COLLABORATIVE
TRAJECTORY
ANALYSIS
PROJECT

Collaborative Learning from Patient Data in Rare Disease

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Collaborative Trajectory Analysis Project - cTAP

- Pre-Competitive coalition
- Pan-stakeholder
- Global
- Multi-registry, multiple trial
- Collaborative analytics

- ➢ “Smarter” Trials
- ➢ Current focus on Duchenne muscular dystrophy

Disclosures

- The funds for cTAP are contributed by member drug companies and patient foundations
  - Susan Ward receives collaboration management fees
  - The Analysis Group, at which James Signorovitch is a partner, receives fees for analytic services
- I am not a statistician!

Duchenne muscular dystrophy

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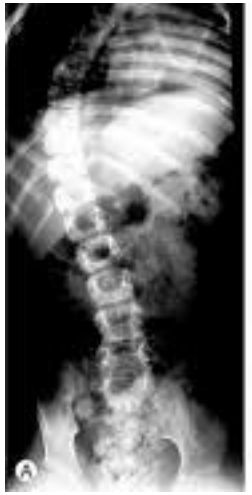
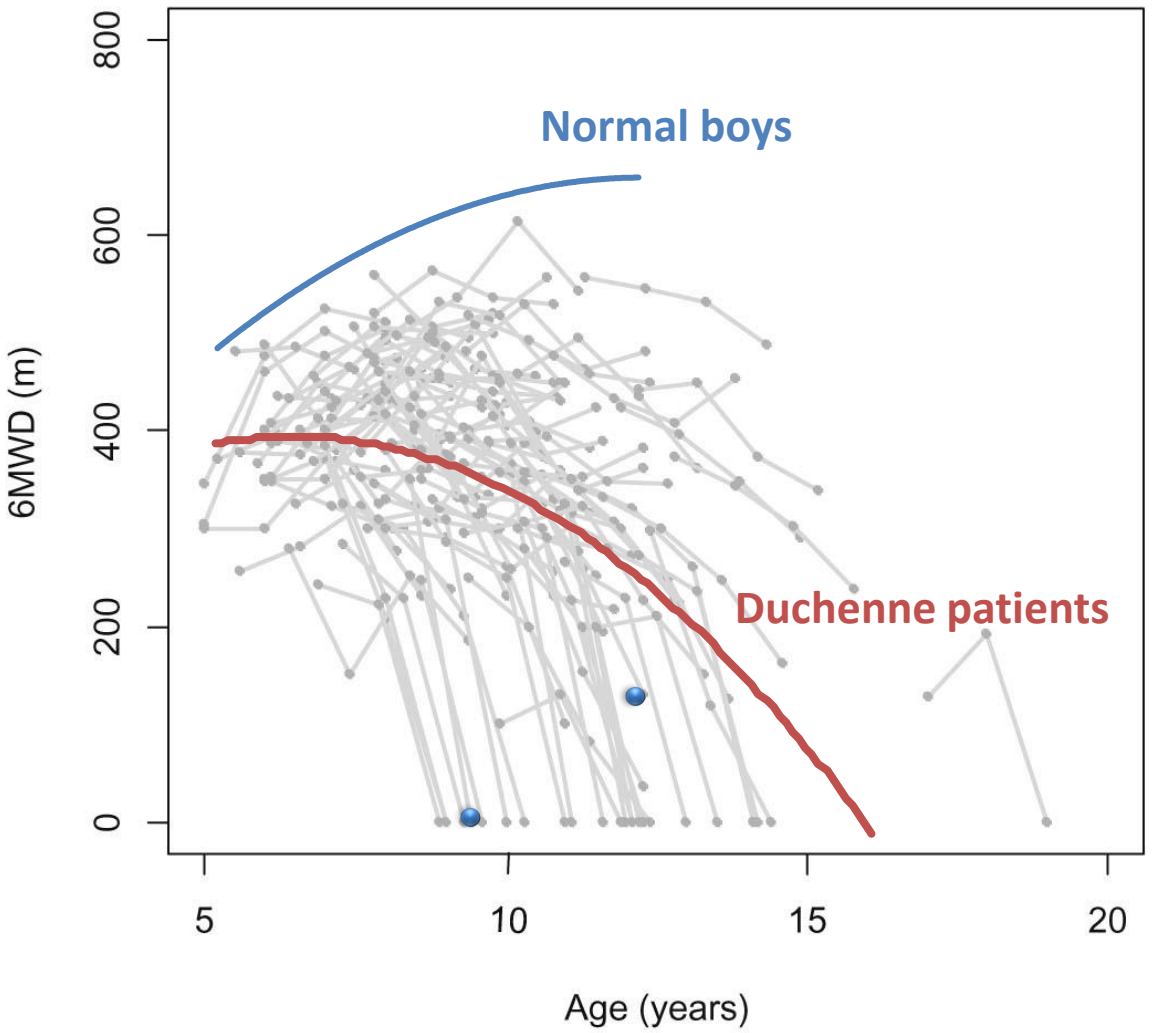
"A thousand little deaths"



Prescient capture of natural history

Ambulatory Function in Duchenne – complicated by maturation



- Symptom-prompted diagnosis of DMD occurs between 3-5 yrs of age
- Average trajectory of ambulatory function in DMD is progressive decline from ~ 7 yrs
- Normal boys approach peak ambulatory performance at ~10 yrs of age
- Heterogeneity in observed functional decline in DMD is likely a balance between maturation and disease progression

Goemans N, Klingels K, van den Hauwe M, Boons S, Verstraete L, et al. (2013) Six-Minute Walk Test: Reference Values and Prediction Equation in Healthy Boys Aged 5 to12 Years. PLoS ONE 8(12): e84120. doi:10.1371/journal.pone.0084120

Impetus – iterative clinical failures

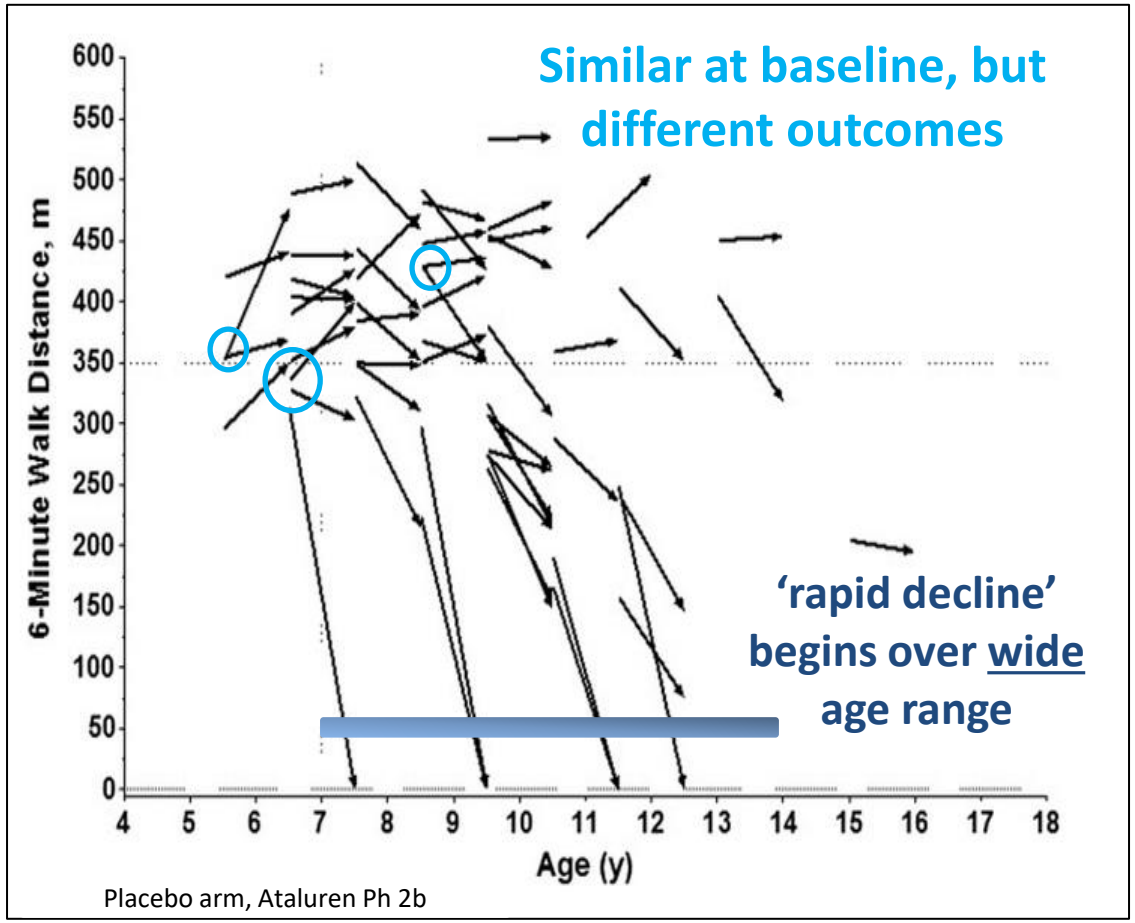
Placebo Arm Results, Ambulant at Baseline

PIVOTAL TRIAL	6MWD 1yr change	SD	n	Met endpoint?
DEMAND III	-53	81	61	no
PTC 007	-44	88	57	no
TADALAFIL	-51	100	116	no
PTC 020	-61	99	115	no

higher than anticipated variance

- *Why was high variance not anticipated?*
- *Do we have failed Drugs? or failed trials?*

Dominant driver of *failed trials* in Duchenne is …….
heterogeneity of disease progression



Placebo arm, Ataluren Ph 2b

- Similar profile of heterogeneity also seen in natural history studies
- Data held by leading clinicians in large clinicals and in curated clinical registries
- Limited data-sharing by clinical centers, ZERO sharing of clinical registry data

"We need to design trials that test efficacy of a drug, not how much we don't know about natural history"

Exec Dir, Clinical Development, Pharma cTAP member 2015

cTAP mission

COLLABORATIVE TRAJECTORY ANALYSIS PROJECT

Explain - and account for - heterogeneity in disease progression

- Collaborate to learn from patient data
- Bridge gaps in analytic approaches in DMD
- Create tools and insights for drug development
- Share broadly with the entire DMD community
- Deliver near-term impact for trials

'Smarter' Trials

- *Fully powered*
- *Smaller*
- *Leverage NH*

'Better' Evidence

- *Real World data*
- *Tie near-term to downstream*

Therapies to Patients sooner

How We Collaborate

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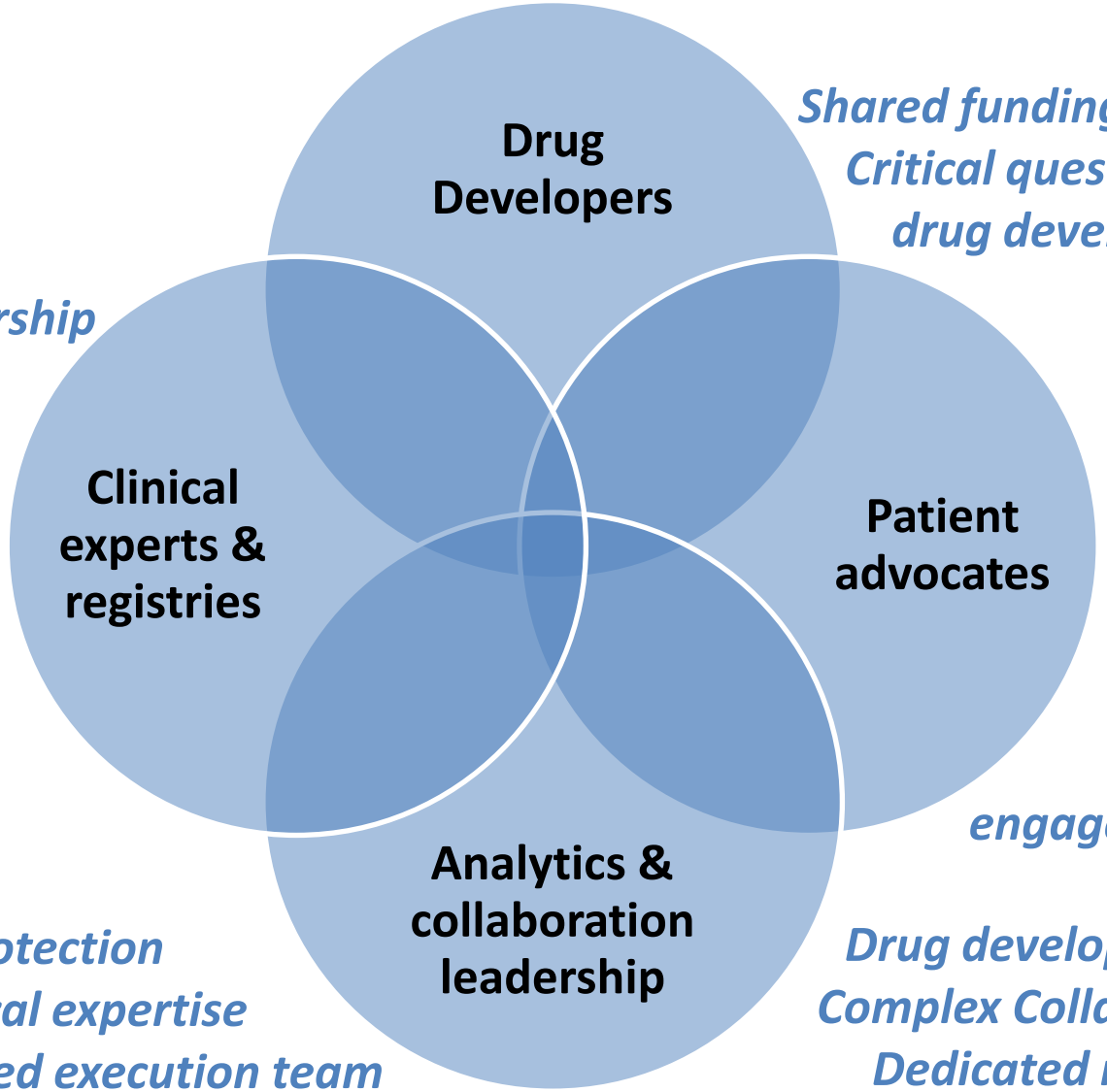

Shared funding
Critical questions for drug development

Scientific leadership & authorship
Clinical insights
Patient data

Seed funding, engagement, advice

Data protection
Analytical expertise
Dedicated execution team

Drug development enablement
Complex Collaboration Expertise
Dedicated management team

cTAP Members and Collaborators

Clinical experts and registries

Eugenio Mercuri

Nathalie Goemans

Francesco Muntoni

Brenda Wong

Hank Meyer

Craig McDonald

Krista Vandenborne

Therapy Developers

Patient Groups

Collaboration Lead

Susan J. Ward, PhD

Data Science Lead

James Signorovitch, PhD

Patient data accessed by cTAP

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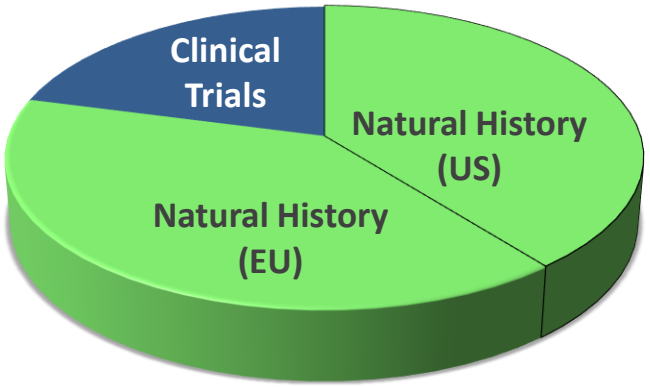
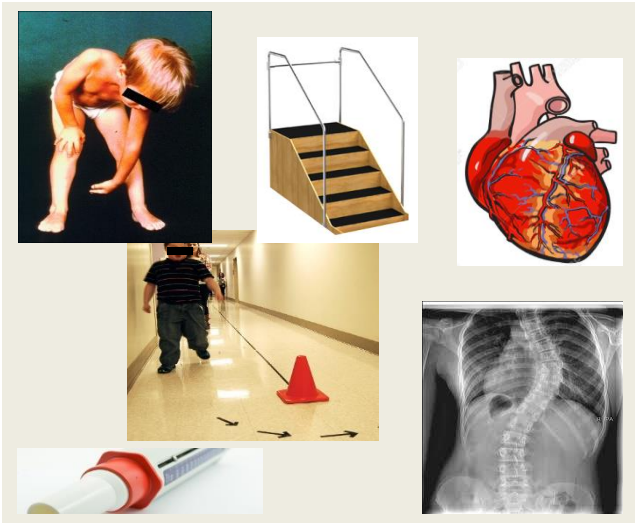
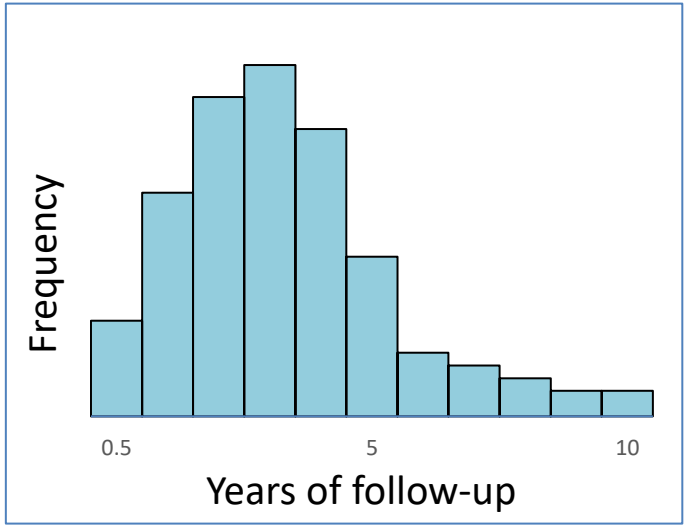
>2,300
boys



>15,000
clinic visits



>1,000
patient-years



LARGE & REPRESENTATIVE

RELEVANT & COMPREHENSIVE

DISEASE PROGRESSION

How we operate scientifically

- Governed by a Joint Steering Committee
- Prioritize goals based on most critical needs for drug development and evaluation
- Collaborate on research plans, interpretation, publications
- Analytic results – not raw data -- are shared within cT
- Analyses conducted per SAP by Analysis Group/other
- Findings validated (or not) across data sources

- *Neutral 3rd party*
  - *Equitable for drug companies*
  - *Objective process (no cherries)*
  - *Equal benefit, equals costs*

- *Impact -Focused , Nimble*
  - *Rigor, High Quality, objective*
  - *Shared knowledge, shared problem-solving*

Builds confidence and trust

cTAP Pipeline (leading outcome measure)

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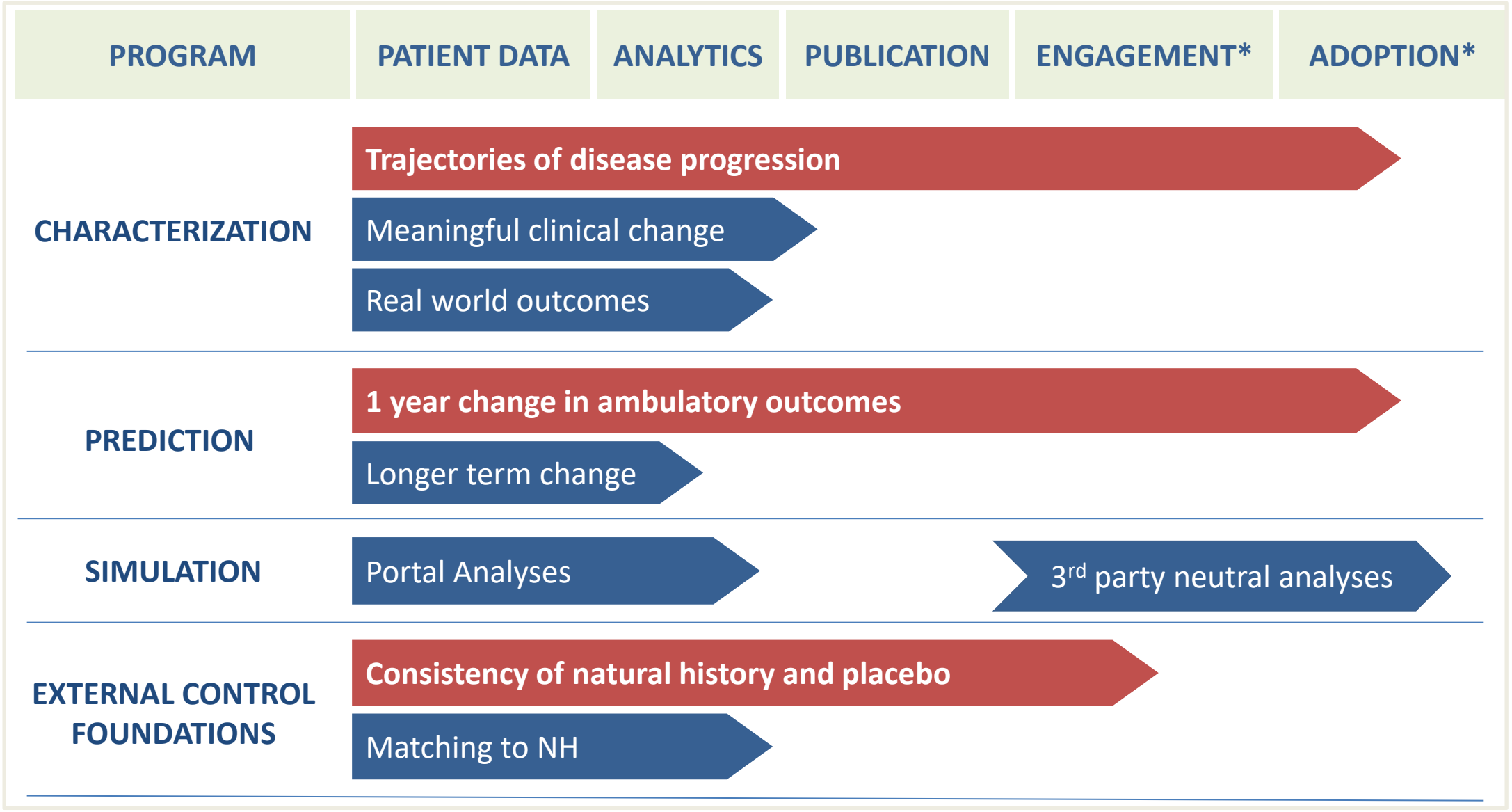

**With primary target group – academic, regulators, payors/health authorities – dependent on program*

Latent Class Growth modeling of Longitudinal Trajectories of Disease Progression in DMD

Clustering of Longitudinal Trajectories of DMD natural history

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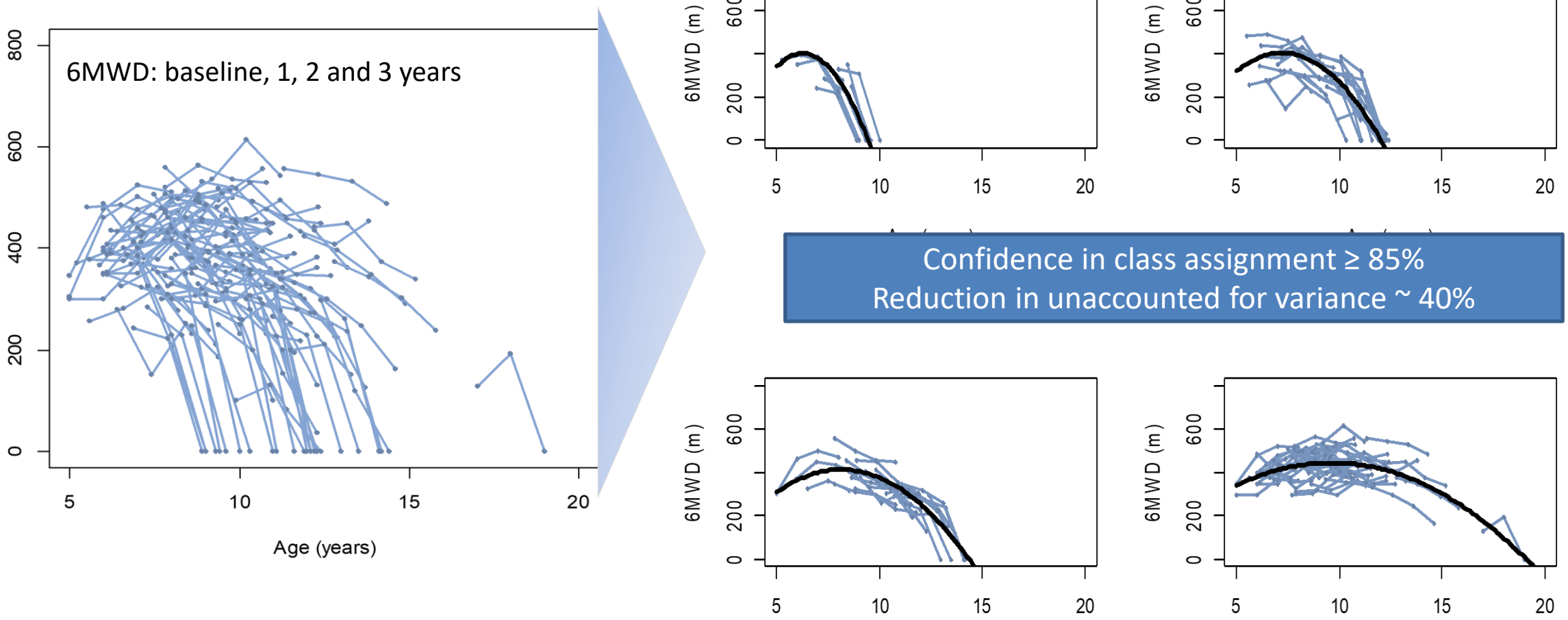

DMD progresses at different rates in different groups of patients

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*

Clustering of Longitudinal Trajectories of time from enrollment

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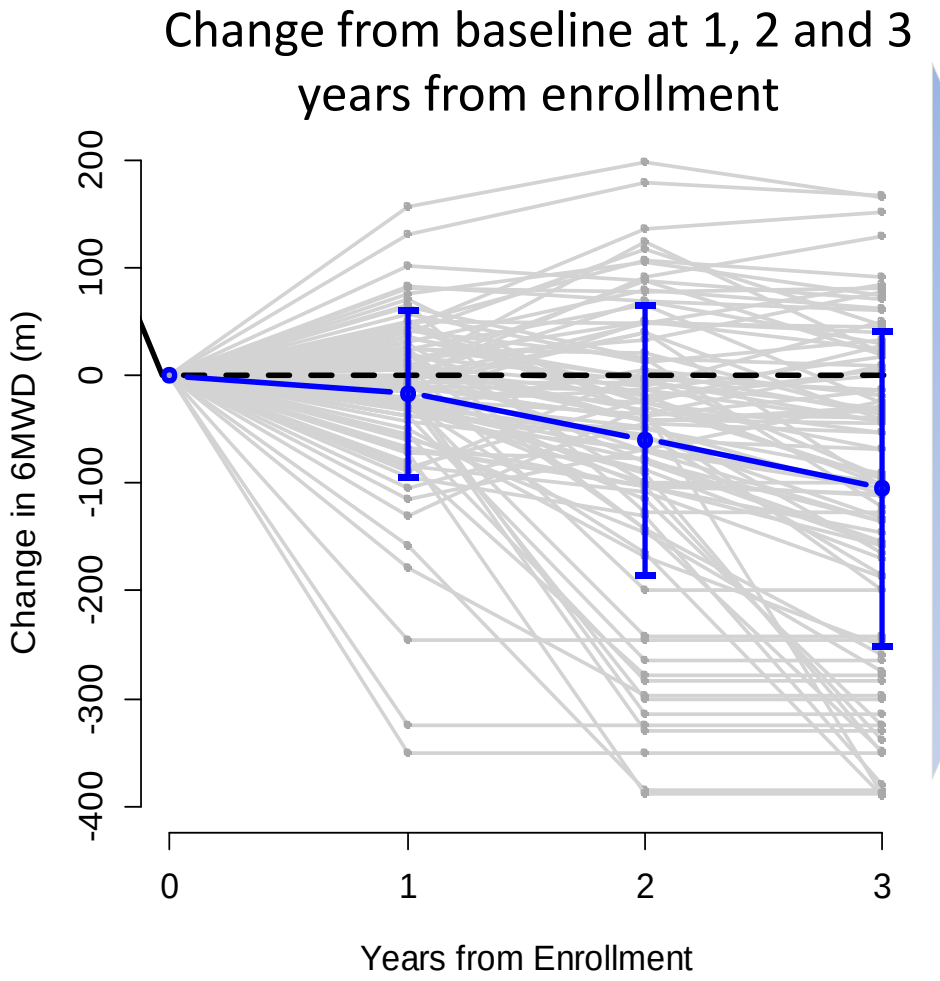
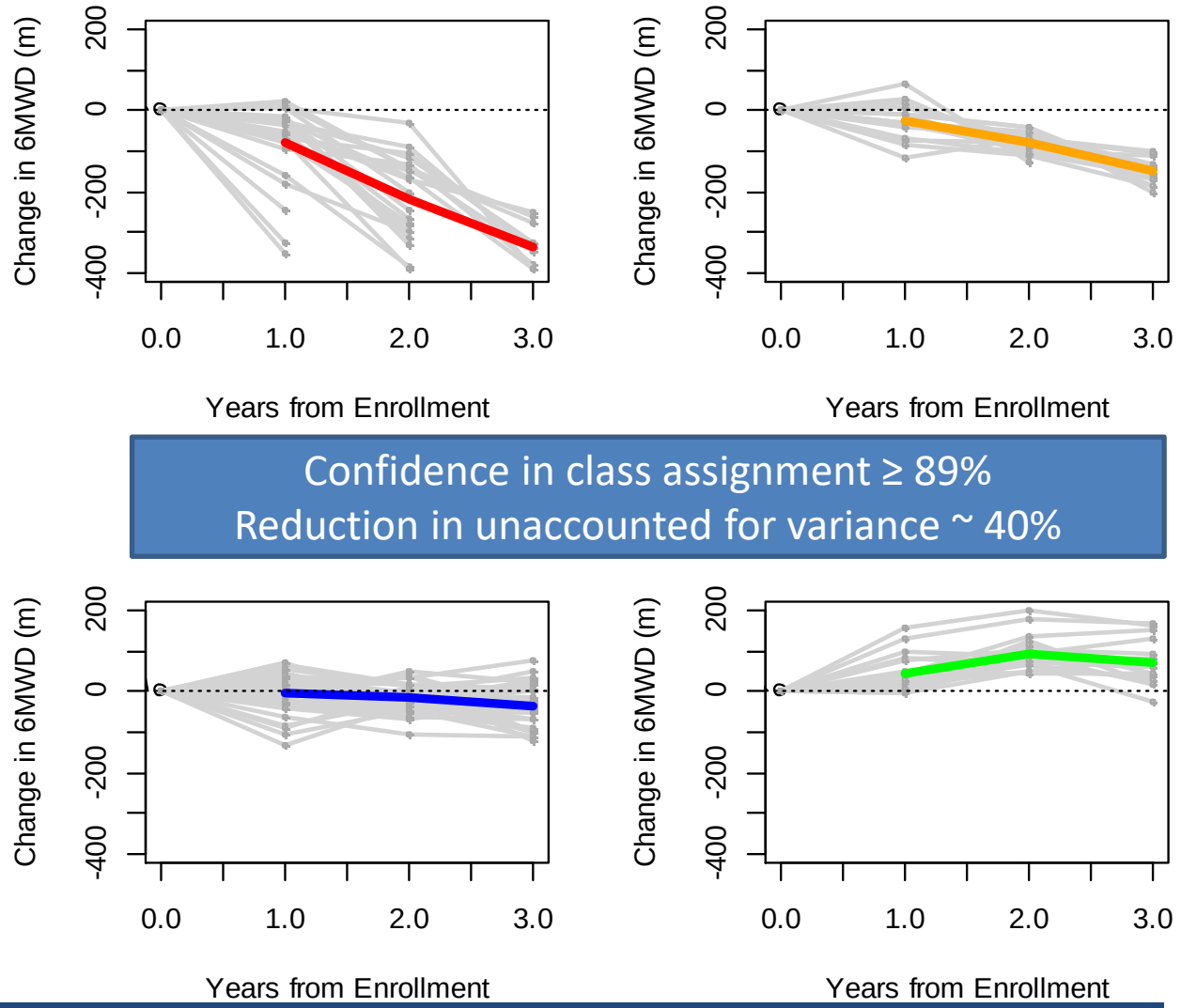
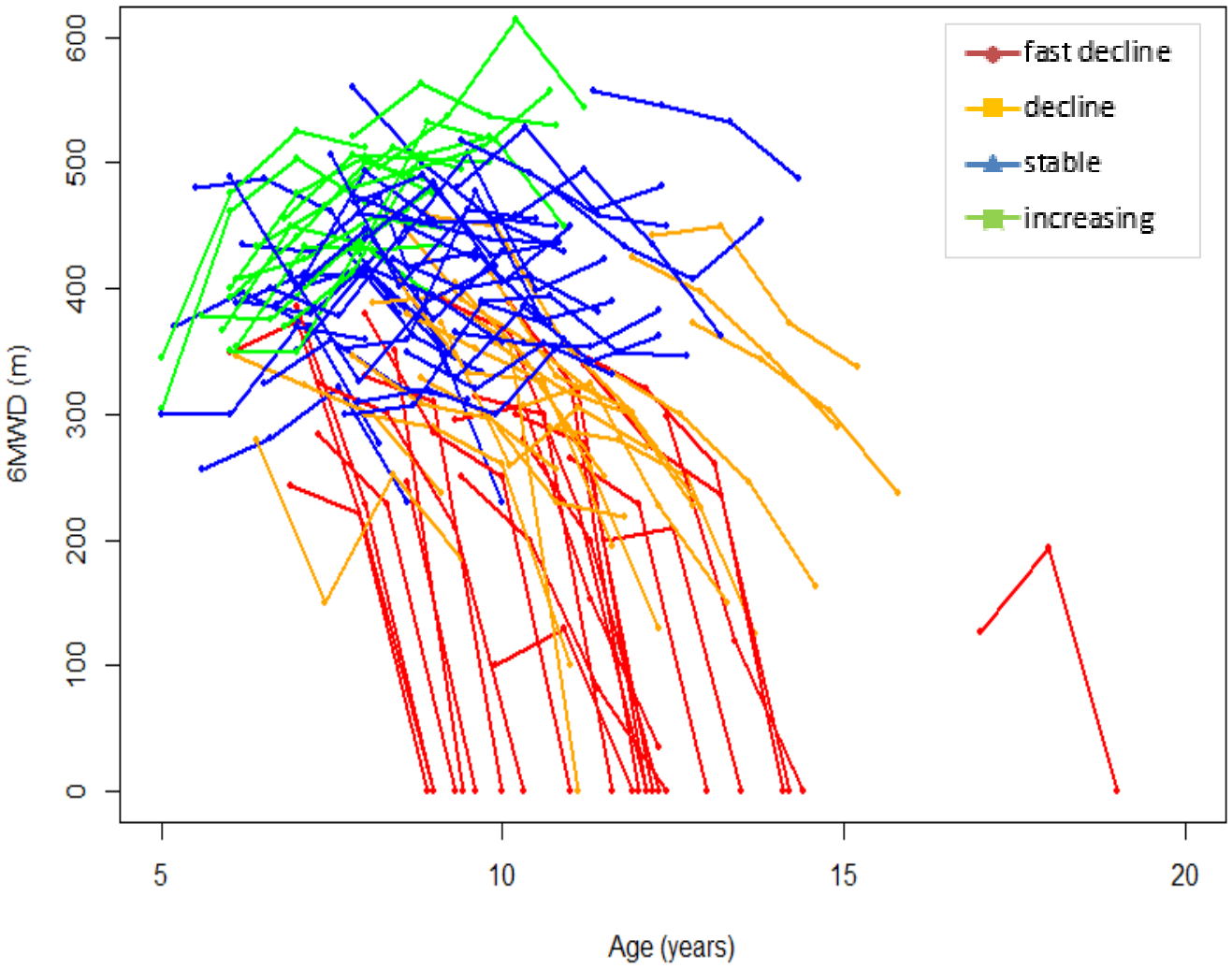




Different Patients may be in different Phases of Disease progression

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*

What we've learned



Clustering of Disease Progression

- suggests underling structure
- is consistent across databases
- is seen with other (ambulatory) outcome measures
- is concordant across outcomes

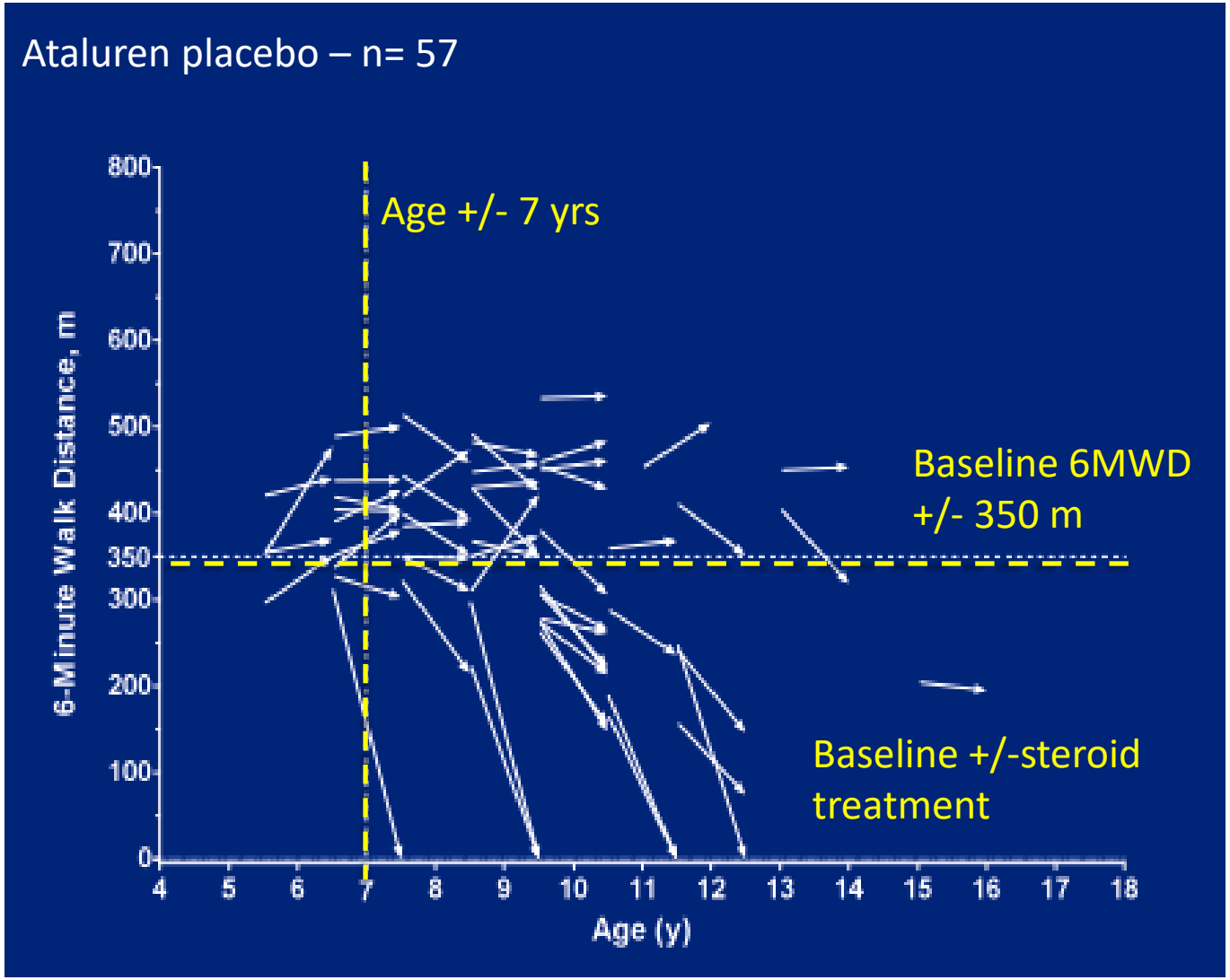
"Value" of characterisation studies

- Resonates with non-statisticians
- "Makes sense"
  - maturation+disease
- Framework for associations

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*

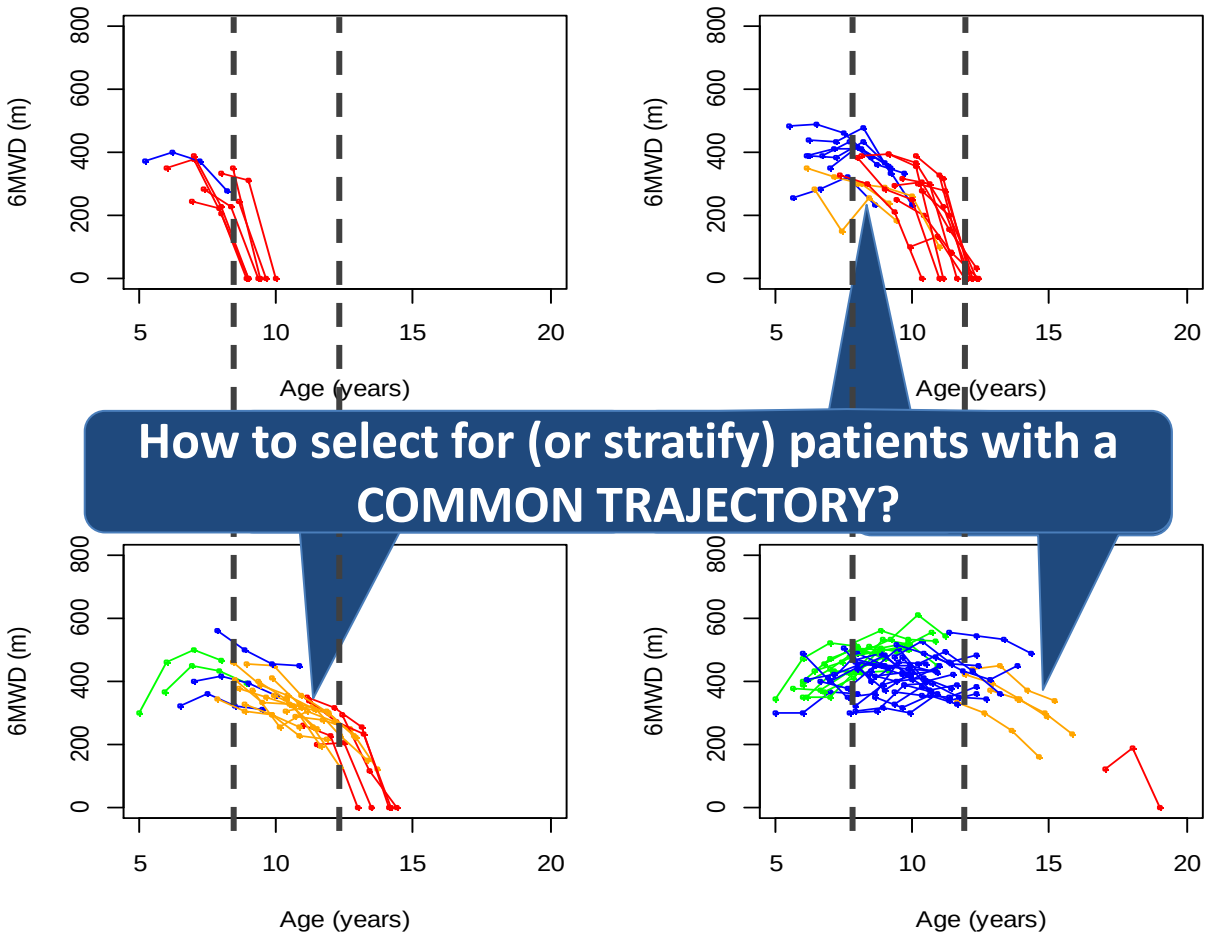
Prognostic Factors

Prognostic factors - Benchmark in 2015



- Developed post-hoc
- Determined by eye, not by statistics
- Included in MMRM analyses of trials
- Adopted widely to craft *inclusion criteria*

The challenge of longitudinal heterogeneity in trial design



inclusion/exclusion criteria can narrow eligibility without reducing heterogeneity of sample

Premise: More accurate pre-defined stratification => improve power

Objectives

- How informative are the conventional baseline factors (age, 6MWD and steroid use) for predicting 1-year change in 6MWD?
- Can prognostic accuracy be improved?
- What are the most important prognostic factors?

Study Design

COLLABORATIVE TRAJECTORY ANALYSIS PROJECT

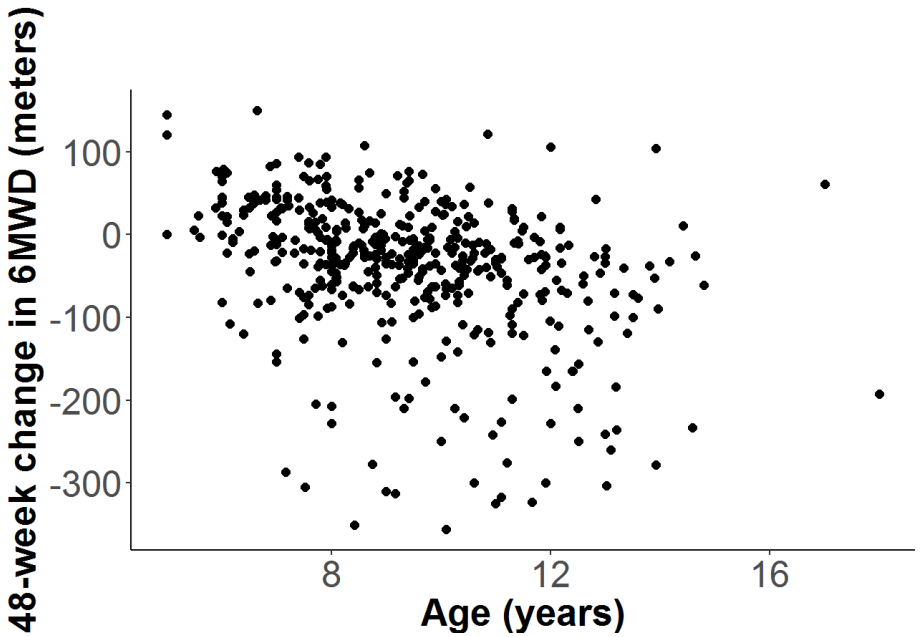
Develop prognostic model

- Natural history data from UZ Leuven

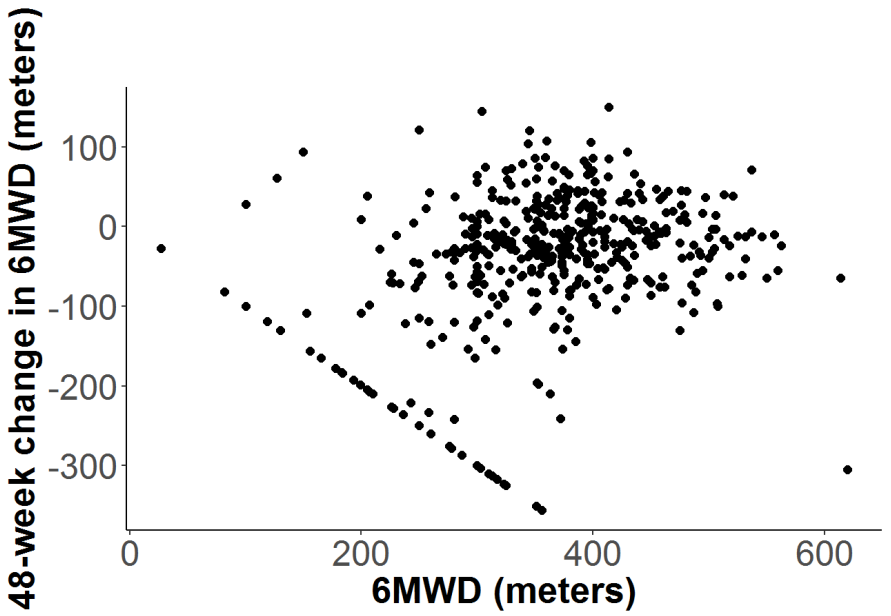
Validate prognostic model

- Placebo arm data from clinical trials

Age and baseline 6MWD are each only weakly correlated with Δ6MWD



Correlation Coefficient = -0.35



Correlation Coefficient = 0.25

Data Pooled from the Italian Group, UZ Leuven and Lilly Placebo arm.

Conventional Prognostic Factors account for only one quarter of observed variance in 1 yr Δ6MWD

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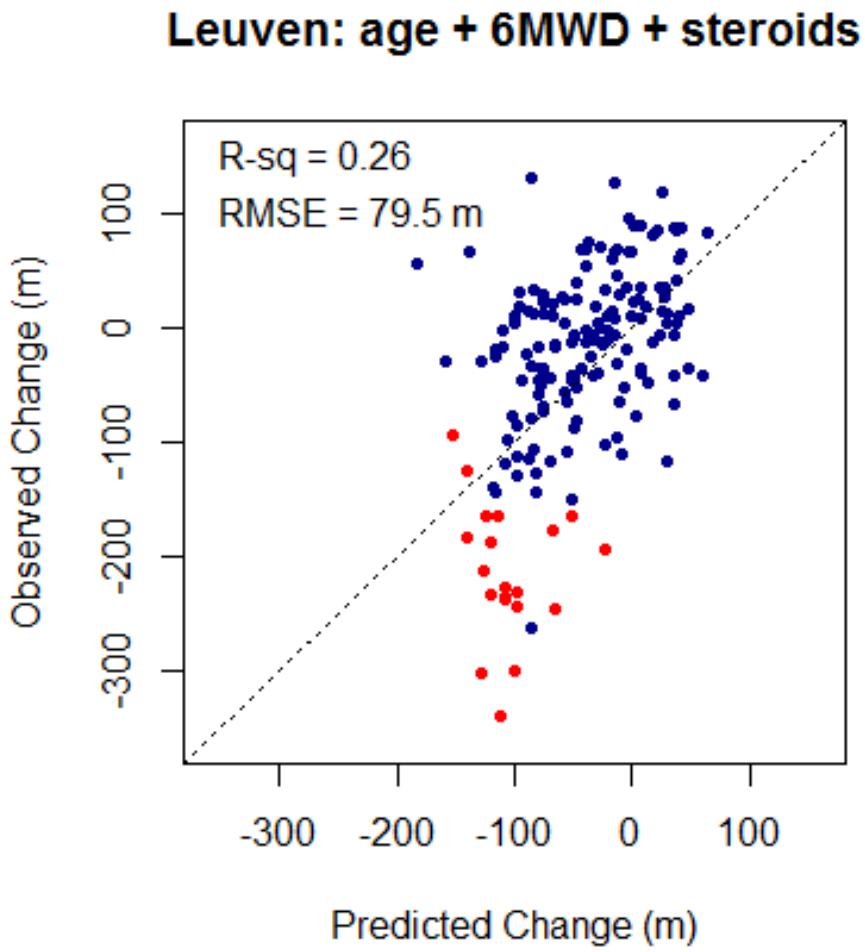
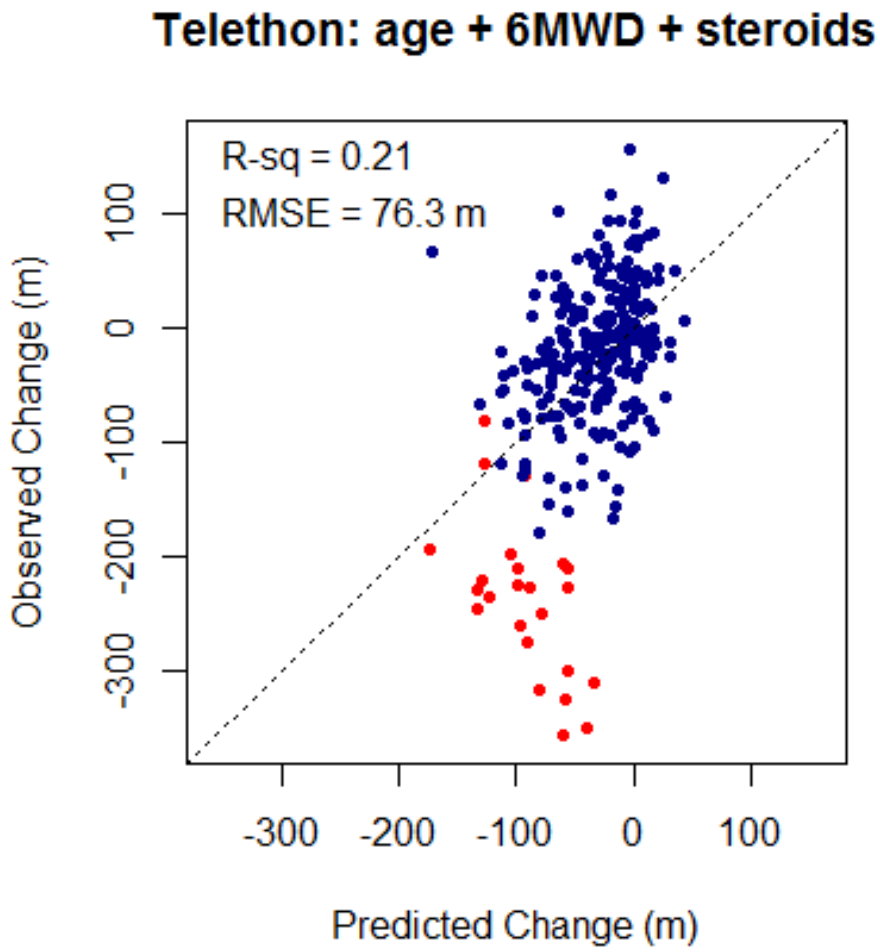
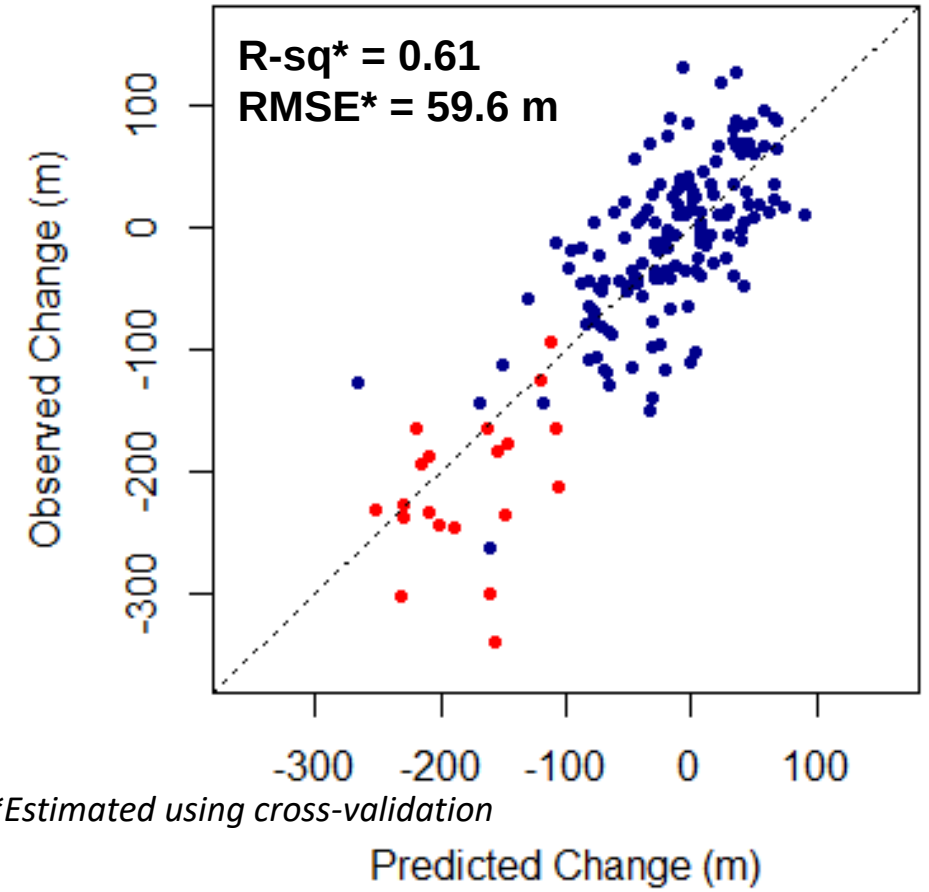
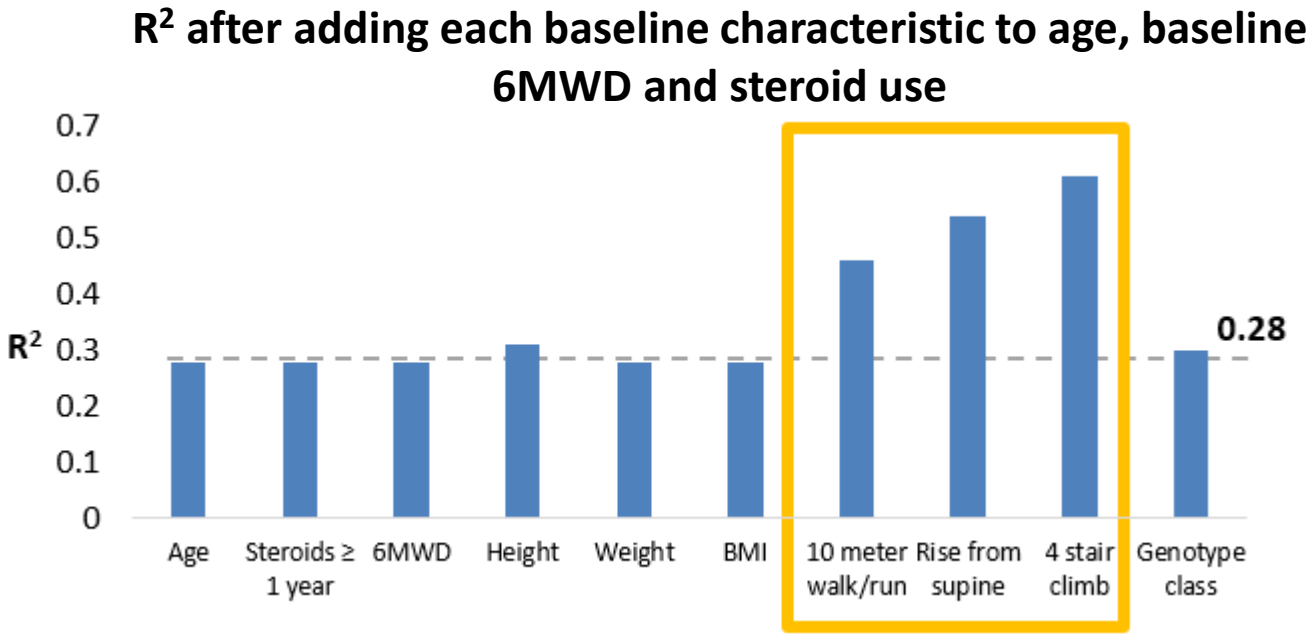




Composite prognostic model more than doubles prognostic accuracy, reduces unaccounted for variance



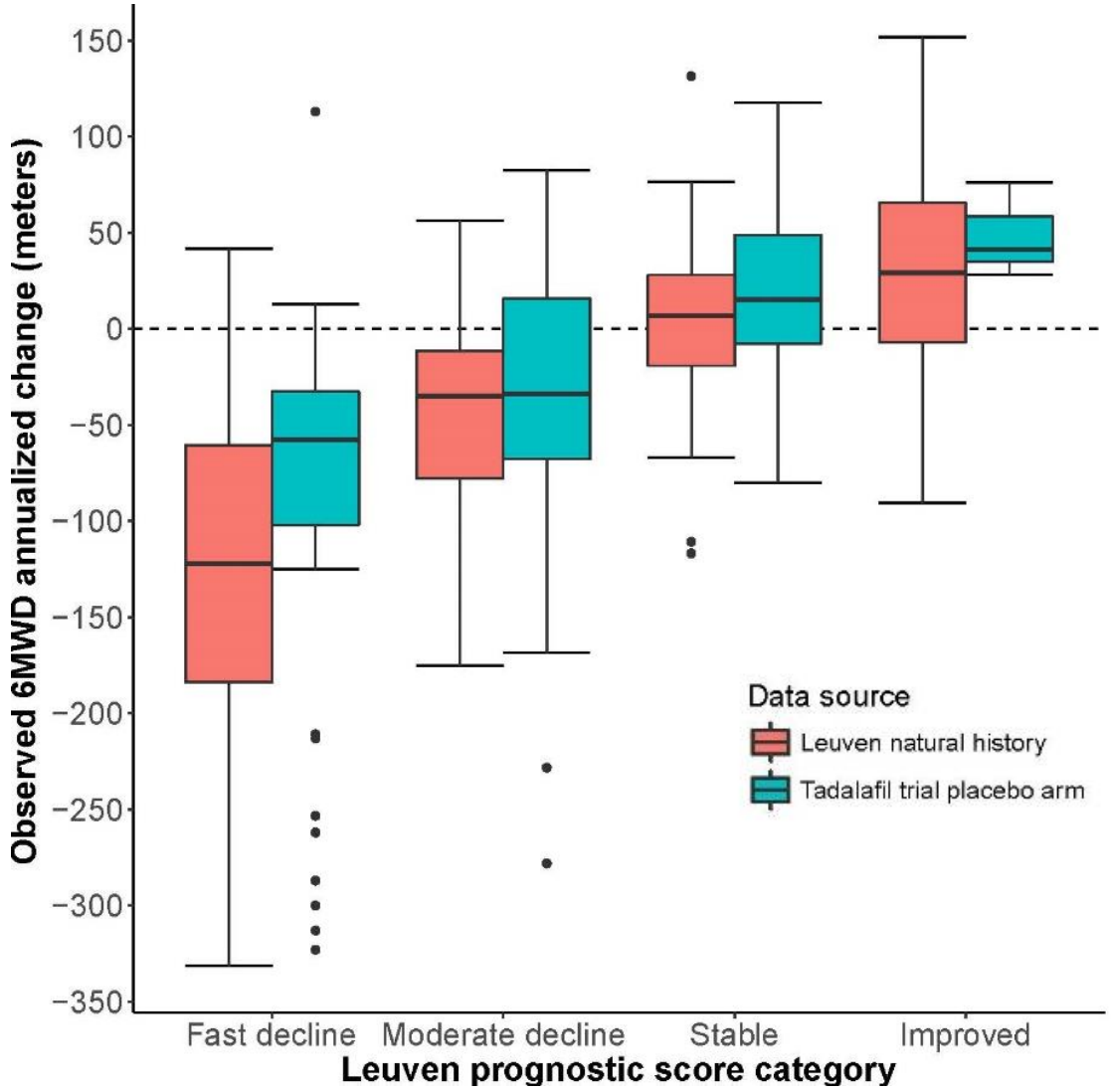
*Estimated using cross-validation



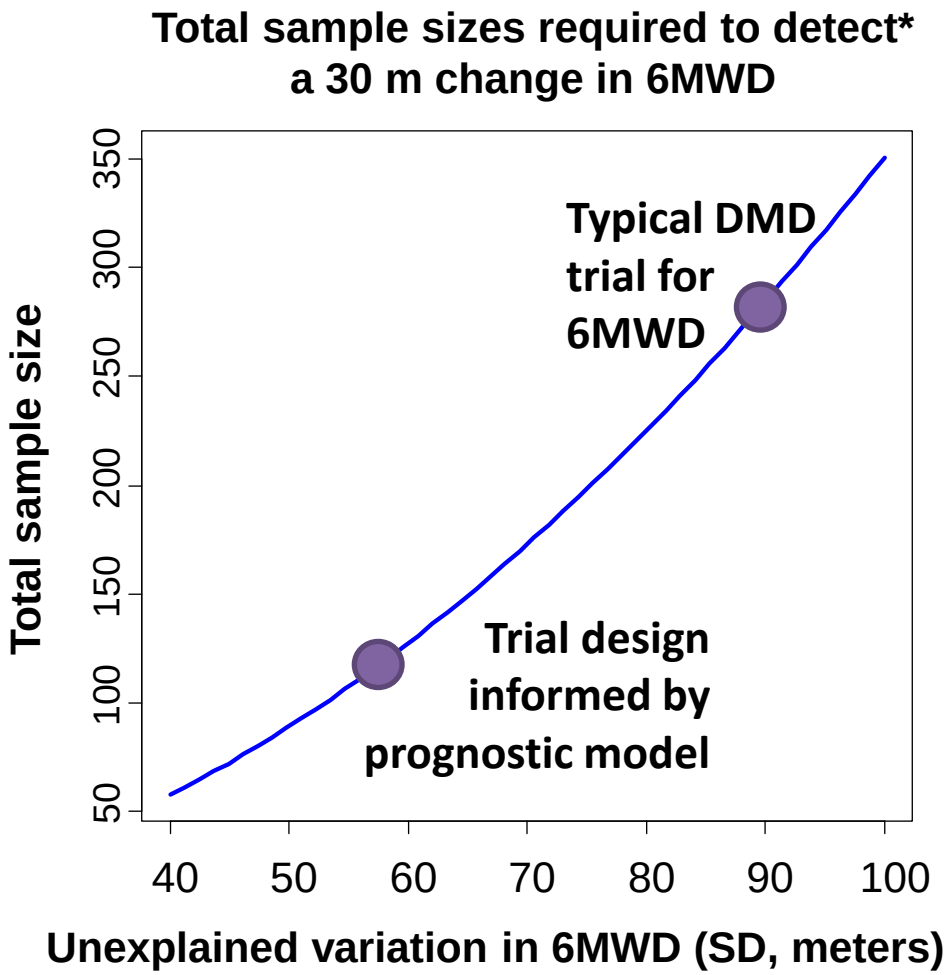
Goemans N, vanden Hauwe M, Signorovitch J, Swallow E, Song J, CollaborativeTrajectory Analysis Project (cTAP) (2016). Individualized Prediction of Changes in 6-MinuteWalk Distance for Patients with Duchenne Muscular Dystrophy. PLoS ONE 11(10): e0164684. doi:10.1371/journal.pone.0164684

Validation in placebo arm data

- Placebo arm data from the tadalafil phase 3 trial
- No statistically significant differences in Δ6MWD between data sources within any baseline prognostic category (all p > 0.05).



Impact of selection/enrichment guided by a prognostic score



**with 80% power and equal allocation to two groups*

- explain and reduce variability in outcomes
- enrich for modifiable trajectories
- greater power to detect drug effects
- smaller trials with 100s fewer patients

Conclusions

In this analysis of prognostic factors for 1-year change in 6MWD

- Baseline 6MWD, age and steroid use were not strong prognostic factors; together they explained only ~25% of variation
- A composite model that combined multiple measures of ambulatory function more than doubled explained variation to 60%
- This model performed well when applied to placebo arm data from a clinical trial
- Composite prognostic scores should prove superior in defining inclusion/exclusion criteria and/or stratification factors

What we've learned

- Prognostic modeling also more than doubles prognostic power for 1-year change in additional ambulatory outcome measures
- consensus prognostic model for 6MWD
- Developing approaches for establish prognostic factors and model for 18 month, 2year and 3year follow-up

Natural History as an external control?

Natural History External Controls

- Reducing trial size is a high priority for everyone
- Smaller (or no) placebo arm in trials is a high priority for patients
- Gene therapy trials
- However, comparisons of functional outcomes such as 6MWD between drug trials and NH controls could be biased by differences in patient motivation, supportive care or assessment procedures
- This concern has been raised by regulators (e.g., April 2016 AdComm briefing documents for eteplirsen)

Objectives

- Systematically identify and compare 48-week changes in 6MWD among natural history data sources and clinical trials placebo arms in DMD
- Do we see consistency across natural history data sources?
- Is there any evidence of systematic bias, in either direction, between placebo arms and natural history?

Clinical trials reporting 6MWD
48-week changes on placebo arms

Placebo Arm	Number of patients	Inclusion/Exclusion Criteria			
		Steroid use (m)	Age (yrs)	6MWD (m)	Rise from supine (s)
Tadalafil Phase 3	116	≥6	7-14	200-400	-
Ataluren Phase 2b	57	≥6	≥5	≥75	-
Ataluren Phase 3	115	≥6	7-16	≥150	-
Drisapersen Phase 2*	34	≥6	≥5	≥75	≤7
Drisapersen Phase 3	61	≥6	≥5	≥75	-

Notes:
- Identified via systematic review of PubMed, clinicaltrials.gov and FDA briefing documents; baseline characteristics and 48-week changes in 6MWD extracted by two reviewers working independently

**Pooled two phase 2 trials*

Natural history studies reporting 6MWD

Source	Peer-reviewed publication(s) reporting longitudinal changes in 6MWD	cTAP access
Italian Group (Telethon)	Mercuri et al. 2016 Mazzone et al. 2011, 2013, 2016 Pane et al. 2014a, 2014b, 2014c	Shared
UZ Leuven	Goemans et al. 2013, 2016, 2017	Shared
CINRG	McDonald et al. 2013a, 2013b Henricson et al. 2012, 2013	Parallel analyses via collaboration and shared SAP
Imaging DMD	Willcocks et al. 2016	In discussion for data sharing

Notes:

- Identified via systematic review of PubMed for Duchenne and ('six minute walk' OR 6MWD OR 6MWT)
- Required > 30 DMD patients with serial assessments of 6MWD
- Unpublished sources of serial 6MWD assessments include the AFM and Biomarin natural history studies; cTAP is in discussions to obtain collaborative access to both of these sources

Study Design

- Identified non-overlapping periods of ~48-week follow-up in NH (9-13 months)
- Subjected each interval to the inclusion/exclusion criteria used in the clinical trials
- Compared mean 48-week changes in 6MWD between trial placebo arms and harmonized (matched on I/E), and between sources of NH
- Accounted for use of repeated measures via generalized estimating equations

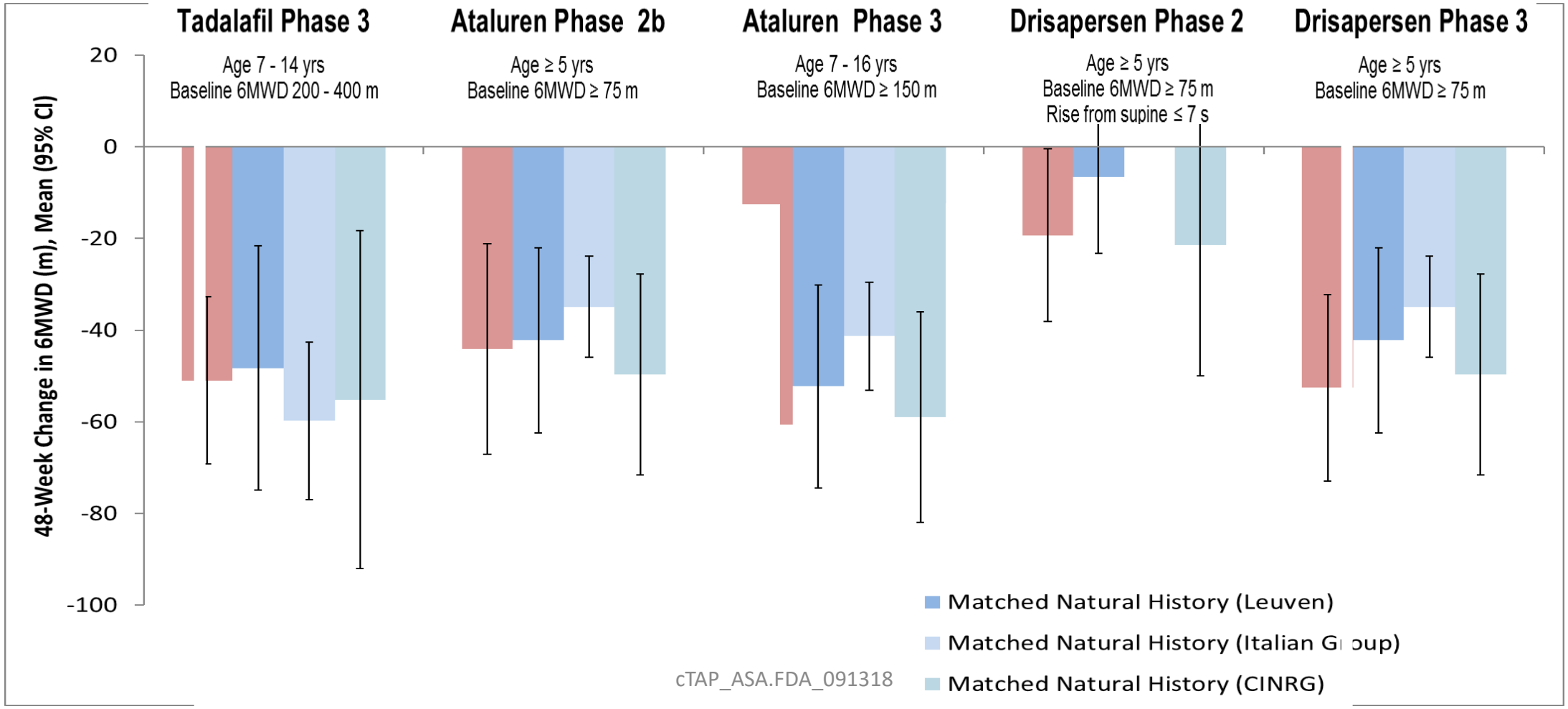
Natural history patients were matched to trial inclusion criteria

Repeated measures of 6MWD were used: all non-overlapping pairs of assessments separated by approximately 48 weeks

Statistical analyses accounted for within-patient correlation

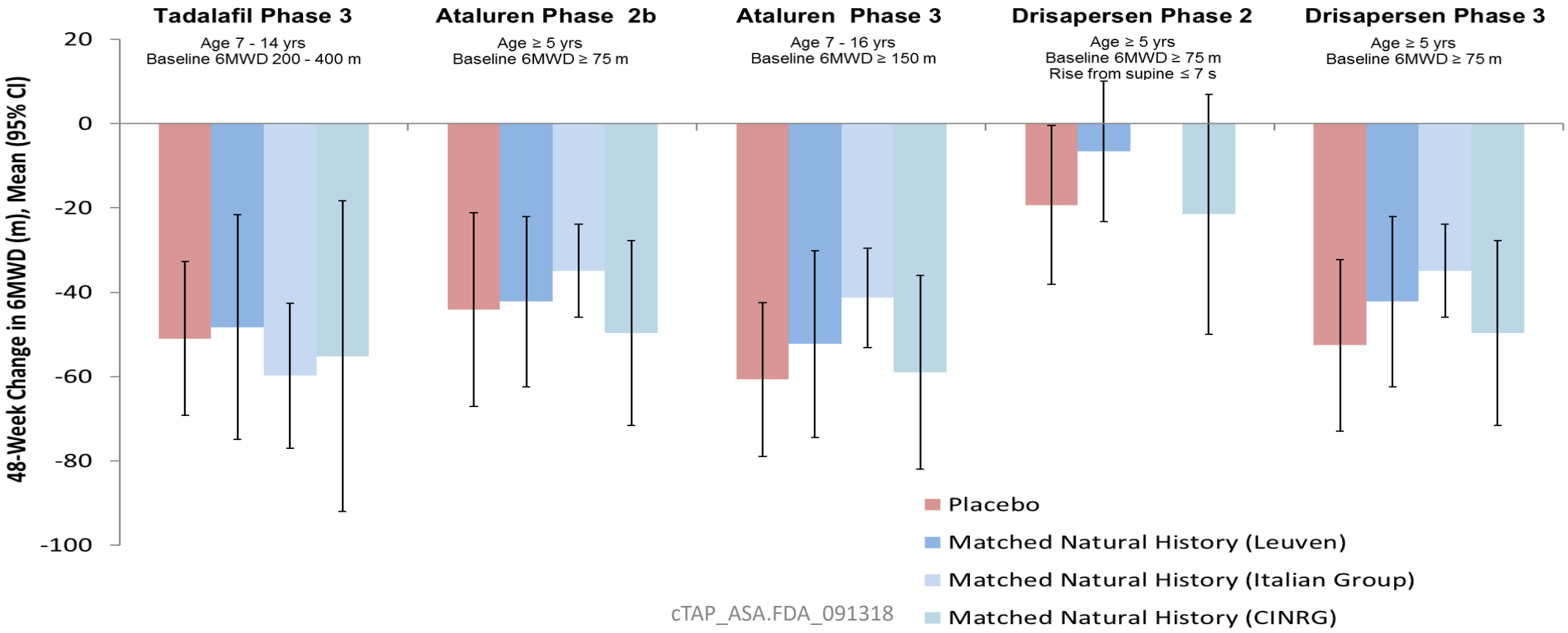
Comparison of 48-week changes in 6MWD

- No statistically significant differences in mean Δ6MWD among natural history data sources
- All were all within ± 18 meters of each other after matching I/E criteria



Comparison of 48-week changes in 6MWD

- No statistically significant differences in mean Δ6MWD between placebo and matched natural history
- Tendency is for placebo to have greater declines in 1 yr change 6MWD



What we've learned

- No evidence for bias between NH and placebo for 1 yr change in 6MWD in this study
- Comprehensive assessment of sensitivity, and hidden sources of bias
- Study extended to now include 5 natural history sources and 3 placebo arms
- Currently replicating for additional outcome measures
- Assessing boundaries for when drug effect is too small for NH comparisons to be valid

Summary perspectives

COLLABORATIVE TRAJECTORY ANALYSIS PROJECT

- **Natural history is crucial in rare disease drug development**
  - To learn from, to enrich trials
  - but only if researchers (and regulators) can access it
  - Patients have more power over access than they realize (yet)
- **Collaborative Problem-solving can be >>> the sum of its parts**
  - Heterogeneity has structure (relates to disease, not outcomes)
  - Methodology not necessarily fancy (doubled prognostic power)
  - Important questions might languish (consistency of outcomes across dbs)
- **Making it work**
  - Align incentives (crack the toughest nut first)
  - Independent, objective 3rd party can lowers barriers, diffuse issues
  - Build Trust: be competent, be transparent, and transparently fair

What might future trials look like?

COLLABORATIVE TRAJECTORY ANALYSIS PROJECT

DRIVERS

- Stronger patient voice
- Wider adoption of data-sharing
- Faster learning through collaborative problem solving
- Robust foundation for natural history/real world evidence as controls
- Independent, SAP-driven matched comparisons for specific trials

- Smarter stratification and inclusion/exclusion criteria (independent of design)
- Smaller trials, fewer patients in placebo, enrichment with NH
- Objective, fact-based selection of controls for gene therapy trials
- Greater regulatory confidence, faster path to patient access

Therapies to patients sooner

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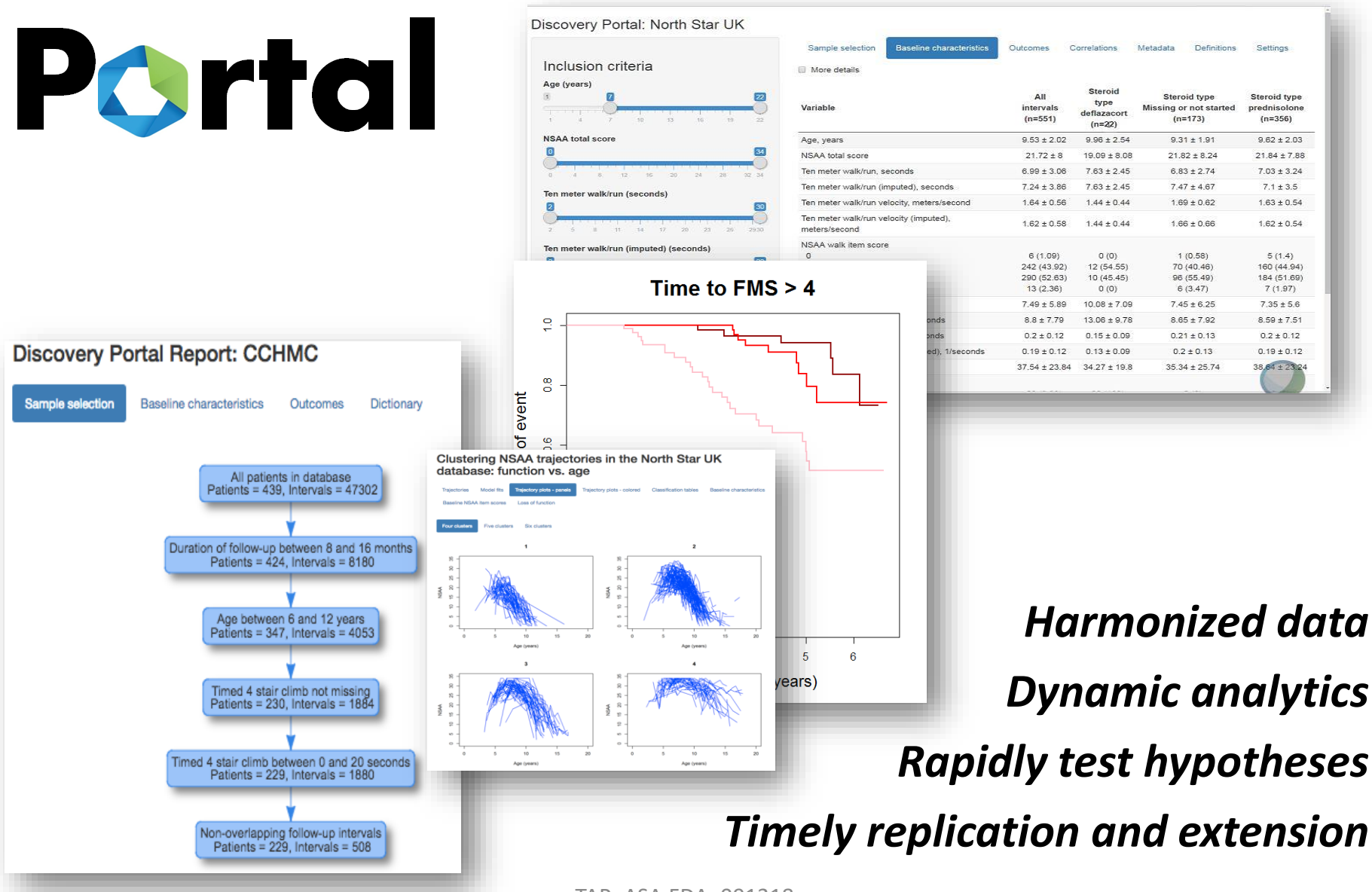
COLLABORATIVE TRAJECTORY ANALYSIS PROJECT

Portal



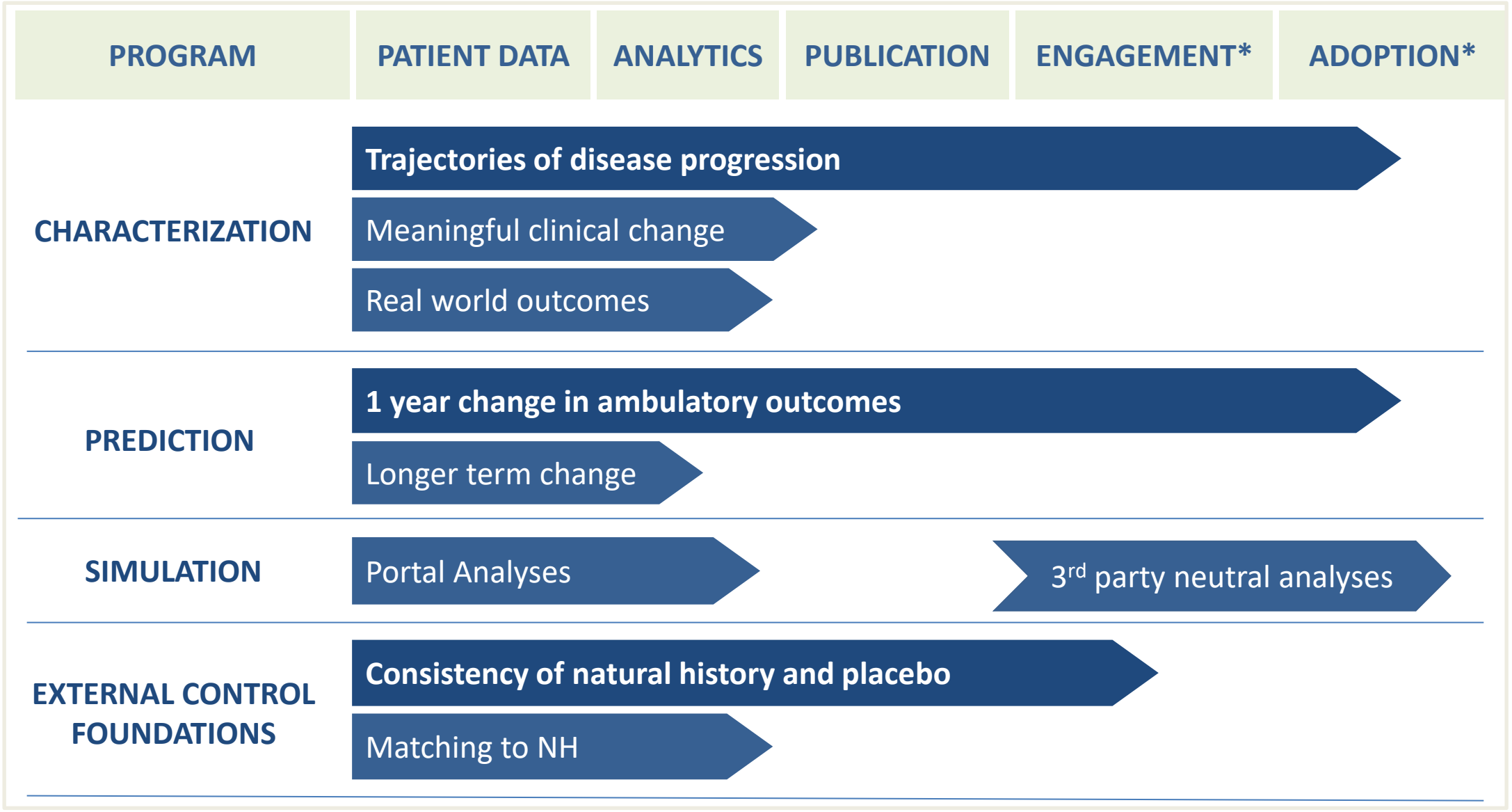
Harmonized data

Dynamic analytics

Rapidly test hypotheses

Timely replication and extension

cTAP Pipeline (leading outcome measure)



*With primary target group – academic, regulators, payors/health authorities – dependent on program

Common mining questions from cTAP members

- Counts: Do you have sufficient data to….
- Design: Given my trials I/Es, what might we anticipate as 1 yr change in my primary outcome measure? How consistent is that estimate across data sources?
- Enrolment: How can I accelerate/improve efficiency of enrolment - without compromising the planned power of my study?
- Interpretation: Using the baseline data of patients in our trial, what are the outcomes for a matched cohort?