Duchenne Regulatory Science Consortium (D-RSC)
Clinical Trial Simulation Tool

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D-RSC
DUCHENNE REGULATORY SCIENCE CONSORTIUM
CRITICAL PATH INSTITUTE

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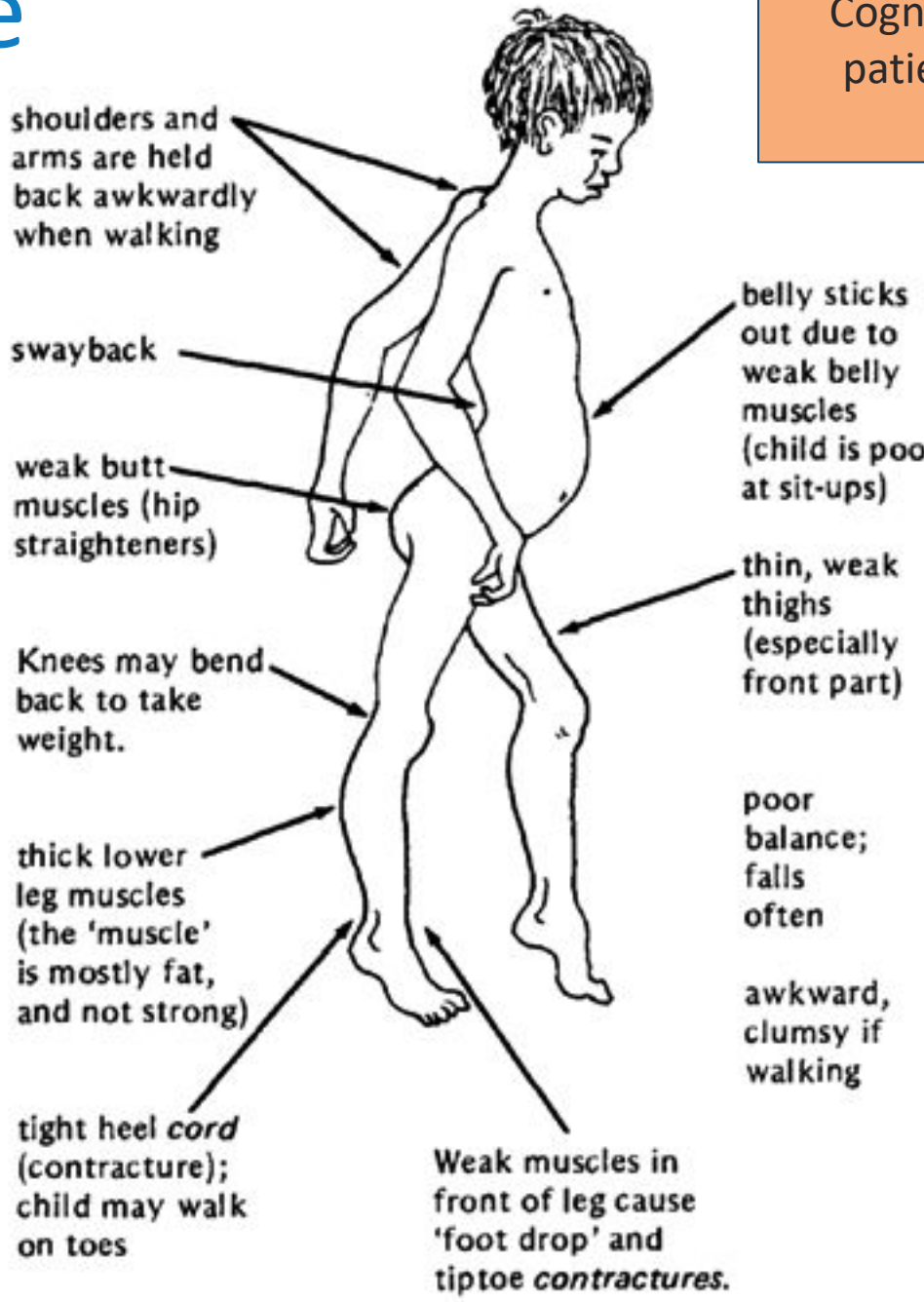
Intro to Duchenne

Cognitive problems in some patients, high incidence of autism

Diaphragm weakness leads to respiratory issues, pneumonia etc.



Develop cardiomyopathy in teens

Difficulty standing, then climbing stairs, then walking

D-RSC
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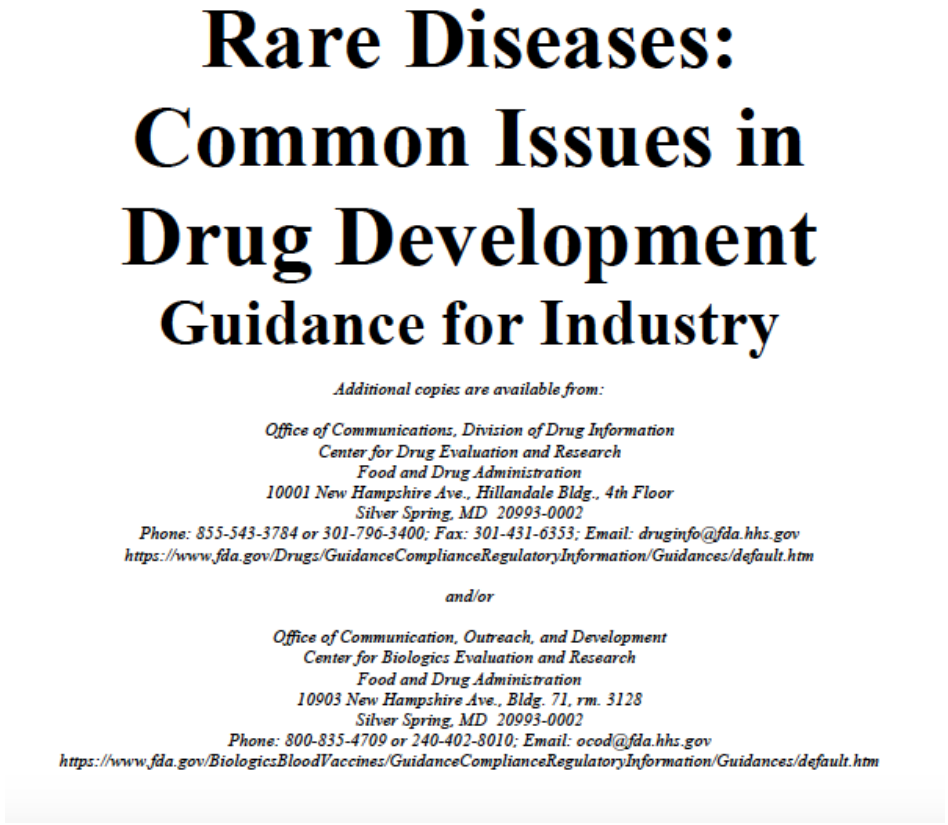
What is the problem in DMD?

- There are many trials going on – and only limited numbers of patients
- Most trials currently use the same subset of patients – many patients are ineligible for all trials.
- Trials often continue into several years of extension study to try and prove effectiveness.
- Most clinical trials in Duchenne do not meet their primary endpoint
    - Is it the drug or the trial protocol?

How can we get to more definitive answers in Duchenne trials faster, using fewer patients?

Why do we need to know about Natural History for Drug Development?



Rare Diseases: Common Issues in Drug Development

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, rm. 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

- Defining patient population and subtypes
- Selection of best patients for trial
- Understand trial length and entry criteria
- Choose or develop sensitive and specific endpoints
- Develop or understand biomarkers

Essentially - optimizing trial design

New approaches are needed

Traditional Drug Development Approach

Reliance on limited information and experience based on:

- A small set of KOLs
- Small, possibly outdated, datasets
- Last paper bias

Data and Quantitative Model Based Drug Development Approach

A modern approach based on:

- Integrated global datasets including relevant populations and endpoints
- Quantitative models of disease progression, patient population and endpoint behavior

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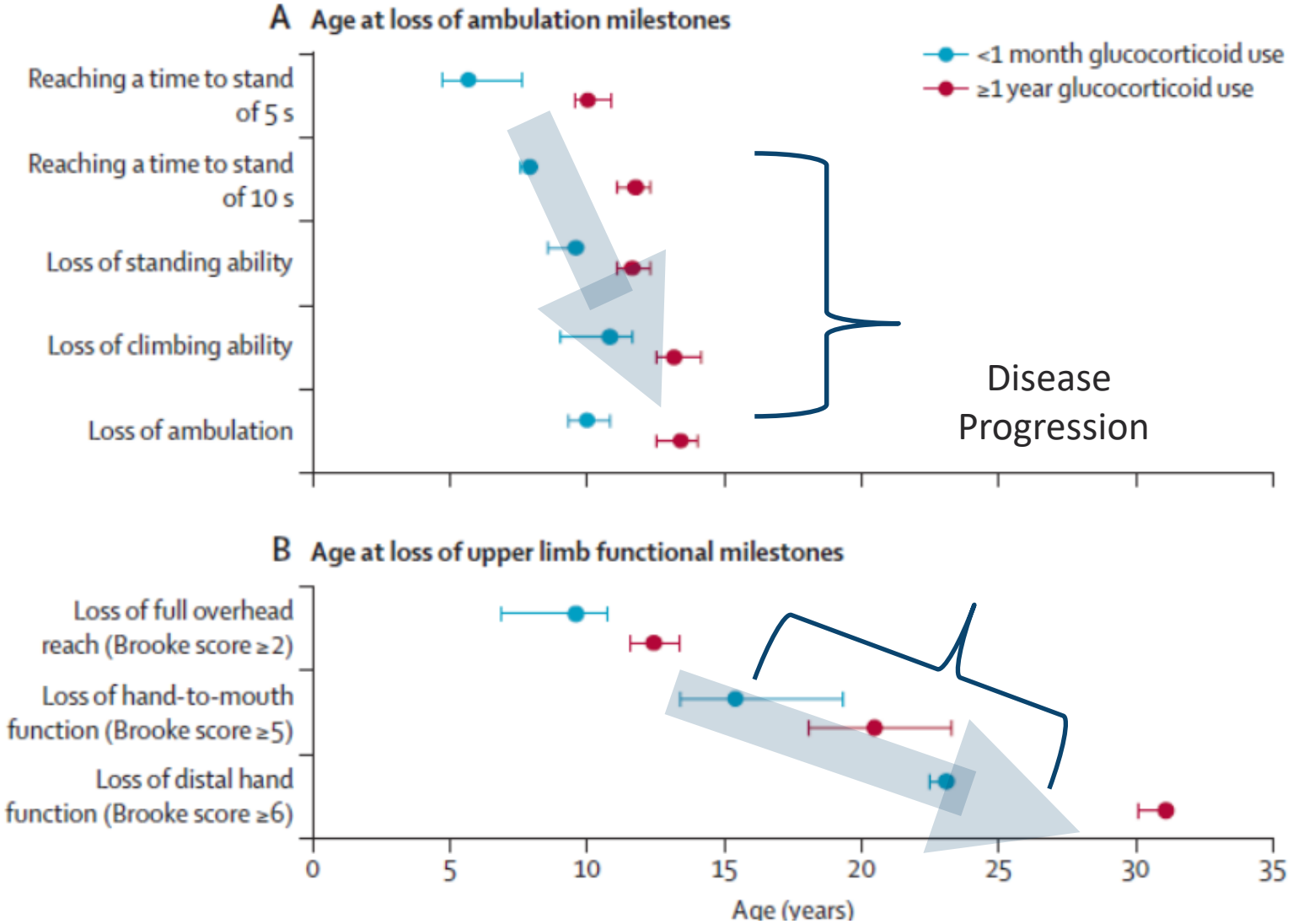
DMD Disease Progression



Figures from McDonald, CM et al. Lancet 2017. http://dx.doi.org/10.1016/S0140-6736(17)32160-8

D-RSC: a non-profit consortium to support collaborative research and regulatory acceptance of new drug development tools (DDTs) for Duchenne muscular dystrophy, to enable the earliest possible patient access to new treatments.

D-RSC Members and Advisors

- **Jane Larkindale, C-Path D-RSC Executive Director**
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  Diane Corey, Data Manager
  Peggy Abbott, Project Coordinator
  Ted Abresch, Consultant
- **Pat Furlong, Parent Project MD CEO, D-RSC Co-Director**
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- **Jacqueline Delfgaauw, Mallinckrodt Pharmaceuticals, Senior Director, Clinical Development**
- **Beth Belluscio, Pfizer, Senior Director, Early Candidate Clinical Lead for Rare Neurological Diseases**
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- **Guenther Metz, Santhera Pharmaceuticals, Sr. VP Business Development,**
  Jodi Wolff, Medical Science Liaison & Patient Advocacy Manager
- **Jon Tinsley, Sarepta Therapeutics, Senior Director, Medical Affairs**
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- Michael Crowther, University of Leicester, UK
- Micki Hill, University of Leicester, UK

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- **Food and Drug Administration – CDER/ FDA**
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  - Atul Bhattaram
  - Veneeta Tandon
- Glen Nuckolls, **NIH/NINDS**
- Tom Cheever, **NIH/NIAMS**

Patient Advisor

- Buddy Cassidy, Patient Representative

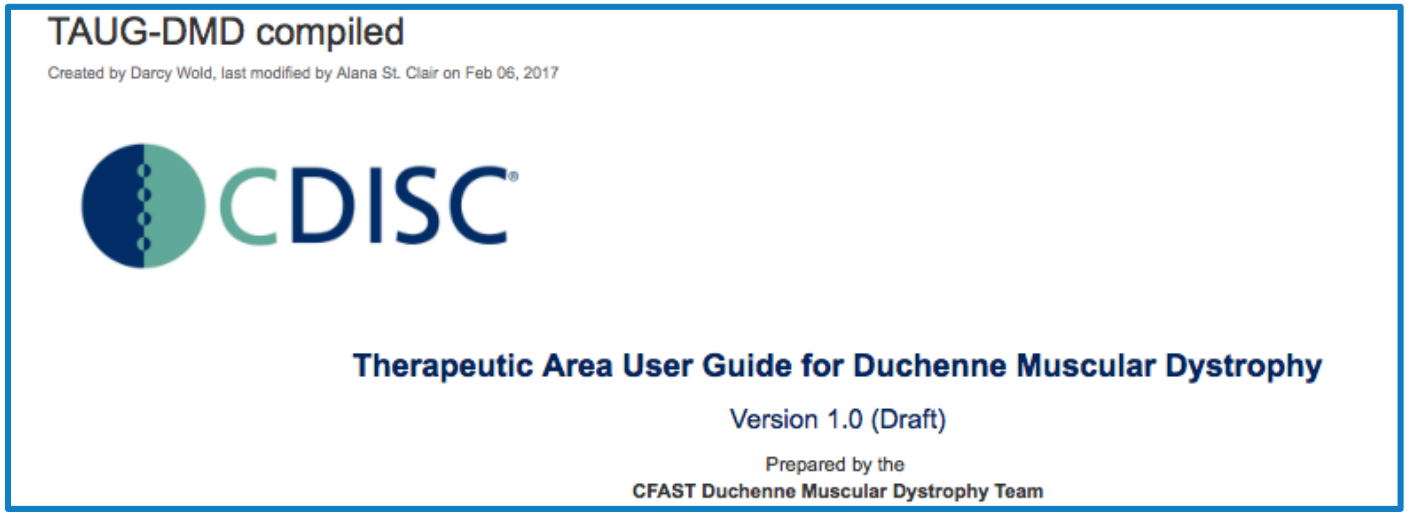
D-RSC is Building Models of Disease Progression

Understanding of natural history, changes in clinical endpoints, and variability specifically for drug development applications:

- Understanding population-wide variability in disease progression
- Understanding causes of variability (covariates that affect progression rate)
- Understanding sub-populations of patients
- Understanding effects of trial factors such as drop out, placebo etc.

D-RSC is building a tool to allow us to simulate clinical trials *in silico* so as to optimize clinical trial protocols across disease course prior to conducting trials.

CDISC Therapeutic Area User Guide


TAUG-DMD compiled

Created by Darcy Wold, last modified by Alana St. Clair on Feb 06, 2017

CDISC

Therapeutic Area User Guide for Duchenne Muscular Dystrophy

Version 1.0 (Draft)

Prepared by the

CFAST Duchenne Muscular Dystrophy Team

- Published on 27 September 2017
- https://www.cdisc.org/standards/therapeutic-areas/duchenne-muscular-dystrophy/duchenne-muscular-dystrophy-therapeutic-area

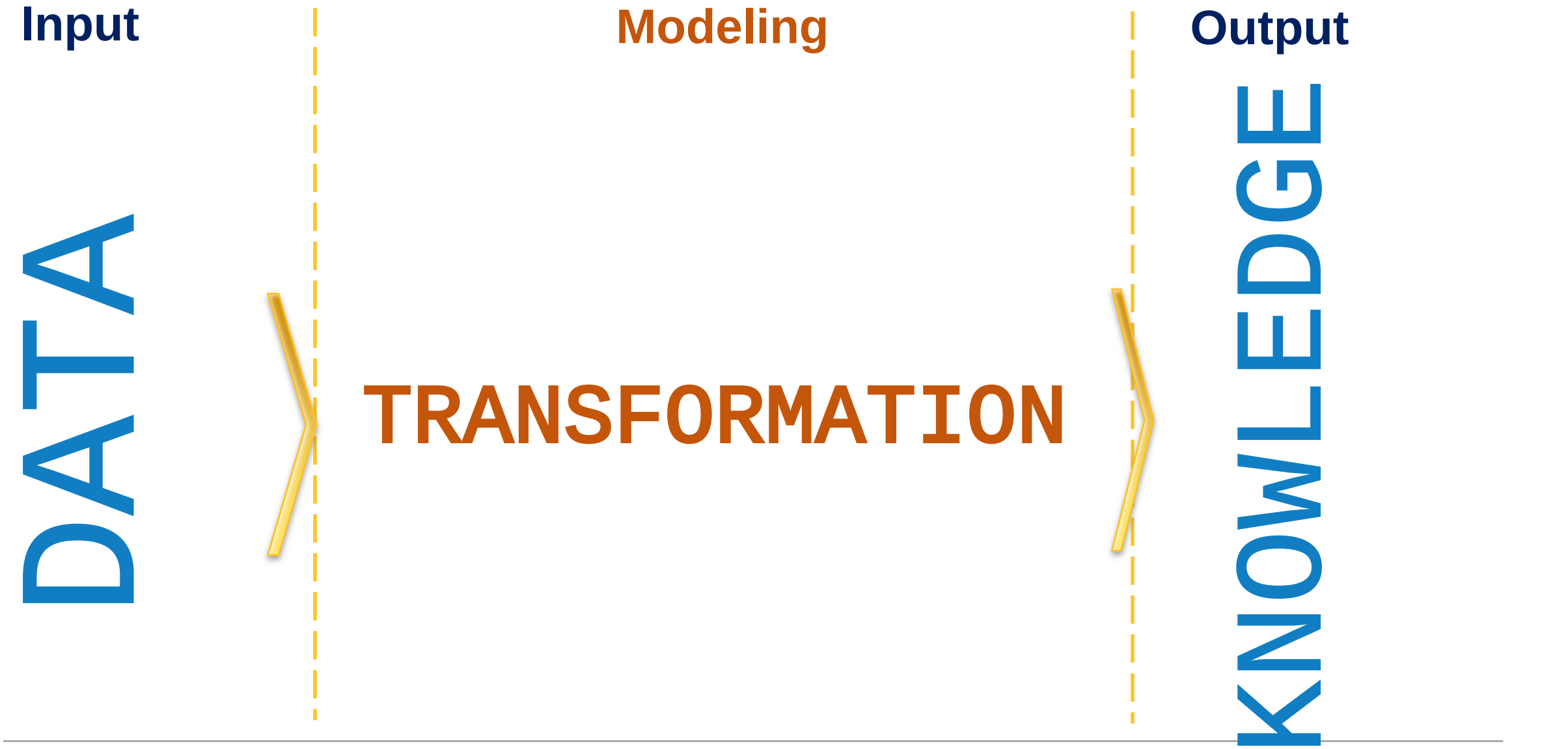
D-RSC Datasets

Database	Type of data	No. patients	Age range	Length of follow up	Types of variables
Santhera DMD 1004	Placebo arm of trial	34	10-18 years	up to 420 days	Respiratory measures, myometry, cardiac
Lilly* DMD 1005	Placebo arm of trial	115	7-14 years	up to 395 days	Functional measures, respiratory measures, cardiac measures
PTC -1 DMD 1009	Placebo arm of trial	57	older than 5	48 weeks	Functional measures, myometry, respiratory measures
PTC -2 DMD 1010		114			Functional measures, myometry, respiratory tar
CHOP* DMD 1006					ures
CCHMC DMD 1002					res, respiratory measures, cardiac
ImagingDMD DMD 1007					res, myometry
CINRG DNHS DMD 1003					res, respiratory measures, myometry
CINRG Steroid DMD 1011	Steroid Clinical Trial	64	4- 12 years	608 days	Functional measures, respiratory measures, myometry
UC Davis* DMD 1000	Natural history	73	2 -31 years	up to 10 years	Functional measures, respiratory measures, myometry
UC Davis 2* DMD 1000A	Test/re-test data for COA	24	4-14 years	1 year	Functional measures, respiratory measures
LUMC* DMD 1008	Biomarker study	14	5-18 years	Up to 5 years	FVC, drug effects, protein biomarkers
Duchenne Registry* DMD 1001	Patient Reported Registry	3736	Reports 1-115 years	none	Questionnaire
					Respiratory measures, MRI/MRS measures,

In analysis dataset (not all data):
TOTAL Number of Individual Patients: 1,137

TOTAL Number of Observations: 23,305

Disease Progression Model



Context of Use for Duchenne Clinical Trial Simulation Tool

General Description: A disease progression model-based CTS tool designed to optimize clinical trial enrichment and design of studies to investigate efficacy of potential therapies for Duchenne Muscular Dystrophy (DMD). **Measurements of DMD disease progression will be based on changes in a series of endpoints –** velocities of completion of the supine-stand test, 4-stair climb test, 10-meter walk/run test and 30-foot walk/run test, forced vital capacity, North Star Ambulatory Assessment and the transition between scores in the Brooke scale.

Target Population for Use: Individuals with DMD 4 years and older (endpoint-dependent), regardless of stage of disease.

Stage of Drug Development for Use: All clinical efficacy evaluation stages of drug development in DMD, including early efficacy, proof-of-concept, dose-ranging, and registration studies.

Disease Progression Model

Input

Clinical studies

UC Davis

UC Davis 2

CCHMC

CINRG DNHS

Santhera

Lilly

CHOP

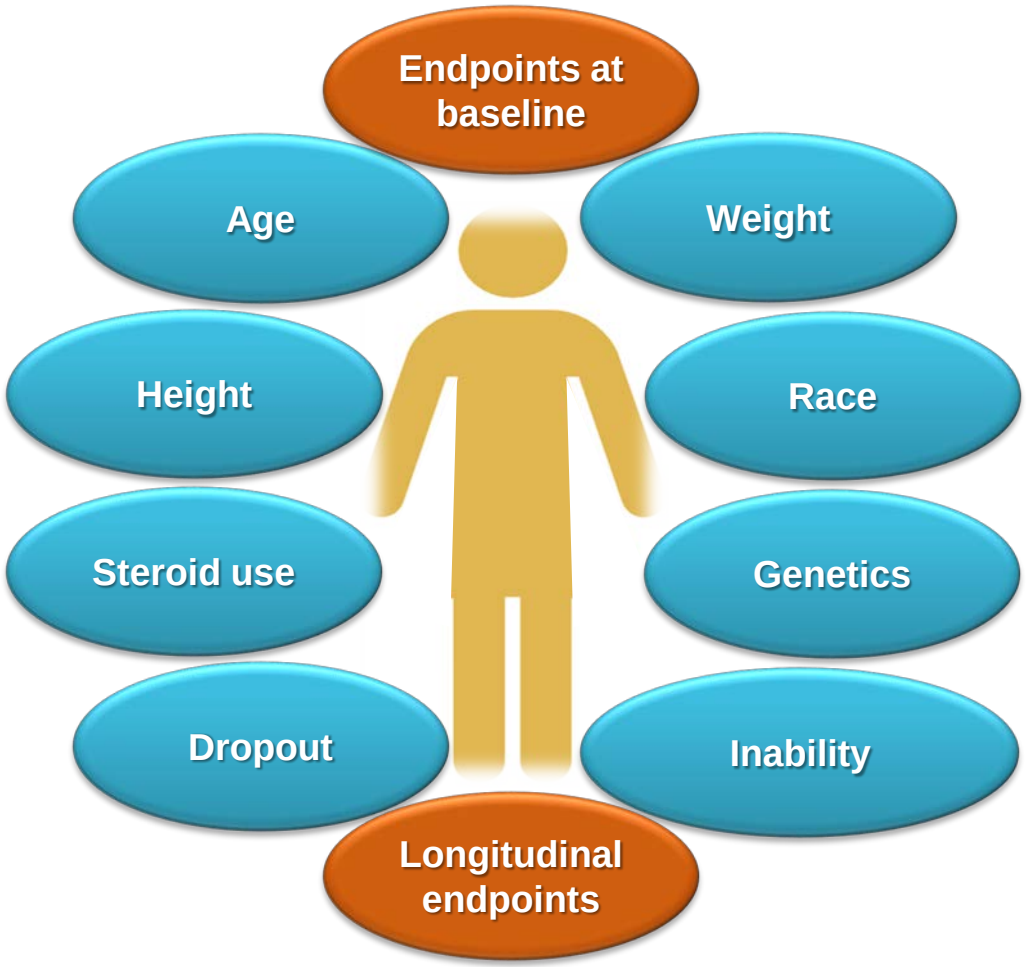
Imaging DMD

PTC 007

PTC 020

CINRG steroid

Modeling



Output

Understanding of disease worsening

Trajectory

Rate

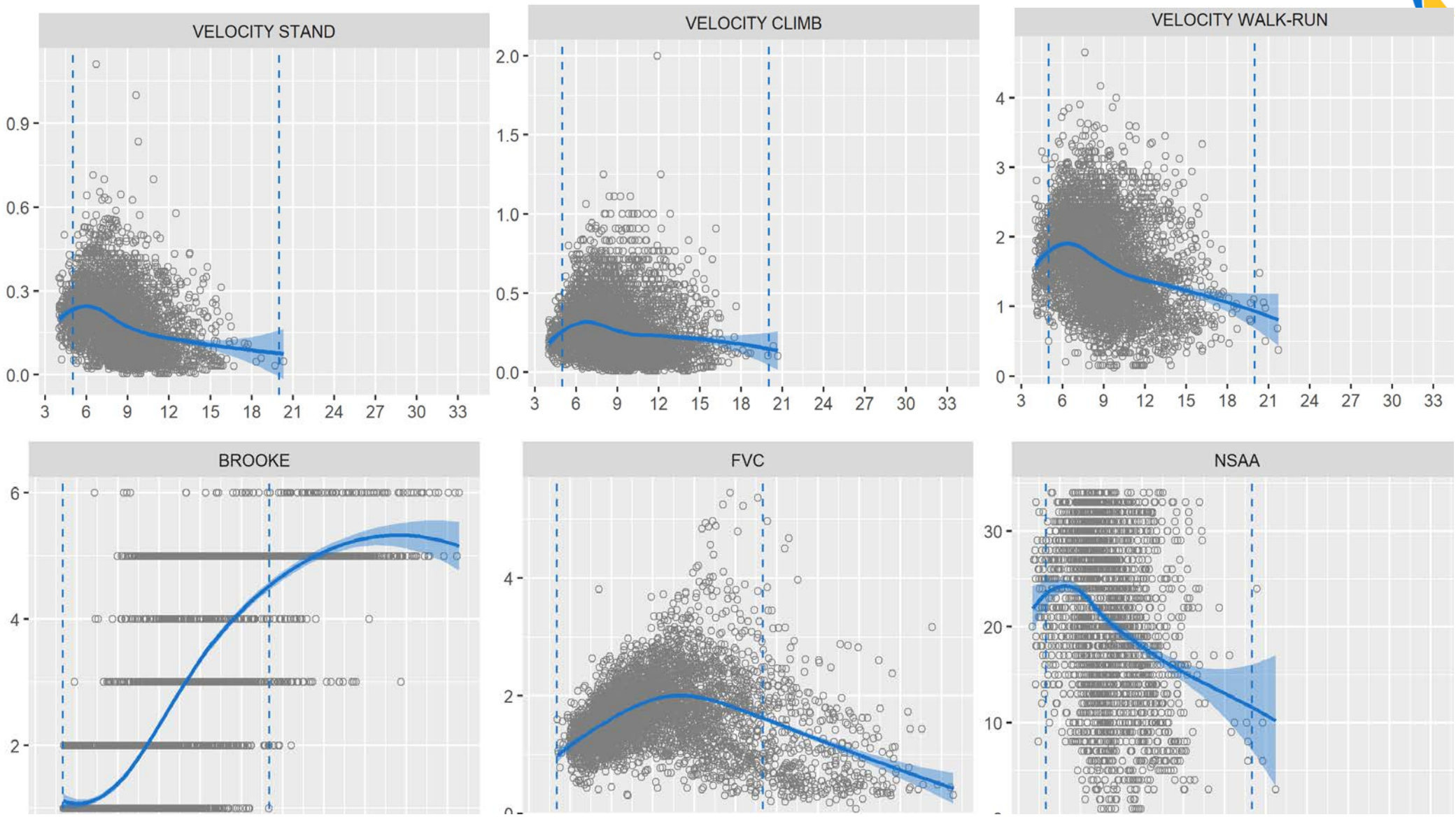
Predictors

Web Clinical Trial Simulator

What will we model?

- Velocity of completion of the supine-stand test
- Velocity of completion of the 4-stair climb test,
- Velocity of completion of the 10-meter walk/run test / 30-foot walk/run test
- North Star Ambulatory Assessment
- Forced vital capacity
- Transition between scores in the Brooke scale
- Steroid use: current/past/naïve
- Steroid: prednisone/ deflazacort
- Steroid: age at start of steroid use
- Genetic mutation group
- Body mass index (BMI)
- Race
- [function at earlier ages is incorporated]

Change in Outcome with Age



What is a joint model?

- A joint mixed effects model can describe the longitudinal dynamics of two outcomes:
  - Separate fixed effects are assigned for each outcome (but can be the same)
  - Covariate effects modeled individually or simultaneously with some scaling
  - Correlation between the random effects in the two outcomes is quantified

- Joint models can be formulated similarly to individual mixed models
  - (EXAMPLE) A joint linear model of two longitudinal outcomes is of the form:

$$Y_1(t)_{ij} = X_i\alpha_X + (\alpha_0 + \alpha_{0i}) + (\alpha_1 + \alpha_{1i})t_{ij} + \varepsilon_{ij}$$
$$Y_2(t)_{ij} = X_i\beta_X + (\beta_0 + \beta_{0i}) + (\beta_1 + \beta_{1i})t_{ij} + \varepsilon_{ij}$$

Endpoints 1,2

Covariate values

Covariate coefficients

Intercept

Random effect for intercept

Slope

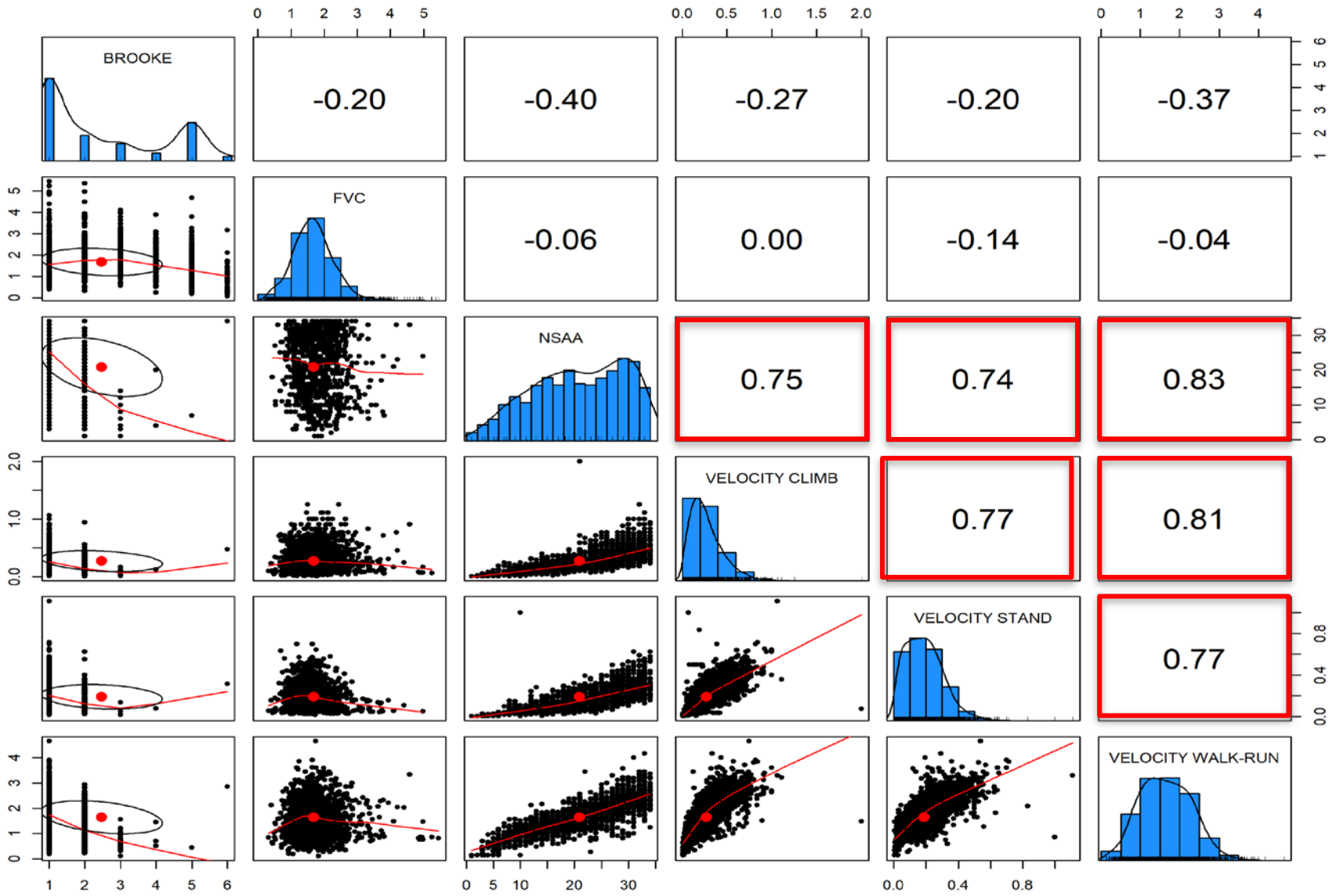
Random effect for slope

Time

Residual variability

$$\begin{bmatrix}\alpha_{0i}\\ \alpha_{1i}\\ \beta_{0i}\\ \beta_{1i}\end{bmatrix} \sim N(0, \Sigma), \qquad \Sigma = \begin{bmatrix}\sigma^2_{\alpha_0} & \sigma_{\alpha_0\alpha_1} & \sigma_{\alpha_0\beta_0} & \sigma_{\alpha_0\beta_1}\\ & \sigma^2_{\alpha_1} & \sigma_{\alpha_1\beta_0} & \sigma_{\alpha_1\beta_1}\\ & & \sigma^2_{\beta_0} & \sigma_{\beta_0\beta_1}\\ & & & \sigma^2_{\beta_1}\end{bmatrix}$$

Correlation Matrix

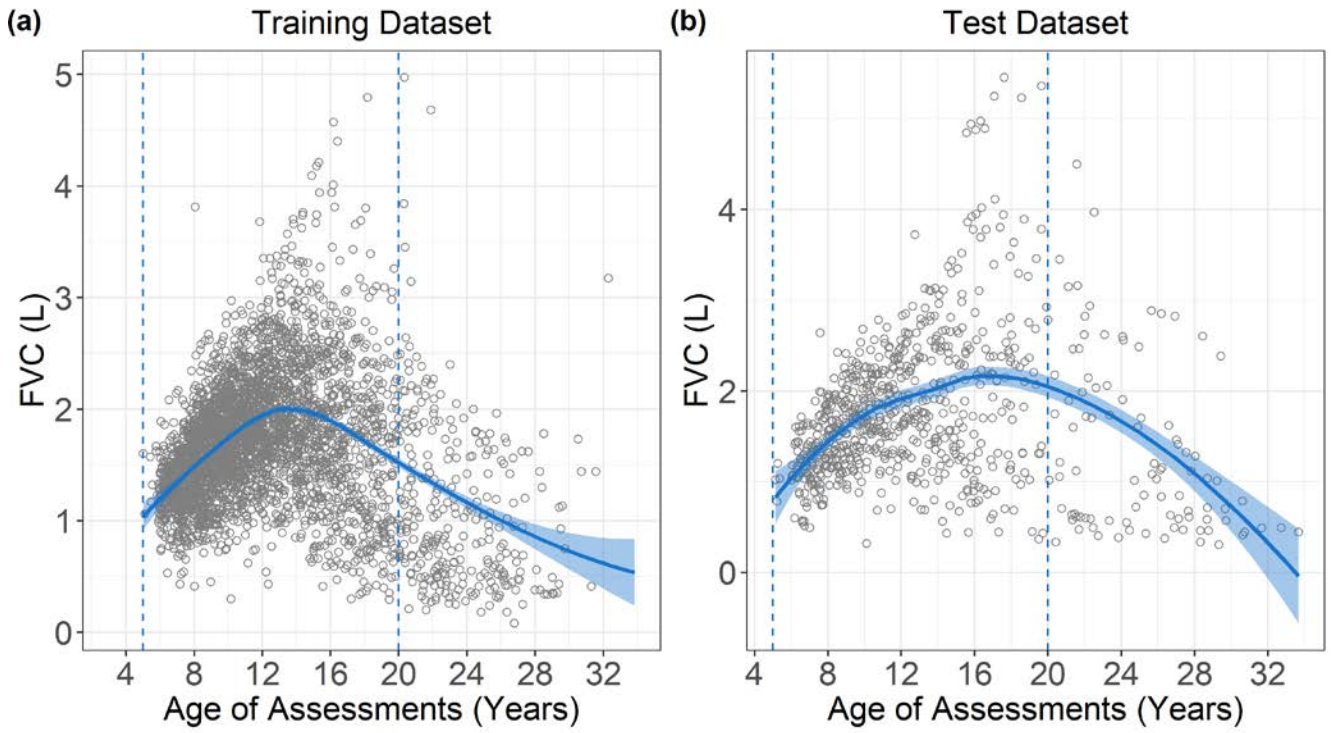


What will these models do to help?

- Developing a mathematical understanding of how endpoints change over disease course
- Understanding sources of variability in rate of change of endpoints
- Understanding the links between how changes in one endpoint relate to changes in later stages of disease
- Models can be used to map disease progression to changes in meaningful outcomes (e.g. time to loss of ambulation, loss of ability to transfer, respirator use etc.)

The Initial FVC Model

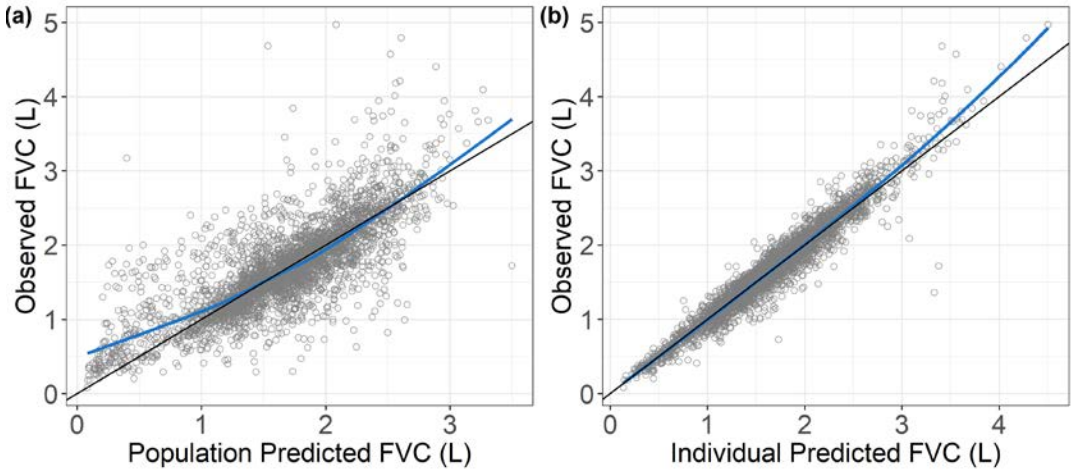
Forced Vital Capacity (FVC) vs. Age of Assessments



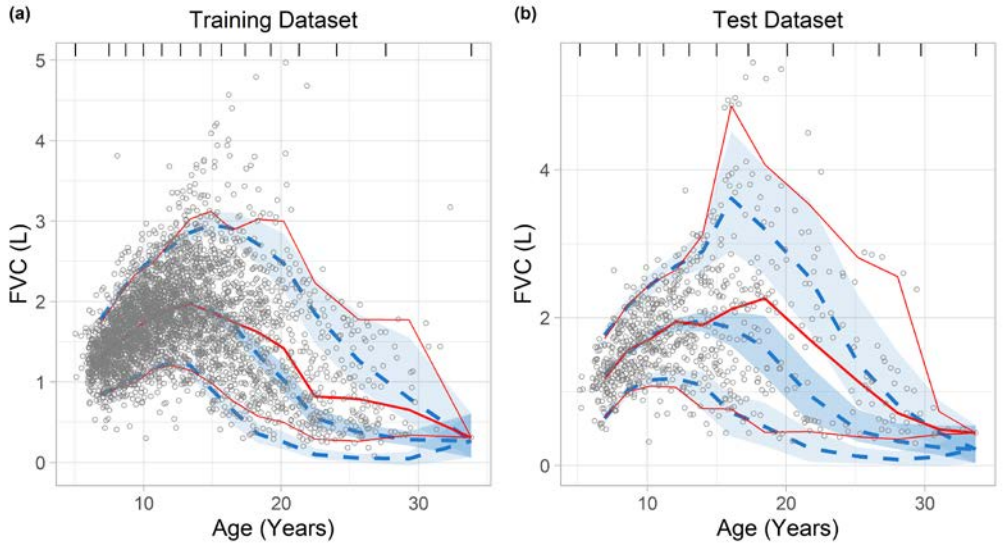
Graphs show the distribution of Forced Vital Capacity (FVC) endpoint measurement with age of patient across all studies. Unit for the dependent variable FVC is liters (L). Open circles are observed data, and lines are LOESS (locally weighted scatterplot smoothing) smooth. Vertical dotted blue lines are for reference and correspond to 5* and 20 years old.

*Minimum age of 5 years for FVC.

Goodness-of-Fit plots



Visual Predictive Checks



NSAA model and Clinical Trial Simulator

Clinical Trial Simulator - Version 1.0

Simulate clinical trials on patients with Duchenne Muscular Dystrophy: NSAA endpoint

Simulate population | Simulate single patient | Upload patient data

Inputs

Number of Subjects: 200

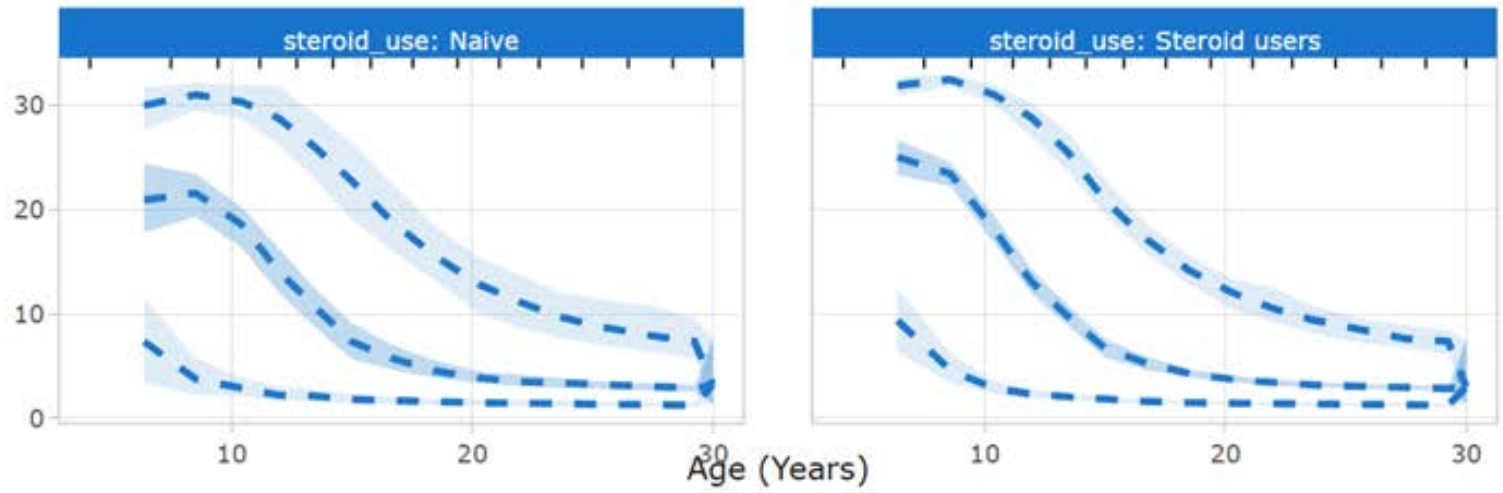
Age range of patients at first visit (Years): 4 – 14

Proportion of Subjects with Steroid (%): 50 – 75 – 100

Number of Simulations: 100

Simulate

Simulation output

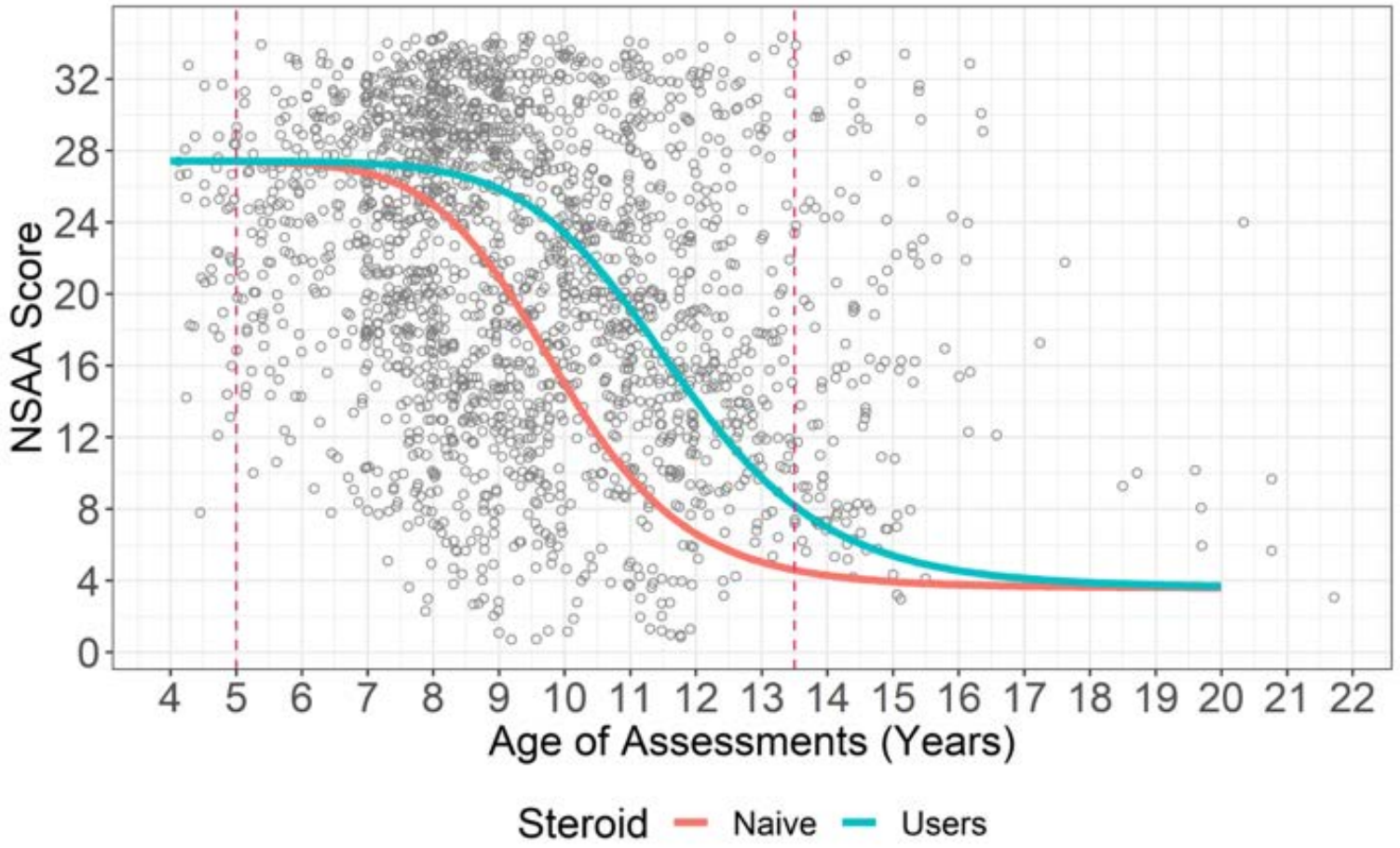


Contact us:

By Karthik Lingineni & Sarah Kim on behalf of the Critical Path for Duchenne Regulatory Science Consortium. E-mail sarahkim@cop.ufl.edu with questions or comments.

Northstar and steroids

Northstar – prediction of steroid effect.



D-RSC – next steps

- Plans for models are under review by both FDA and EMA
- Individual models are being built
- Joint model of as many endpoints as supported by data will be constructed
- Final clinical trial simulation tool will be constructed
- Final regulatory review
- Models and simulation tool will be made available
- [We hope] Duchenne clinical trials will be designed better, include broader ranges of patients, and demonstrate therapies that really change the progression of disease!

D-RSC is building models that will help describe DMD disease progression across populations of patient from age 5 until end-stage disease in terms of dynamics of change in six outcome measures, how outcomes relate to each other across disease, and identifying covariates that affect the rate of progression.

Thank you to those who contributed data

Santhera

Lilly

PTC

Summit Plc

CHOP – Hank Mayer

CCHMC- Brenda Wong

ImagingDMD

CINRG

UC Davis – Ted Abresch and other investigators

LUMC – Pietro Spitali and other investigators

Duchenne Connect - PPMD

Special thanks to the CINRG DNHS investigators and the Imaging DMD investigators

Questions about our work can be sent to jlarkindale@c-path.org