COLLABORATIVE
TRAJECTORY
ANALYSIS
PROJECT

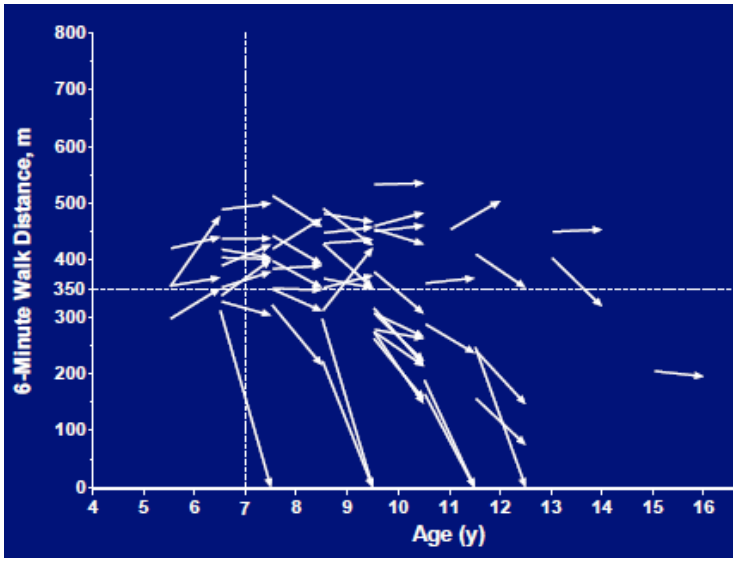
Enabling the right trial design, the first time

Supporting new therapies to patients sooner

Impetus

Pivotal trials in Duchenne have failed to meet primary endpoints – largely due to high patient heterogeneity

TRIAL	PHASE	PATIENTS**	Met end point?
DEMAND III	Ph 3*	186	no
PTC 007	Ph 2*	174	no
DMD-ACT	Ph 3*	228	no
Tadalafil	Ph 3*	331	no



- Burden and disappointment for patients and families
- Uncertainty and wasted resources for drug development
- Disincentive for investors

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

cTAP mission

Collaborate to learn from patient data

Adopt successful approaches from other fields

Create tools and insights for drug development

Share broadly

Deliver near-term impact

cTAP Members and Collaborators

Clinical experts and registries	• Eugenio Mercuri; Catholic University, Rome • Nathalie Goemans; UZ Leuven • Francesco Muntoni; University College London • Brenda Wong; Cincinnati Children's Hospital • Fondazione Telethon • Northstar UK
Sponsors	• BioMarin • Pfizer • PTC Therapeutics • Sarepta Therapeutics • Shire PLC • Solid Biosciences • Catabasis • BMS
Patient advocates	• Cure Duchenne • Parent Project Muscular Dystrophy
Analytic and Collaboration leads	• Analysis Group • Susan J. Ward

What we do

- Access longitudinal data from de-identified patients in natural history and placebo arm studies
- Apply statistical methods to explain phenotypic variation and reduce variance
- Publish findings and share broadly (including with regulators)
- Embed in tools to optimize trial design and analysis
- Share costs: data access, analytics, publication, collaboration platform

Progress: Data Access

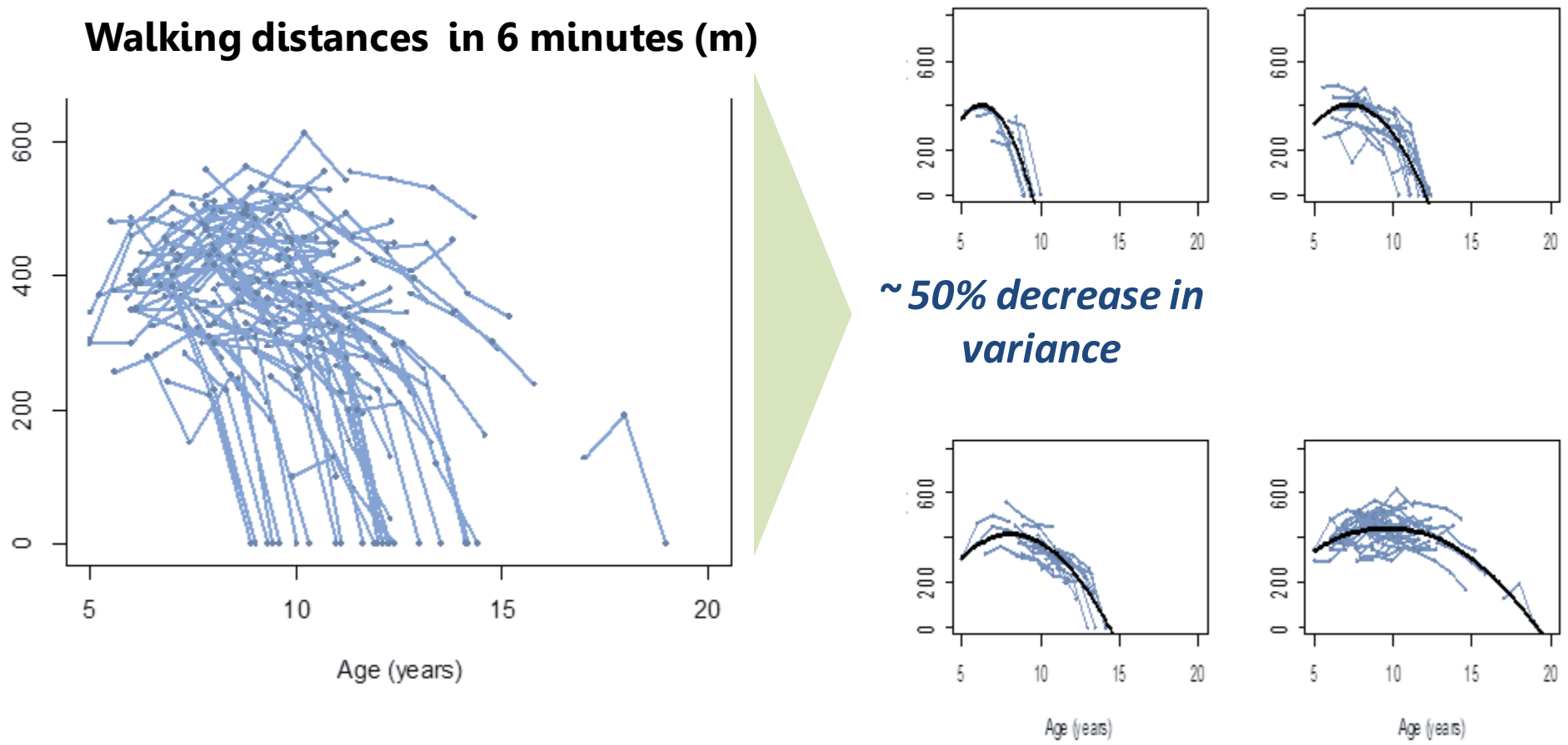
1,261 boys
33 care centers
10,508 clinic visits

Functional Assessments
Ambulation **> 4000**
Pulmonary, Cardiac **>350**
boys ≥ 3 yrs follow-up **> 400**

Patient Characteristics
steroid status, history
dystrophin genotype
body composition (incl. fat)

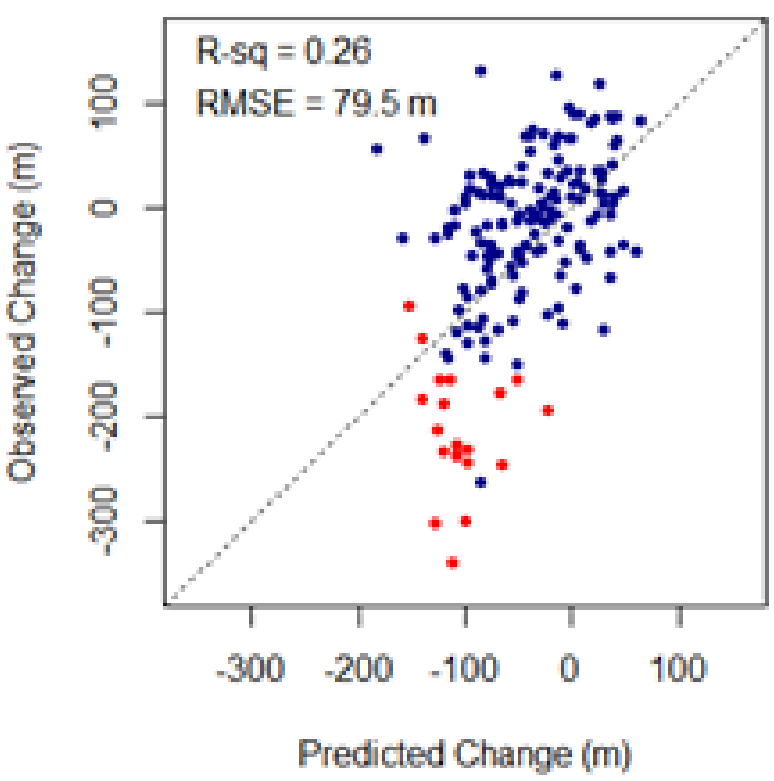
- **Largest clinical database in Duchenne**
- **Majority of data previously never shared**
- **Semi-annual updates**
- **Attractive Data Use/Business structure**
- **New Data, in progress**
  - New data fields: PUL, NSAA sub-scores
  - Large EU cohort
  - Placebo Arms from pivotal trials

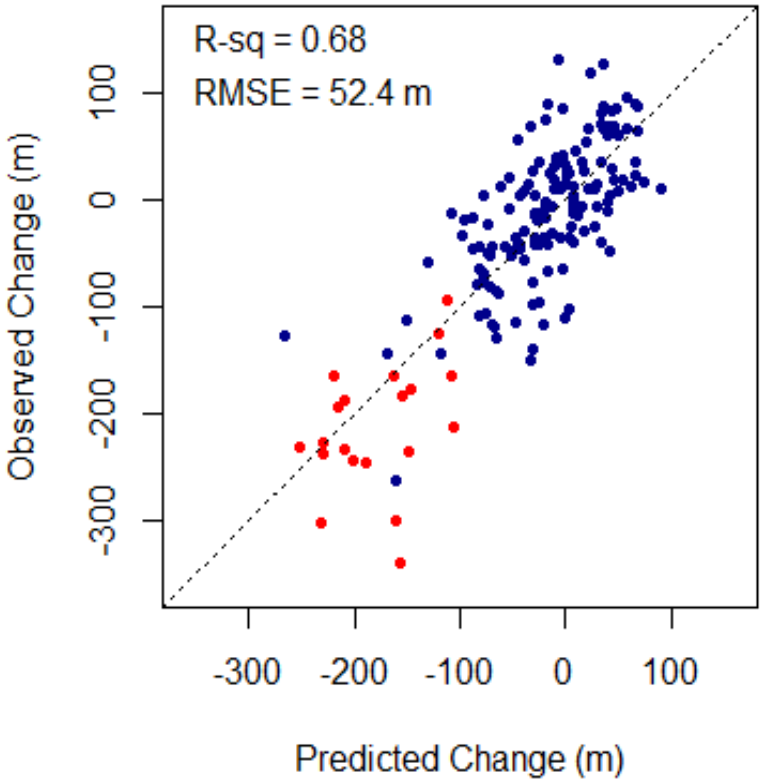
Progress: Analytics (1) Structure



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*

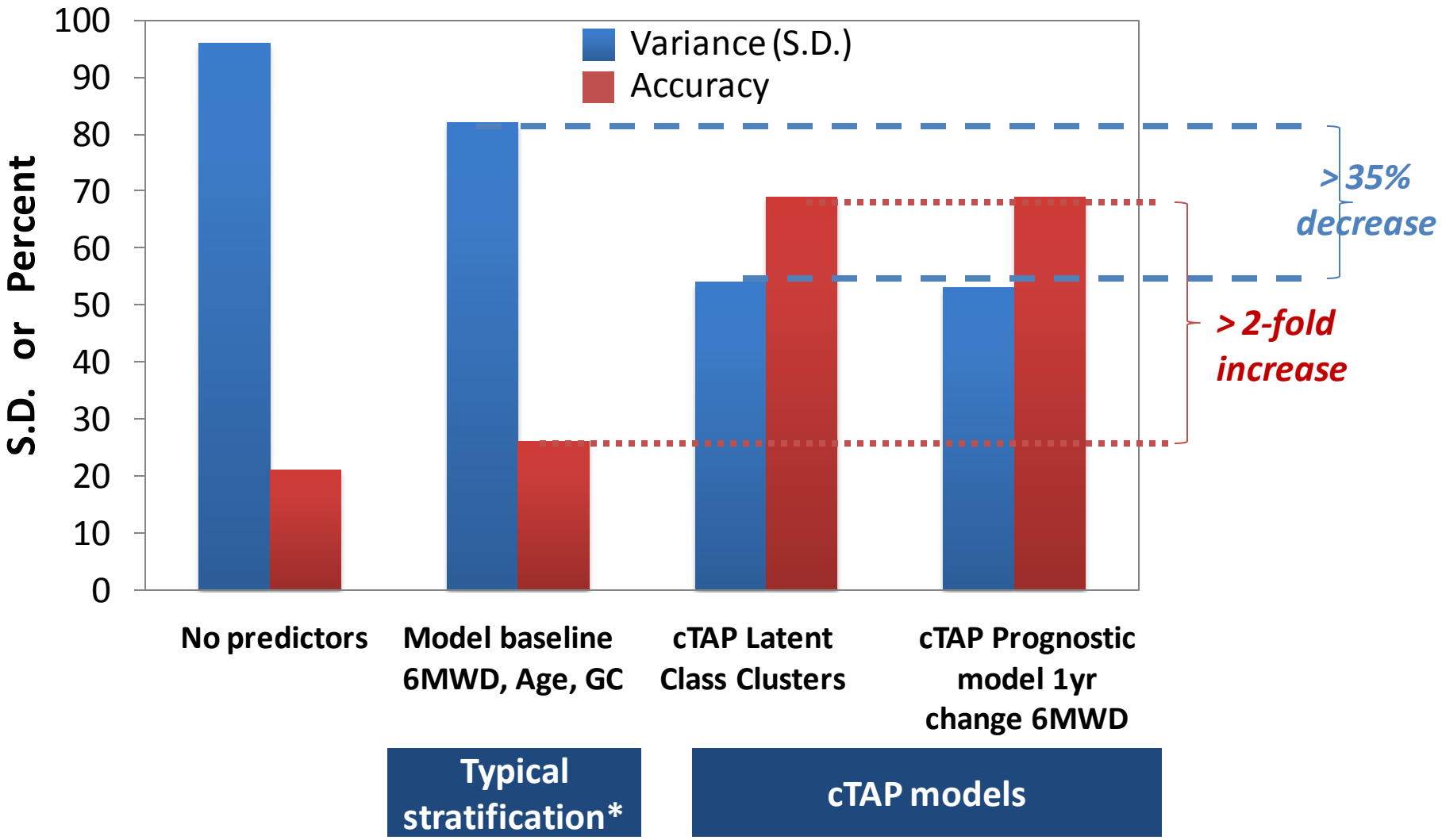
Progress: Analytics (2) Prognostic Model





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

Summary: cTAP models markedly reduce variance of change in 6MWD above and beyond typical stratification strategies

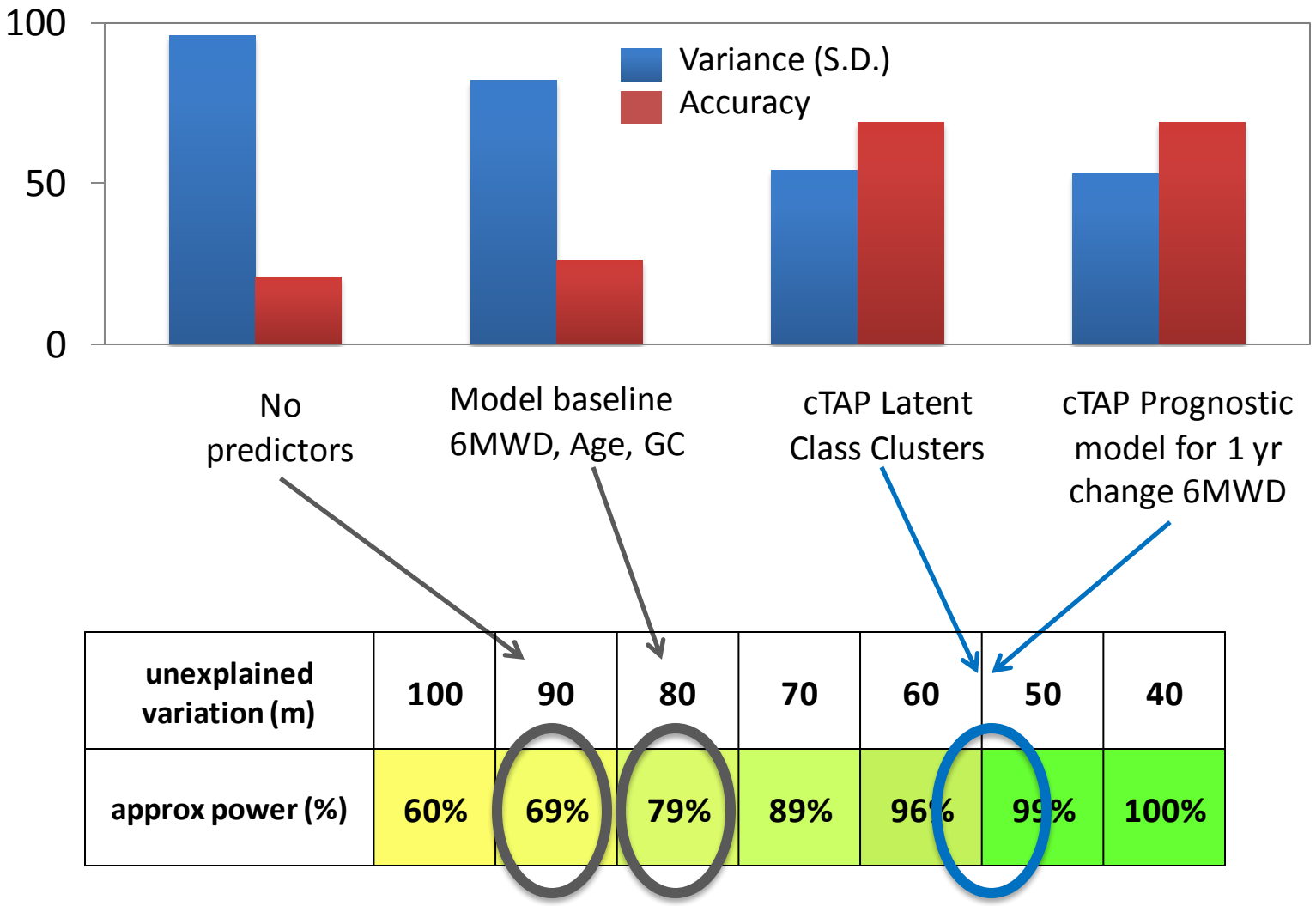


Translation to Drug Development

Describe, Predict, Simulate

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

Impact on Confidence in Trial results



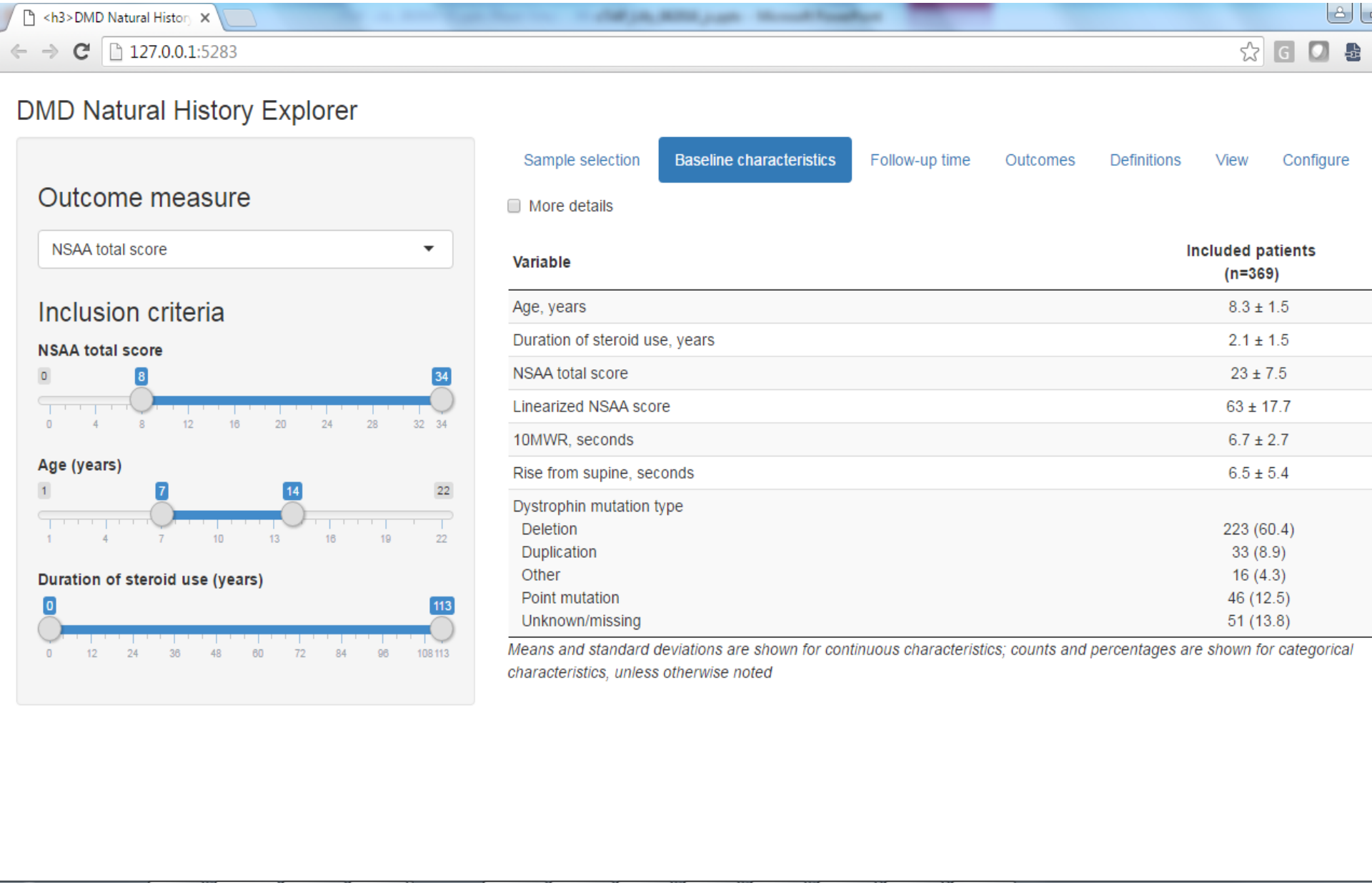
unexplained variation (m)	100	90	80	70	60	50	40
approx power (%)	60%	69%	79%	89%	96%	99%	100%

Marked impact on power, over and above 'standard' adjustments

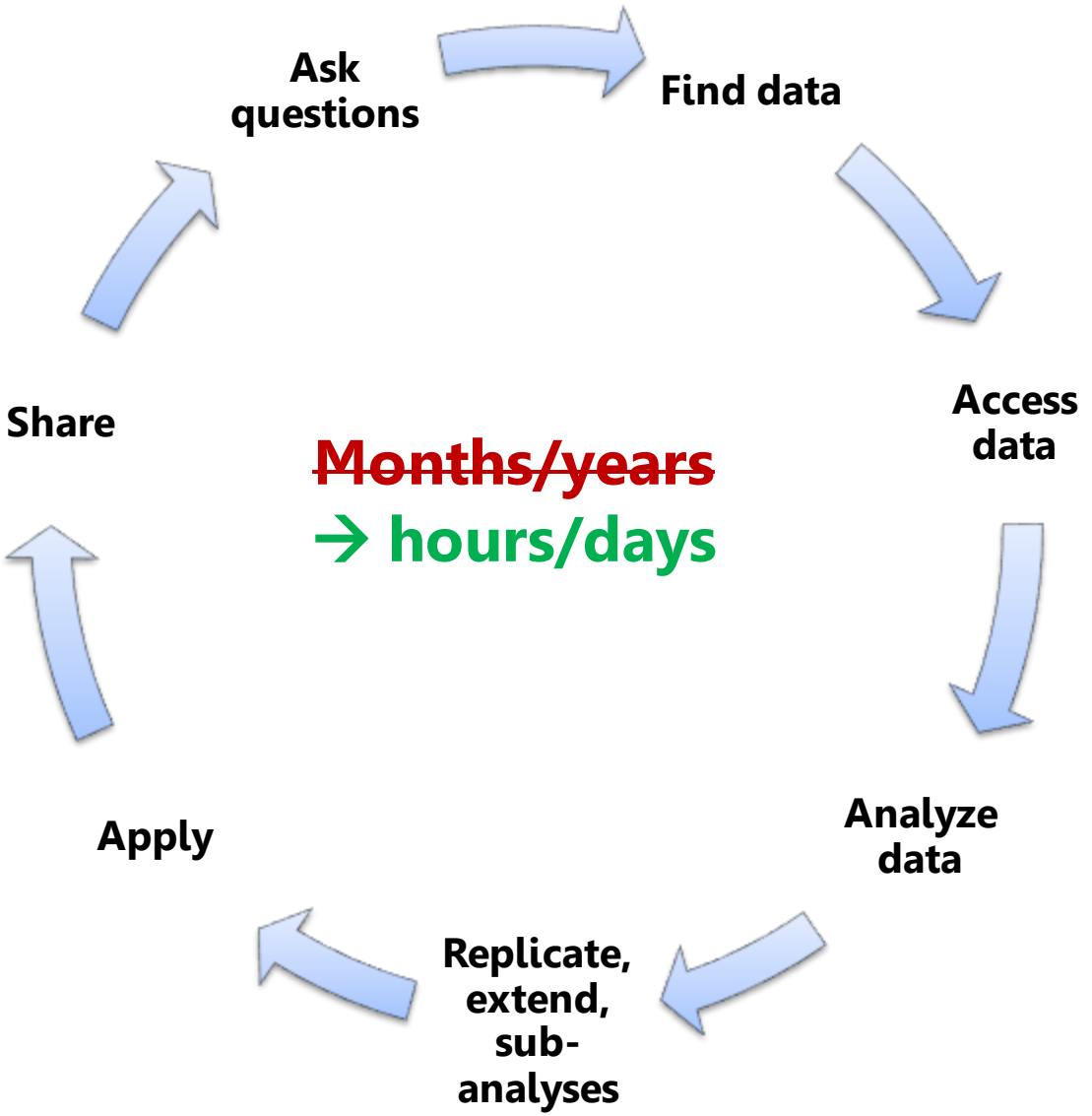
Tools: Duchenne Discovery portal

- 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

Illustration: Summarize patient characteristics



Portal renders laborious data/analytic access redundant



- Who has data?
- What study measures, sample sizes are available?
- Is the data quality adequate?
- What is the process for data access (if one exists)?
- Contract & data use agreement negotiation
- Scientific plan / SAP
- Risks of delay or failure due to: limited responsiveness, hidden agendas, politics, etc.

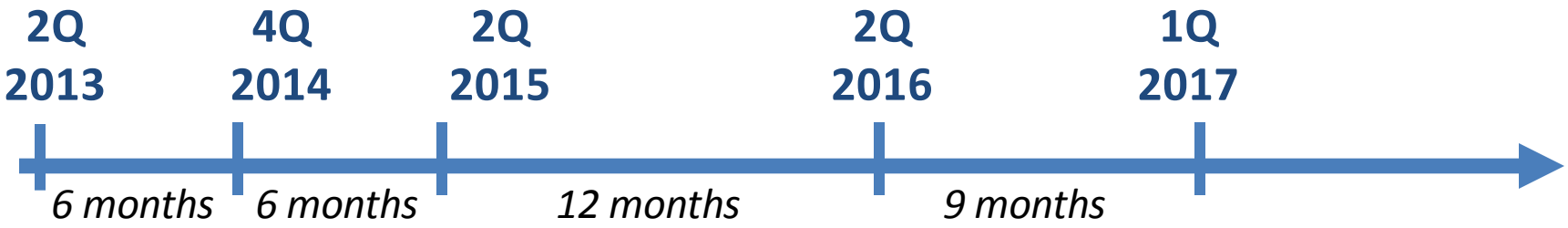
cTAP Benefits to drug developers

- Access analytics on previously inaccessible data
- Get timely answers to systematic questions that drive trial design
- Tangible, practical support to accelerate academic understanding of heterogeneity in Duchenne natural history
- Collaborative access to best in class analysis solutions
- Insights and tools for deployment in drug development
- Shared benefits, shared Costs
- Modular research approach – pay only for your company's priorities
- Credibility of consortium structure with regulators
- Publish and communicate broadly to benefit entire community
- **New members** enjoy immediate access to all unpublished findings, collaborative insights and new tools

Opportunities for Collaborating Clinical Experts & Registries

- Contribute to a data collaboration that benefits patients … while retaining full control of data use and authorship
- Collaborate with peers to quickly share & replicate across multiple databases
- Collaborate with Pharma with efficiency and balance
- Unprecedented access analytics to accelerate research
- Author more publications, strengthen grant applications
- Receive funding support data collection
- Access tools to aid data cleaning

Rapid Progress



Concept

Pilot Study

Replicate, Validate

Translate to Drug Development

Deploy Trial Design Tools

Objectives 2016-2017

- Extend clustering and prognostic modeling beyond 6MWD to other end-points
- Demonstrate consistency (or lack thereof) between natural history databases, clinical sites, and placebo arms
- Tie near term functional changes to long-term outcomes
- Establish matching criteria to support historical controls
- Determine prognostic value of glucocorticoid history
- Assess cost of clinical events and milestones
- Conduct Open Workshop(s); include regulators
- Continue to share findings promptly

COLLABORATIVE
TRAJECTORY
ANALYSIS
PROJECT

Contact Us

Susan J. Ward, Ph.D.
Co-Founder and Collaboration Lead
Executive Director
The TAP Collaboration
info@ctap-duchenne.org

James Signorovitch, Ph.D.
Co-Founder and Analytic Lead
Vice President
The Analysis Group Inc.
James.signorovitch@analysisgroup.com