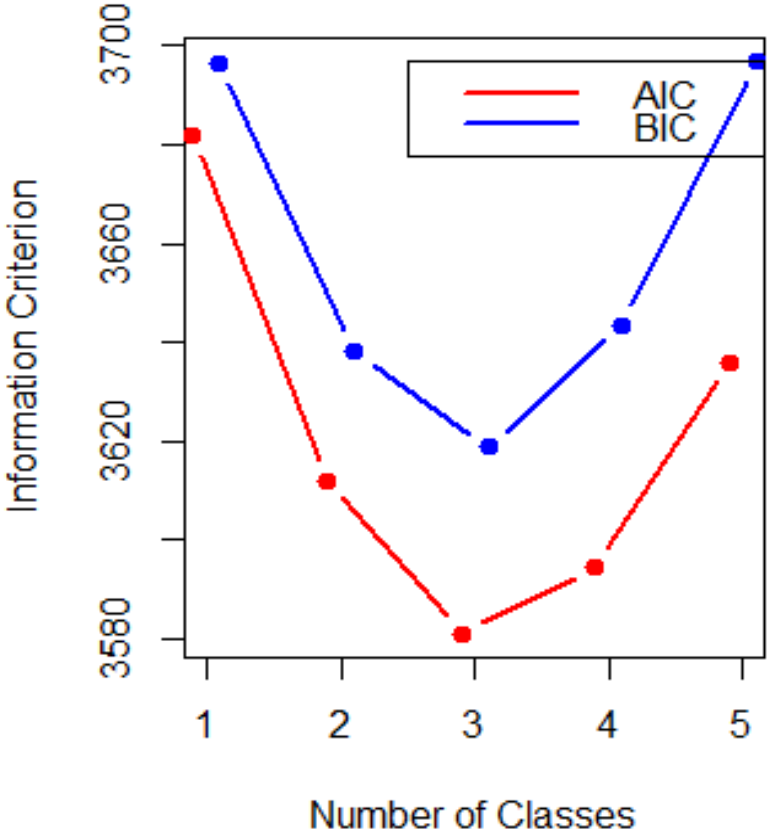
D. age + age^2 with 4 classes

E. age + age^2 with 5 classes

Which model best explains the data?

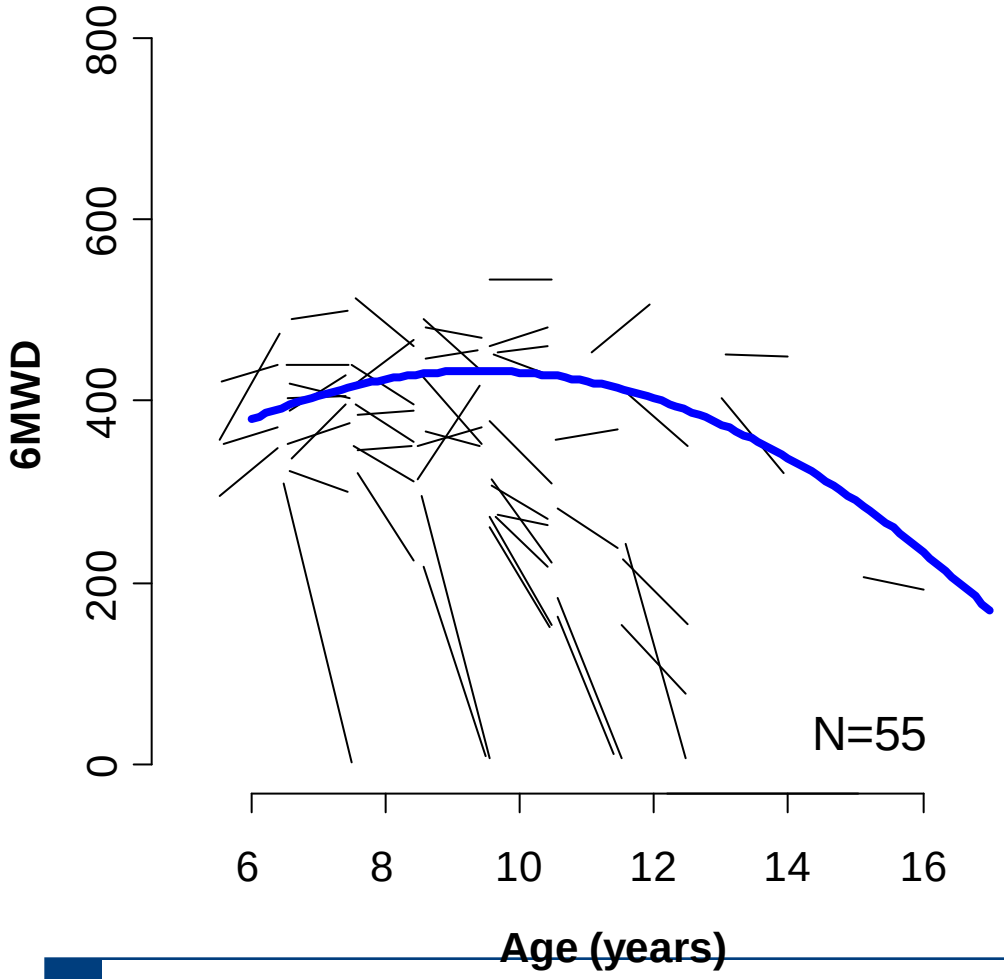
How many clusters?





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

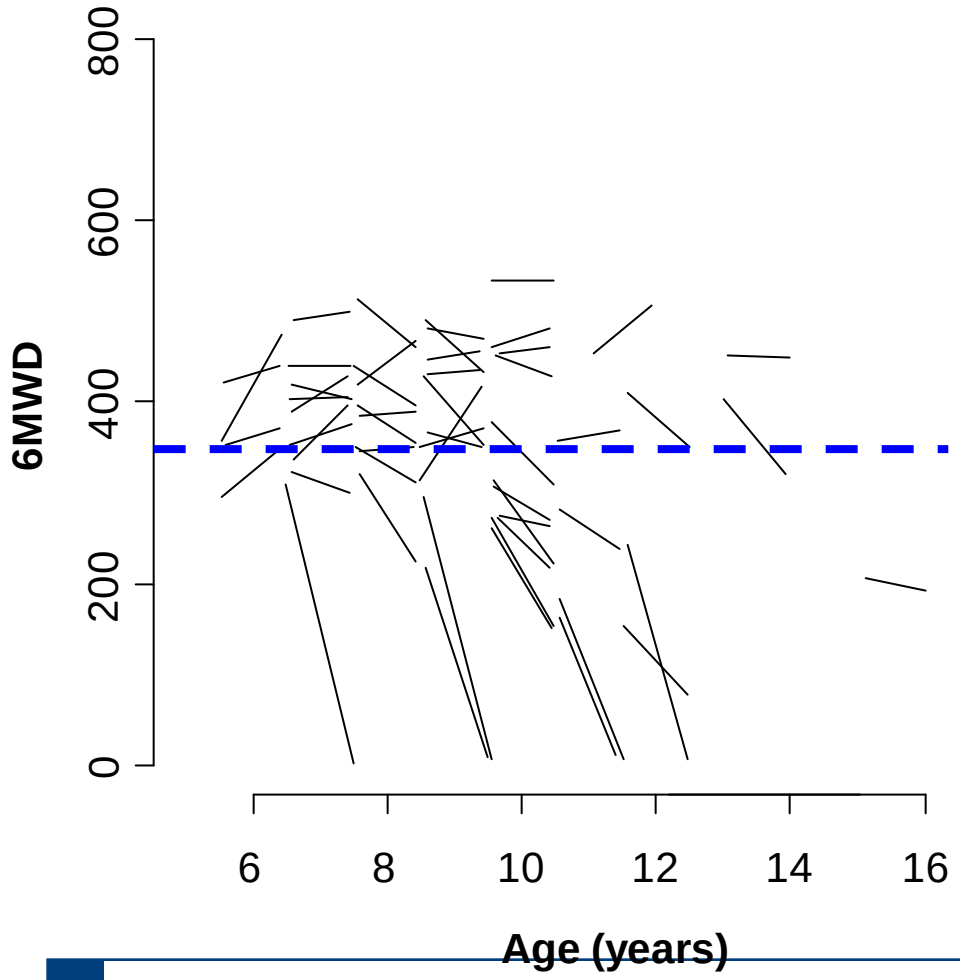
There is evidence for >1 trajectory with only 2 time points for N=55 boys



Two clusters vs. one:

- **Improved statistical measures of model fit (AIC, BIC)**
- **Reduced unexplained variance in 6WMD SD: 90m => 53m**

Focus on boys with baseline 6MWD > 350m

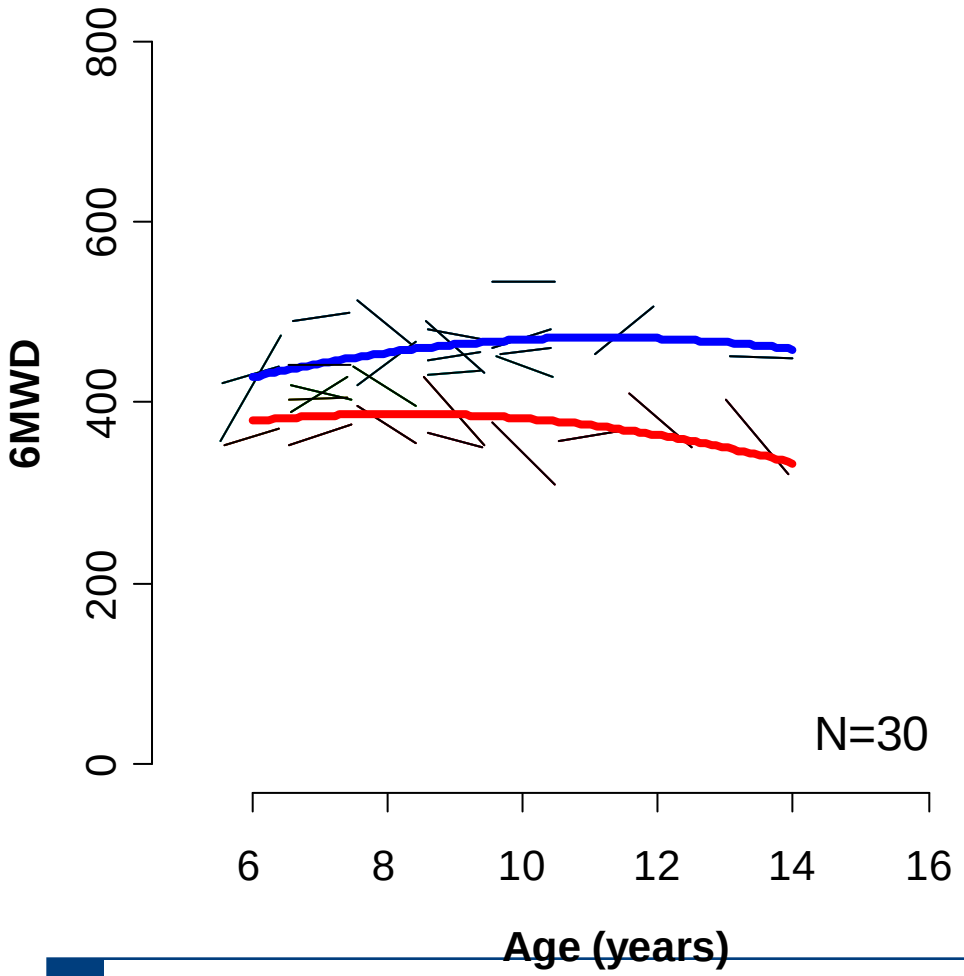


Does a known prognostic factor explain all variation in outcomes?

Or, is there still evidence of clustering?

N=30

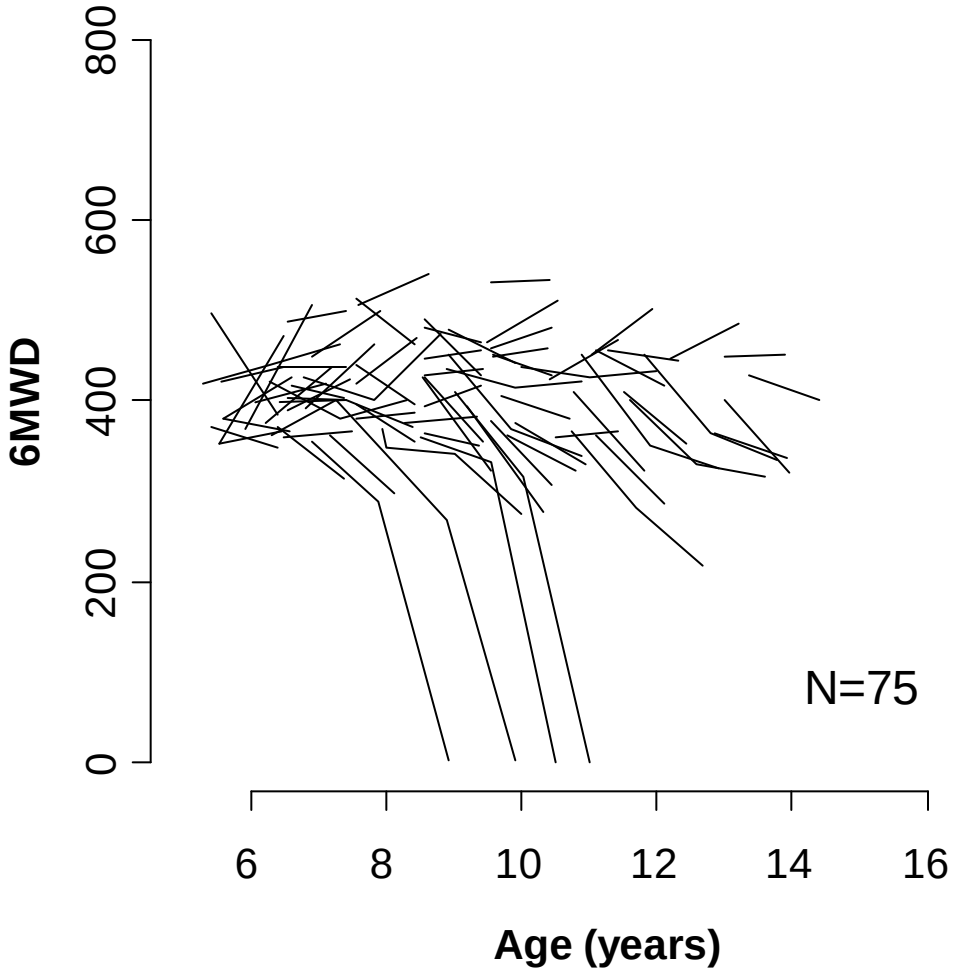
Evidence for >1 trajectory in boys starting with 6MWD > 350 m



Two clusters vs. one:

- **Improved statistical measures of model fit (AIC, BIC)**
- **Reduced unexplained variance in 6WMD by 57%**

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

Two to three clusters were detected in sample sizes of N=30 to N=75 with only 1 to 2 years of data – even for boys starting with 6MWD> 350 m

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

Encouraging Proof of Concept

cTAP Collaborators – a Growing Family

- Nathalie Goemans, UZ Leuven
- Francesco Muntoni, Valeria Ricotti, Adnan Manzur and Northstar UK
- Brenda Wong, CCHMC

- Solid Biosciences
- Catabasis Pharma

De-identified Patient Data – Progress in Year 1

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

Timed Tests

NSAA

Pulmonary

Cardiac

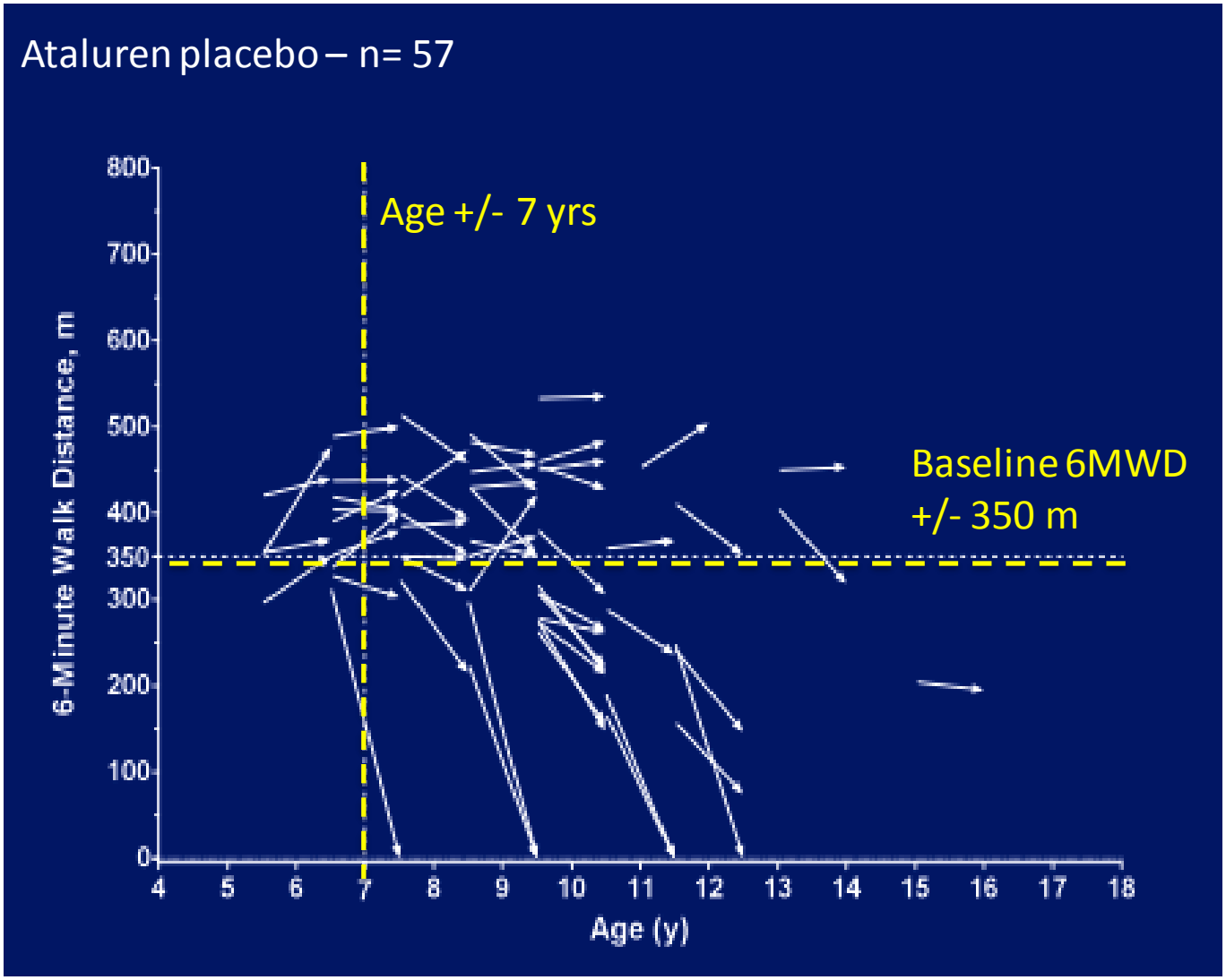
Bone Density

History of GC Use

Height, weight, BMI

Patient Reported Outcomes

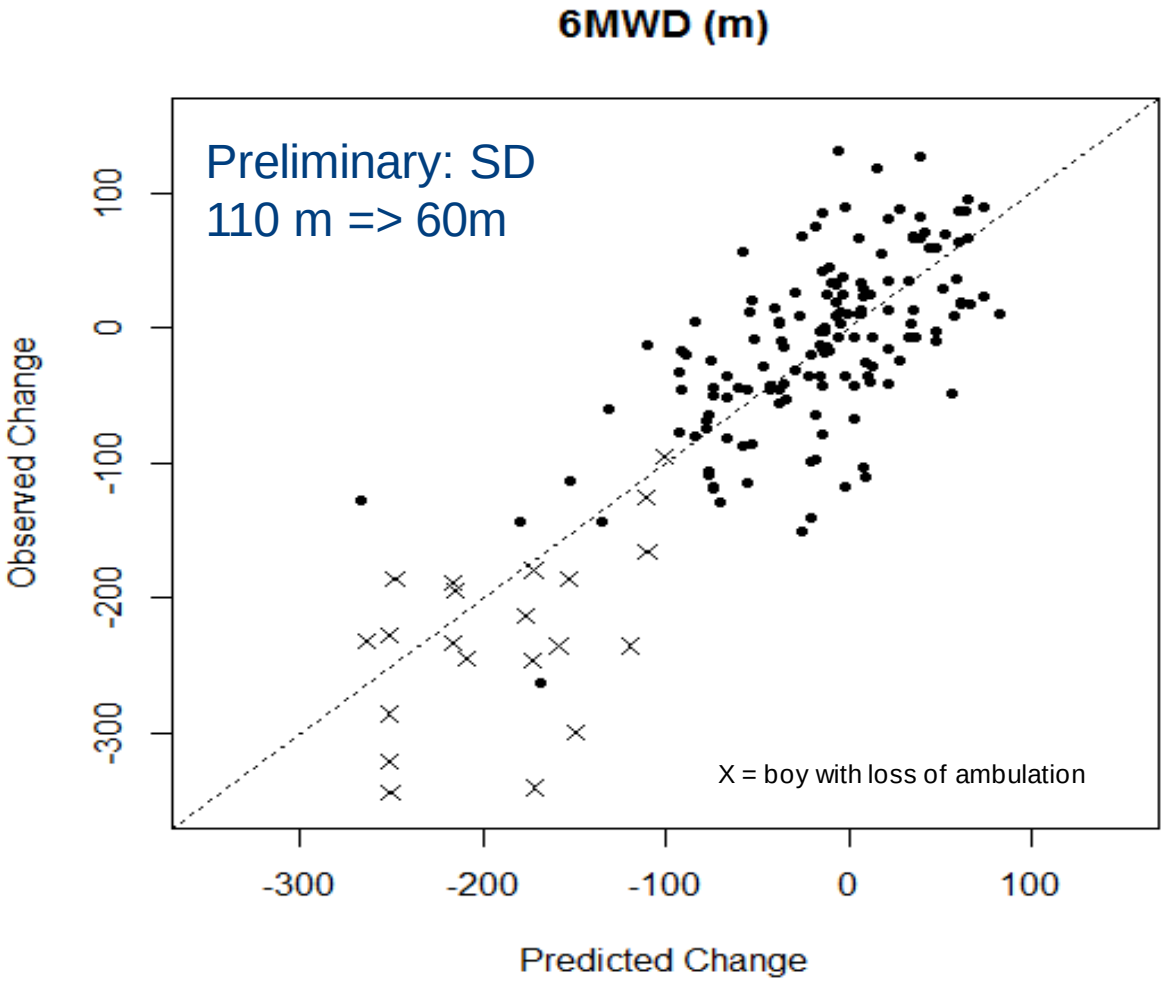
Benchmarks for Variance and prognostic factors



Reduction in variance SD:
97m => 78m
(~ 20%)

Might additional baseline characteristics improve prognostic power?

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



Don't assume traditional methods have been exhausted!

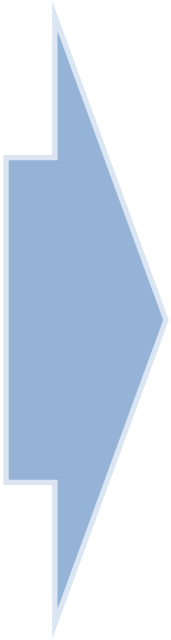
Multiple pivotal trials failed to meet primary endpoint
Impact of reduced variance on power

Treatment effect (m)	Unexplained variation (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

Summary

THE PROBLEM

- > 5 years clinical development
- > 1000 open port biopsies
- # Drug approvals – zero
- Reduction in heterogeneity-based variance ~ 15-20%

The TAP Collaboration – working to find a solution

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

- Larry Charnas
- Mike Binks
- Carl Morris
- Katherine Beaverson
- Giles Campion
- Ed Kaye
- Dallan Murray
- Bob Spiegal
- Ed Xiou
- Serene Josiah
- Joel Schneider
- Charles Legg
- Joanne Donovan
- Rick Modi

And their teams

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

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