

Translating Natural History into Clinical Trial Design

Lessons from Duchenne

The collaborative Trajectory Analysis Project
cTAP

Duchenne muscular dystrophy

“A thousand little deaths”



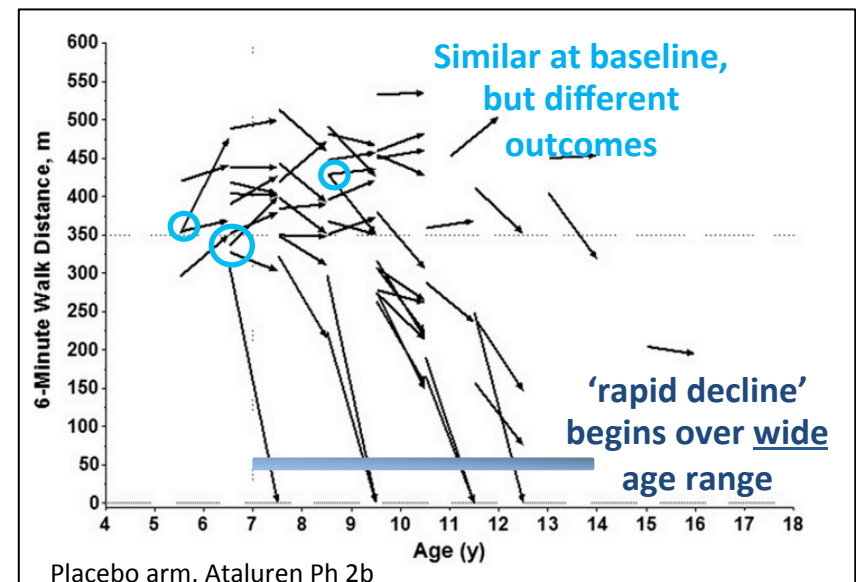
*Prescient capture of
natural history*

Impetus

Most pivotal trials in Duchenne
have failed
to meet their primary endpoint

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

Variance almost 2x greater
than anticipated!



Risk - more trial failures

Why it matters – bigger than Duchenne

- Repeated clinical trial failures can precipitate community-wide downward-spiral
- The “fix” for high variability – run a bigger trial – is not viable in rare disease
- Solutions to trial design in Duchenne are potentially applicable in many disorders

cTAP mission

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

FONDAZIONE



Drug developers

BOMARIN



Bristol-Myers Squibb Company



Patient advocates



Collaboration



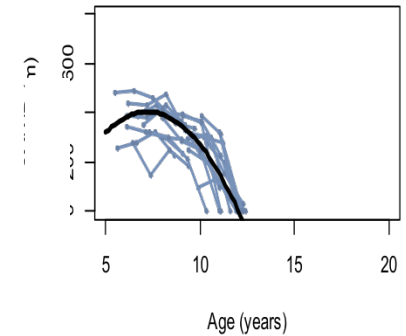
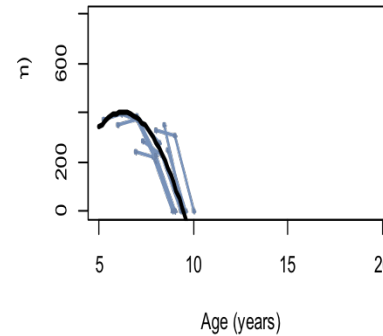
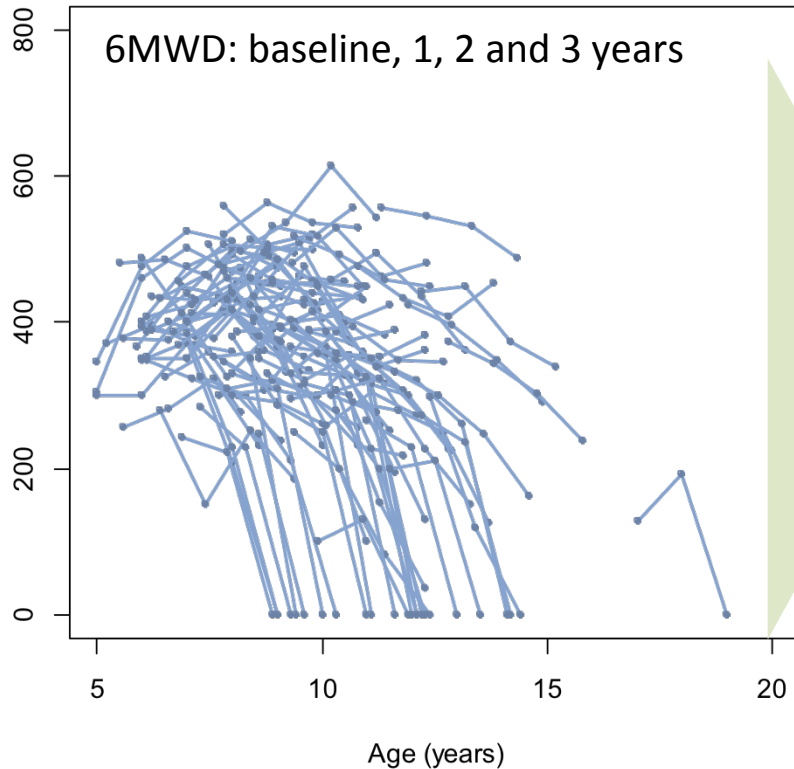
Susan J. Ward, PhD

Data science

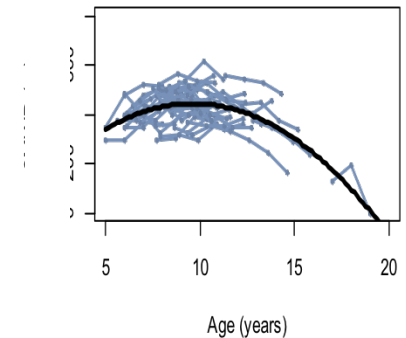
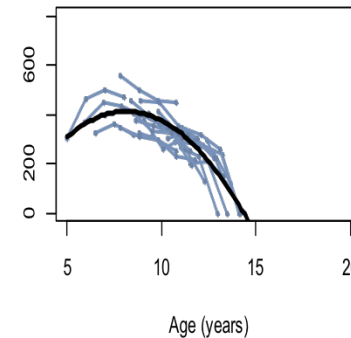


James Signorovitch, PhD

Latent Class Trajectory Analysis of natural history

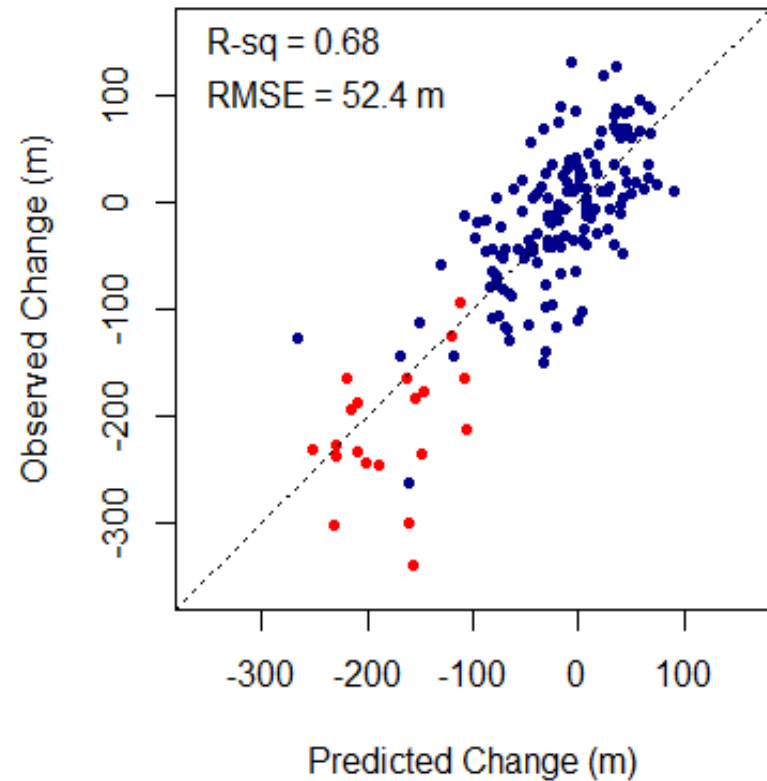
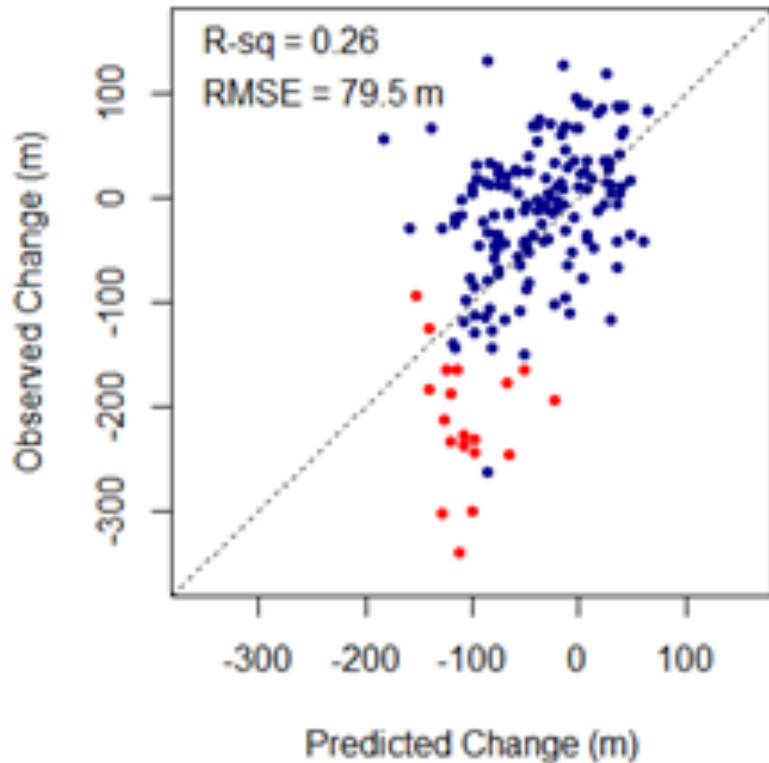


S.D. 71.5m => 55.6m [*~40% decr*]



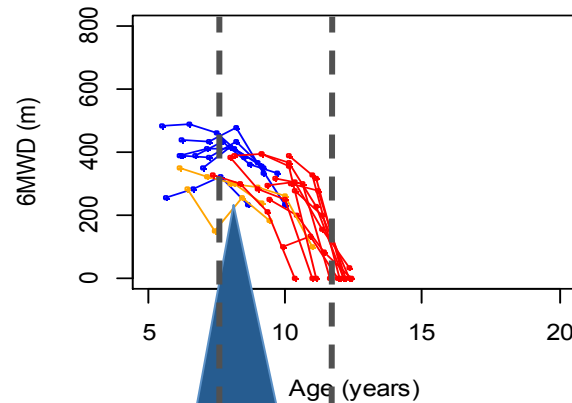
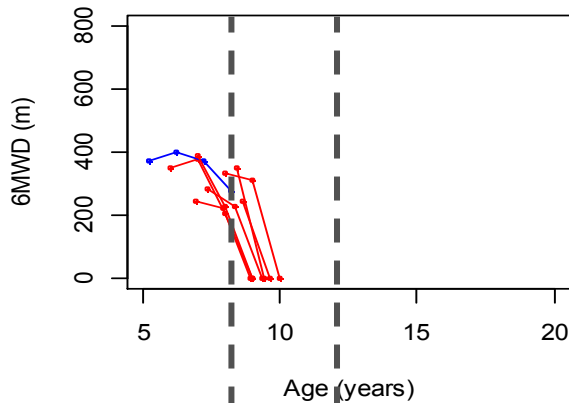
Underlying structure, marked reduction in variance

Multivariable Prognostic Model

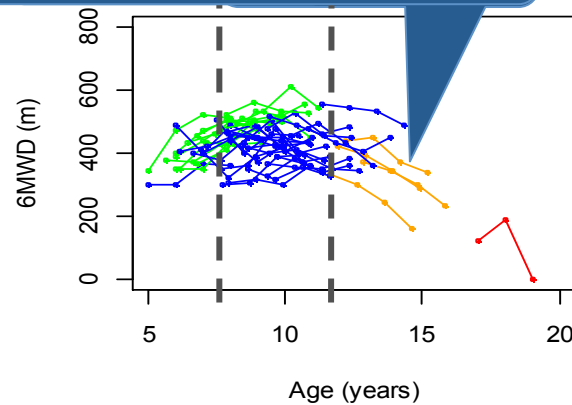
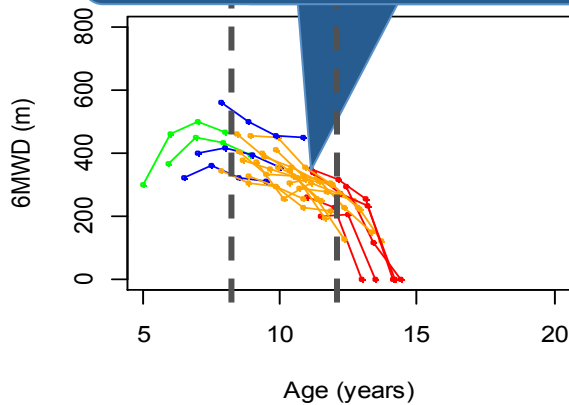


Prognostic accuracy more than doubled

Impact of increasing prognostic power



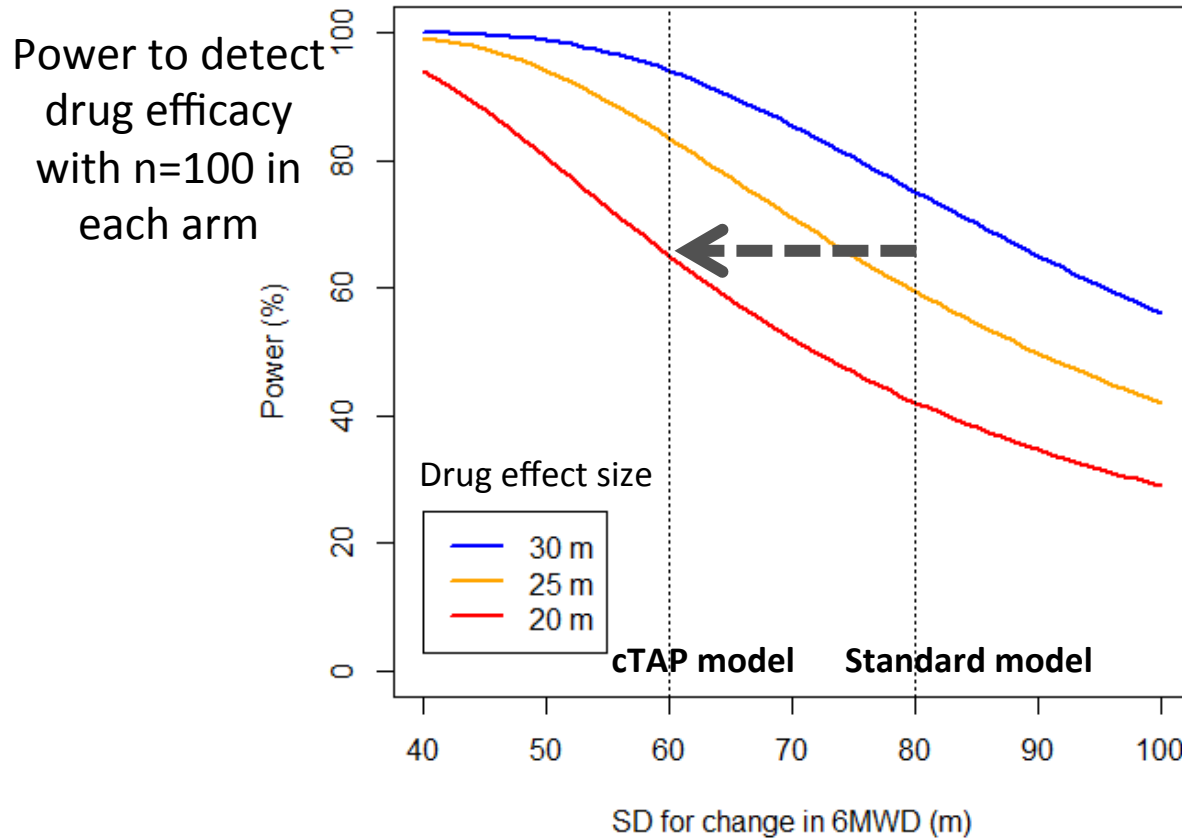
How to select for (or stratify) patients with a
COMMON TRAJECTORY?



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

More accurate pre-defined stratification = greater power

Impact of Reducing Variability



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

More power = more definitive results, smaller trials

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)?

Pre-requisites to address regulatory concerns

- Neutral, apples-to-apples, systematic analytics across multiple natural history sources
- Multiple placebo arm datasets
- Harmonized data fields, aggregatable
- Objective assessment of consistency of measurements, known sources of variability
- Longitudinal patient data spanning multiple clinical milestones

cTAP Duchenne Clinical Data Access

1300+ boys

30+ care centers

10,000 + clinic visits

Functional Assessments

Ambulation > **4000**

Pulmonary, Cardiac > **350**

boys \geq 3 yrs follow-up > **400**

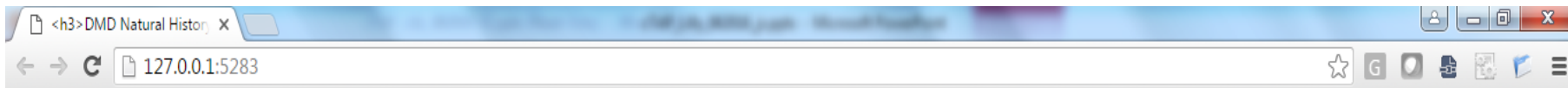
Patient Characteristics

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



DMD Natural History Explorer

Outcome measure

NSAA total score

Inclusion criteria

NSAA total score

0 8 34

Age (years)

1 7 14 22

Duration of steroid use (years)

0 113

Sample selection **Baseline characteristics** Follow-up time Outcomes Definitions View Configure

More details

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

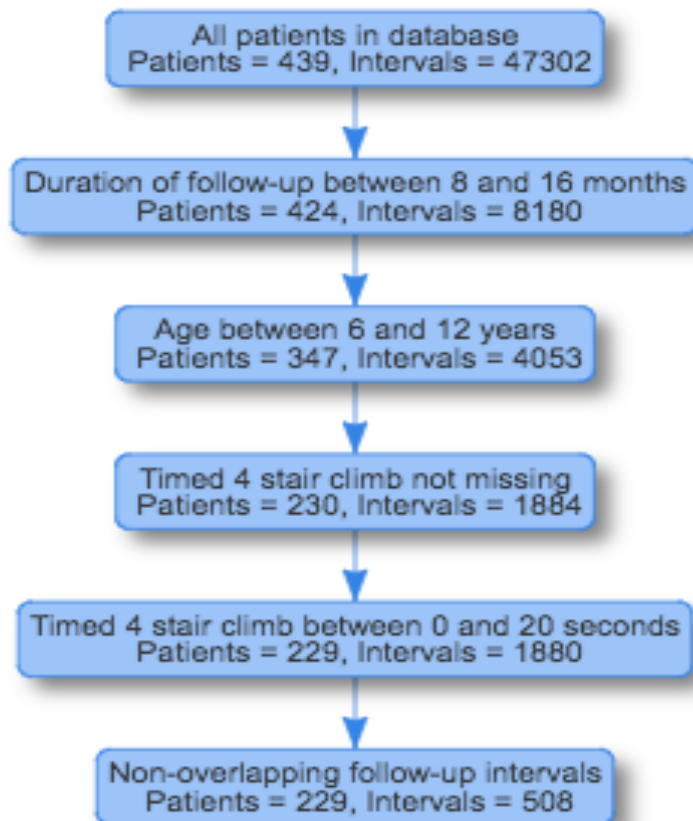
Discovery Portal Report: CCHMC

Sample selection

Baseline characteristics

Outcomes

Dictionary



Natural History NSAA : CCHMC



DMD Natural History Explorer

Sample selection Baseline characteristics Time to event analysis Linear regression **Outcomes** Definitions Settings

Inclusion criteria

Data source

CCHMC Leuven Lilly NSUK Telethon

Stratification

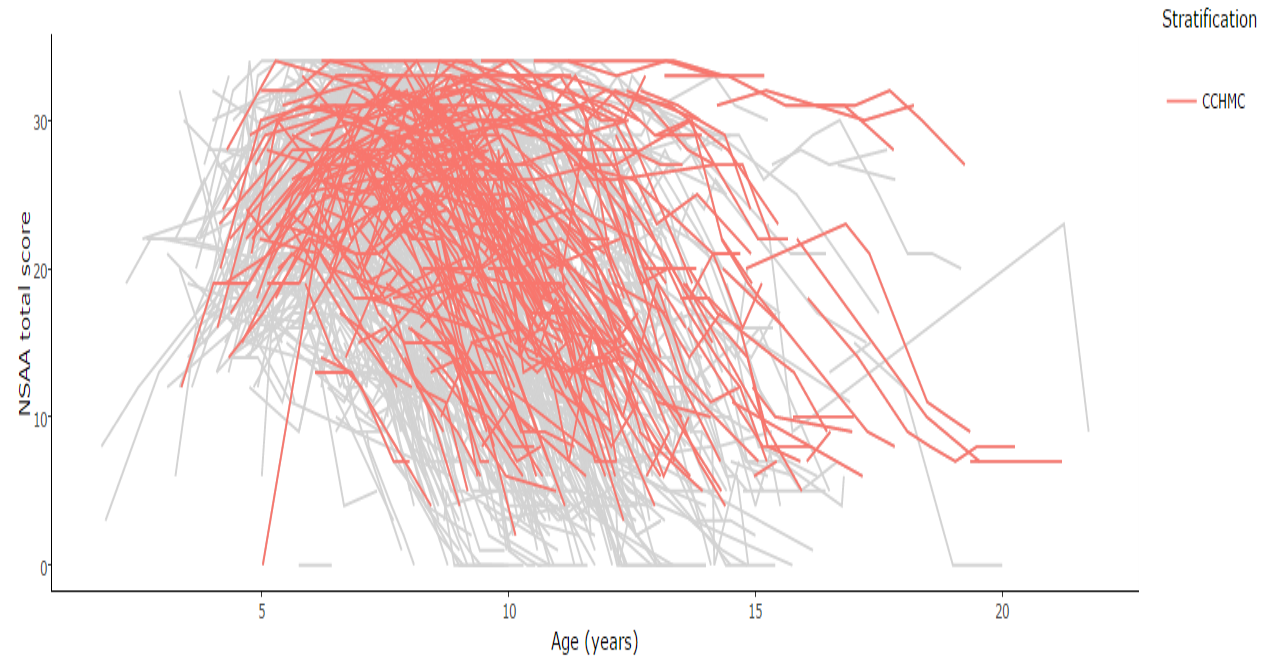
Data source ▼

Select outcome

NSAA total score ▼

Select index

Time from birth Time from index



Show all Show patient information

+ UZ Leuven



DMD Natural History Explorer

Inclusion criteria

Data source

CCHMC Leuven Lilly NSUK Telethon

Stratification

Data source ▼

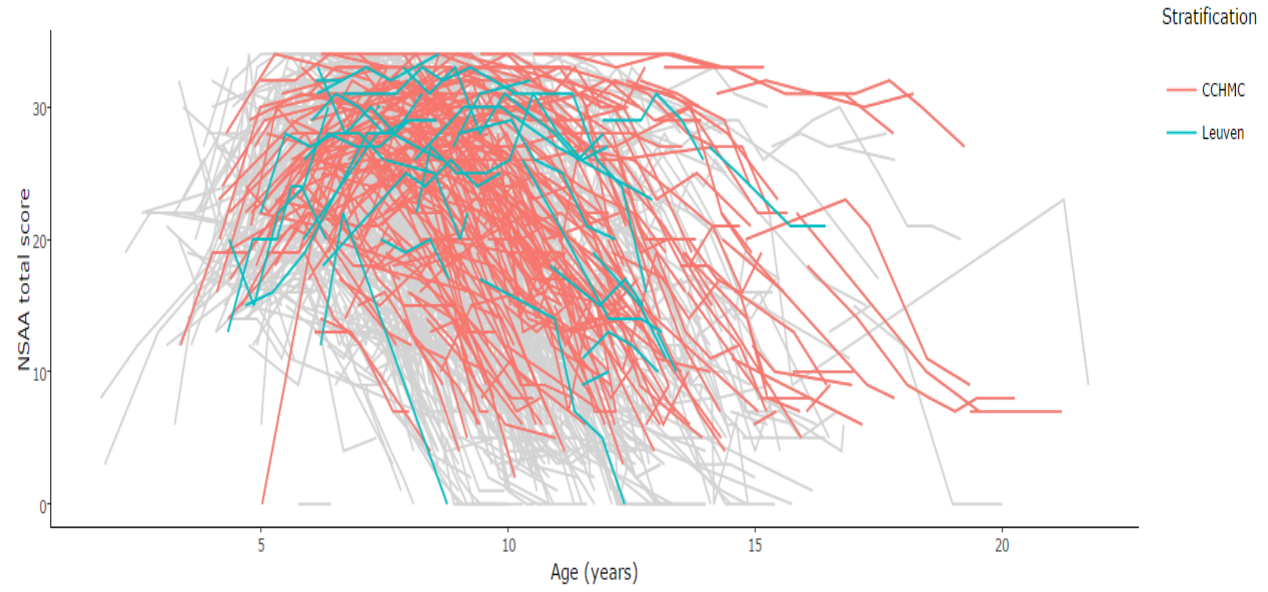
Select outcome

NSAA total score ▼

Select index

Time from birth Time from index

- Sample selection
- Baseline characteristics
- Time to event analysis
- Linear regression
- Outcomes**
- Definitions
- Settings



- Show all
- Show patient information

+Telethon

<h3>DMD Natural Hist

127.0.0.1:5382

DMD Natural History Explorer

Sample selection Baseline characteristics Time to event analysis Linear regression **Outcomes** Definitions Settings

Inclusion criteria

Data source

CCHMC Leuven Lilly NSUK Telethon

Stratification

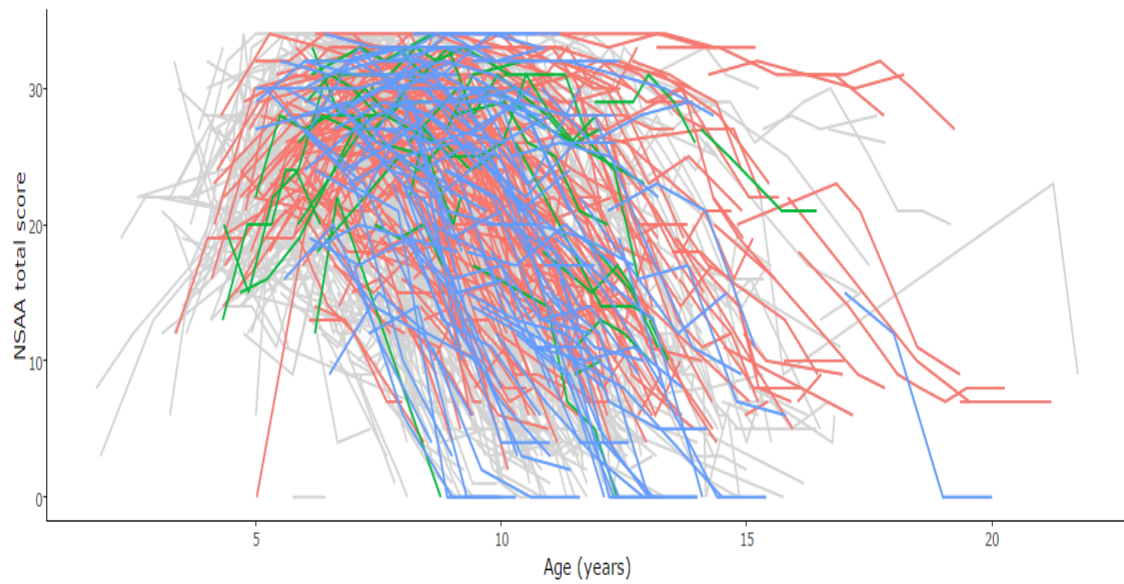
Data source

Select outcome

NSAA total score

Select index

Time from birth Time from index



Stratification

— CCHMC
— Leuven
— Telethon

Show all

Show patient information

+ Northstar UK

DMD Natural History Explorer

Inclusion criteria

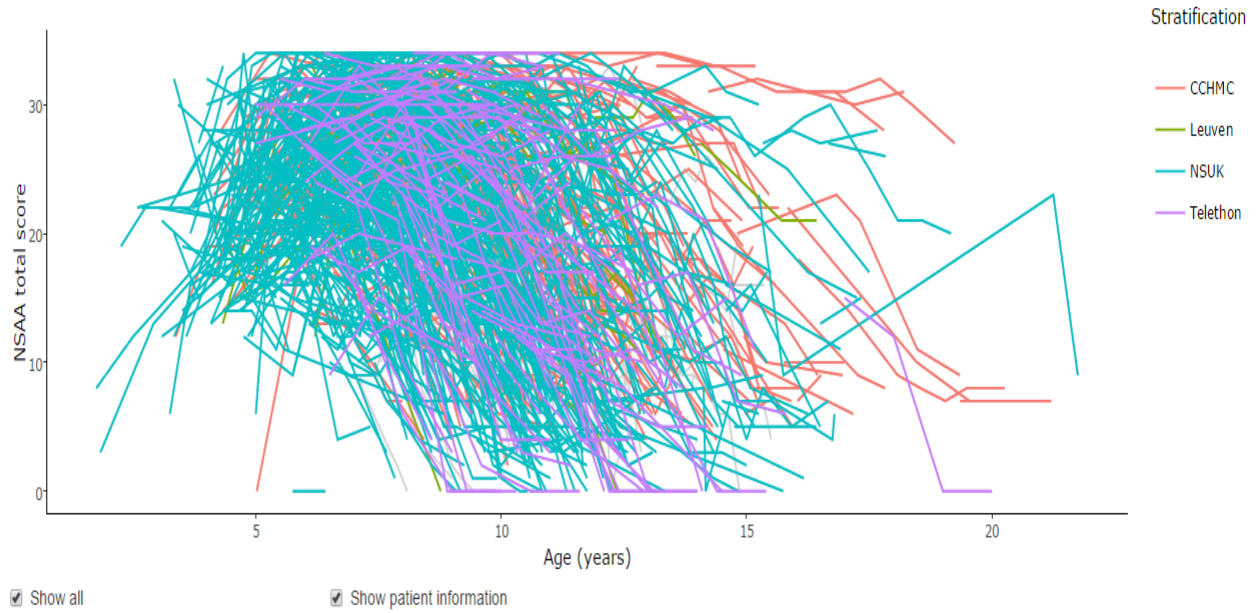
Data source
 CCHMC Leuven Lilly NSUK Telethon

Stratification
Data source

Select outcome
NSAA total score

Select index
 Time from birth Time from index

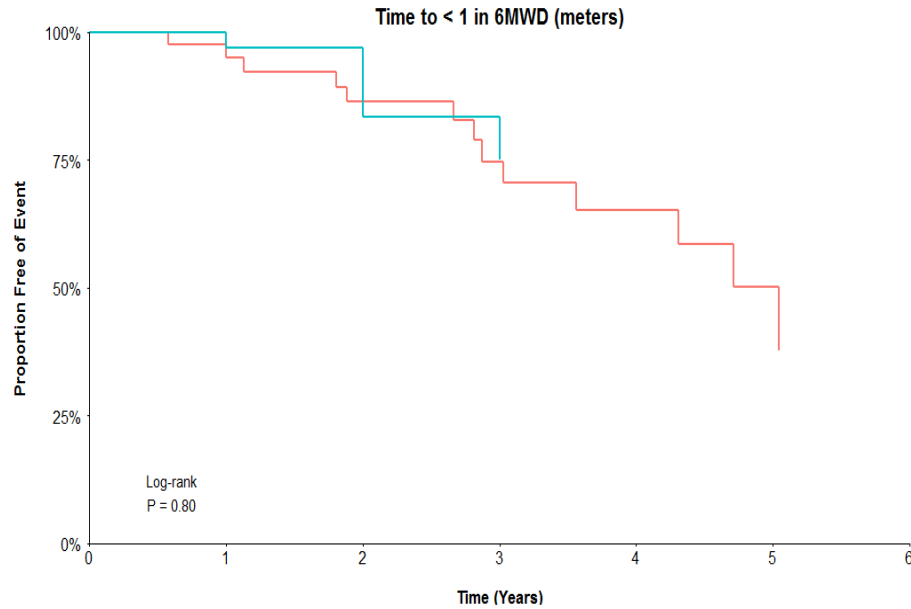
Sample selection Baseline characteristics Time to event analysis Linear regression **Outcomes** Definitions Settings



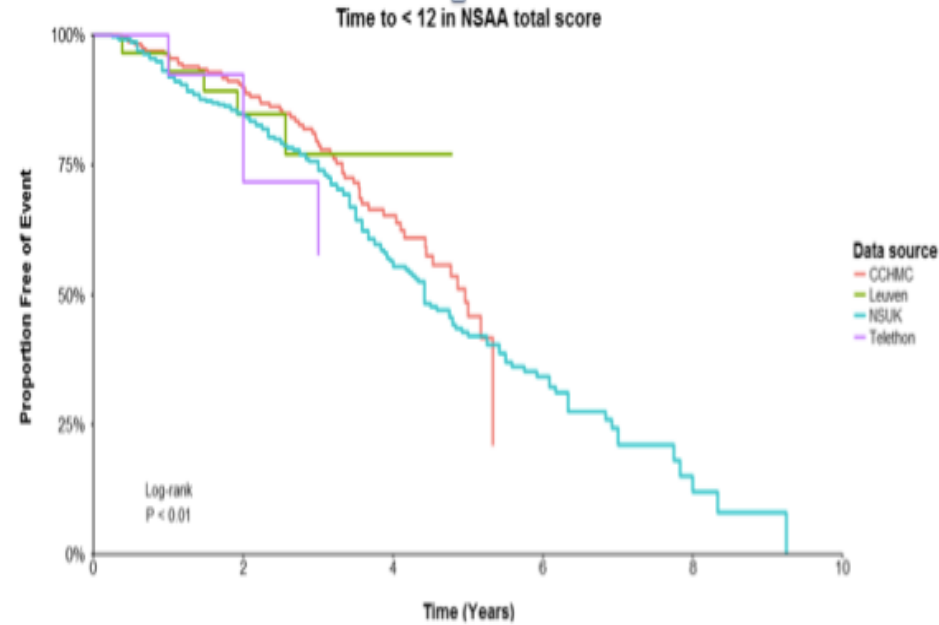
	Overall N = 2145	CCHMC N = 995	Leuven N = 218	NSUK N = 932
Age (years)	8.61 ± 2.83	8.94 ± 3.10	8.58 ± 2.35	8.26 ± 2.59
Dystrophin mutation				
Deletion	1,365 (63.64)	648 (65.13)	155 (71.10)	562 (60.30)
Duplication	294 (13.71)	155 (15.58)	44 (20.18)	95 (10.19)
Other	43 (2.00)	7 (0.70)	0 (0.00)	36 (3.86)
Point mutation	273 (12.73)	158 (15.88)	19 (8.72)	96 (10.30)
Unknown/missing	170 (7.93)	27 (2.71)	0 (0.00)	143 (15.34)
Steroid duration (months)	38.64 ± 29.07	45.56 ± 31.63	30.29 ± 22.91	32.69 ± 25.25
NSAA total score	23.21 ± 7.07	23.35 ± 7.22	25.26 ± 6.48	22.95 ± 6.98
6MWD (meters)	345.09 ± 100.01	- ± -	345.09 ± 100.01	- ± -
Timed rise from supine (seconds)	6.45 ± 6.53	- ± -	5.66 ± 3.91	6.63 ± 6.97
Timed 10 meter walk/run (seconds)	5.84 ± 2.06	5.35 ± 1.87	5.68 ± 2.02	6.41 ± 2.12
Timed 4 stair climb (seconds)	3.35 ± 2.71	3.10 ± 2.55	4.23 ± 3.07	- ± -
FVC %-predicted (%)	95.28 ± 20.86	111.03 ± 17.39	- ± -	86.84 ± 17.39

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Time-to-event comparative natural history



	0	1	2	3	4	5	6
Leuven	65	37	28	18	12	4	1
Telethon	96	96	93	80	0	0	0



Clustering NSAA trajectories in the North Star UK database: function vs. age

Trajectories

Model fits

Trajectory plots - panels

Trajectory plots - colored

Classification tables

Baseline characteristics

Baseline NSAA item scores

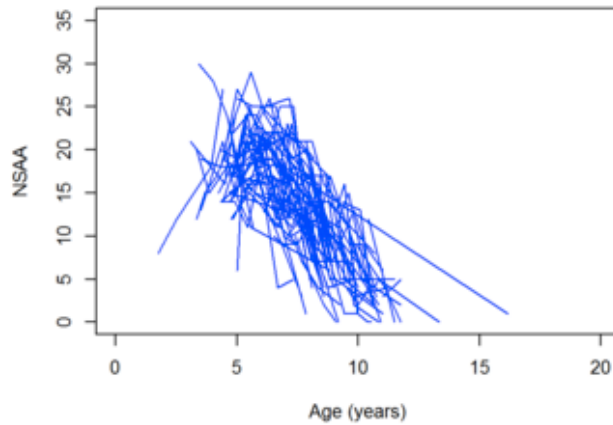
Loss of function

Four clusters

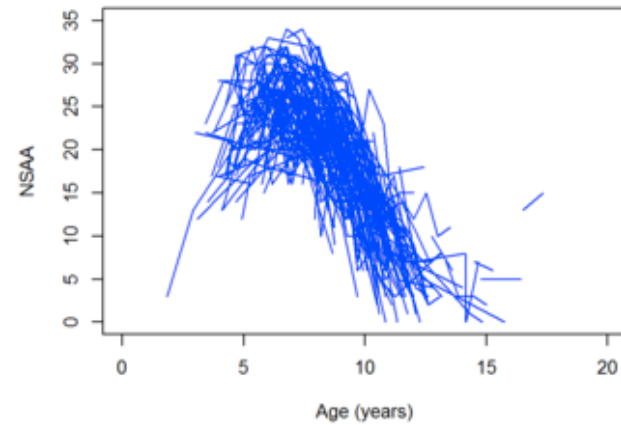
Five clusters

Six clusters

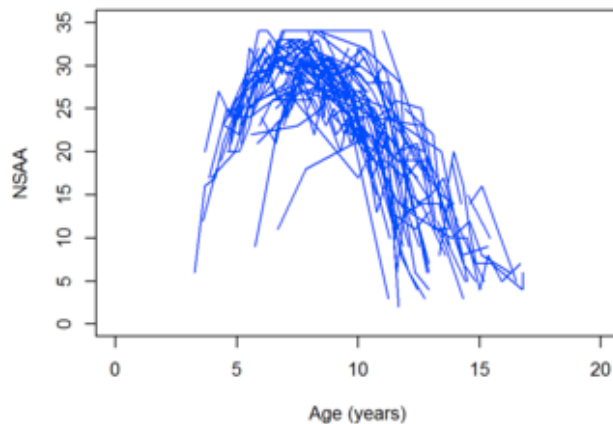
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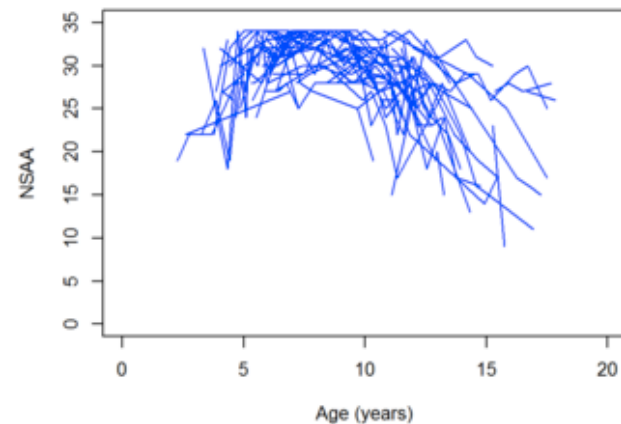
2



3



4



Translation to Clinical trial design

Natural history - necessary, but not sufficient

- **Share** de-identified patient level clinical data
- **Search** for existing successful solutions
- **Solicit** diverse, creative, high quality expertise
- **Systematize** to accelerate discoveries, impact
- **Show** and tell – publish, share broadly

No single researcher, stakeholder, or collaboration could solve translation alone

cTAP Members

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
- Abby Bronson

Drug Developers

- Larry Charnas
- Mike Binks
- Carl Morris
- Katherine Beaverson
- Dana Martin
- Ed Kaye
- Giles Champion
- Jorge Quiroz
- Dallan Murray
- Bob Spiegel
- Ed Xiou
- Tuyen Ong
- Joanne Donovan
- Malaz Abu
- Leslie Jacobsen

And their teams



COLLABORATIVE
**TRAJECTORY
ANALYSIS
PROJECT**

Contact Us

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Publications

Individualized prediction of changes in 6- minute walk distance for patients with Duchenne muscular dystrophy. Nathalie Goemans, Marleen vanden Hauwe, James Signorovitch, Elyse Swallow, Jinlin Song, for the Collaborative Trajectory Analysis Project (cTAP).

<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0164684>

Categorizing natural history trajectories of ambulatory function measured by the 6-minute walk distance in patients with Duchenne muscular dystrophy. Eugenio Mercuri, James Edward Signorovitch, Elyse Swallow, Jinlin Song, and Susan J. Ward for the Trajectory Analysis Project Collaboration (cTAP) and the DMD Italian group.

<http://www.nmd-journal.com/article/S0960-8966%2816%2930076-1>