Parent Project Muscular Dystrophy

LEADING THE FIGHT TO END DUCHENNE

Natural History Studies and Measuring Effectiveness of Care in Duchenne Muscular Dystrophy

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Professor of Pediatrics

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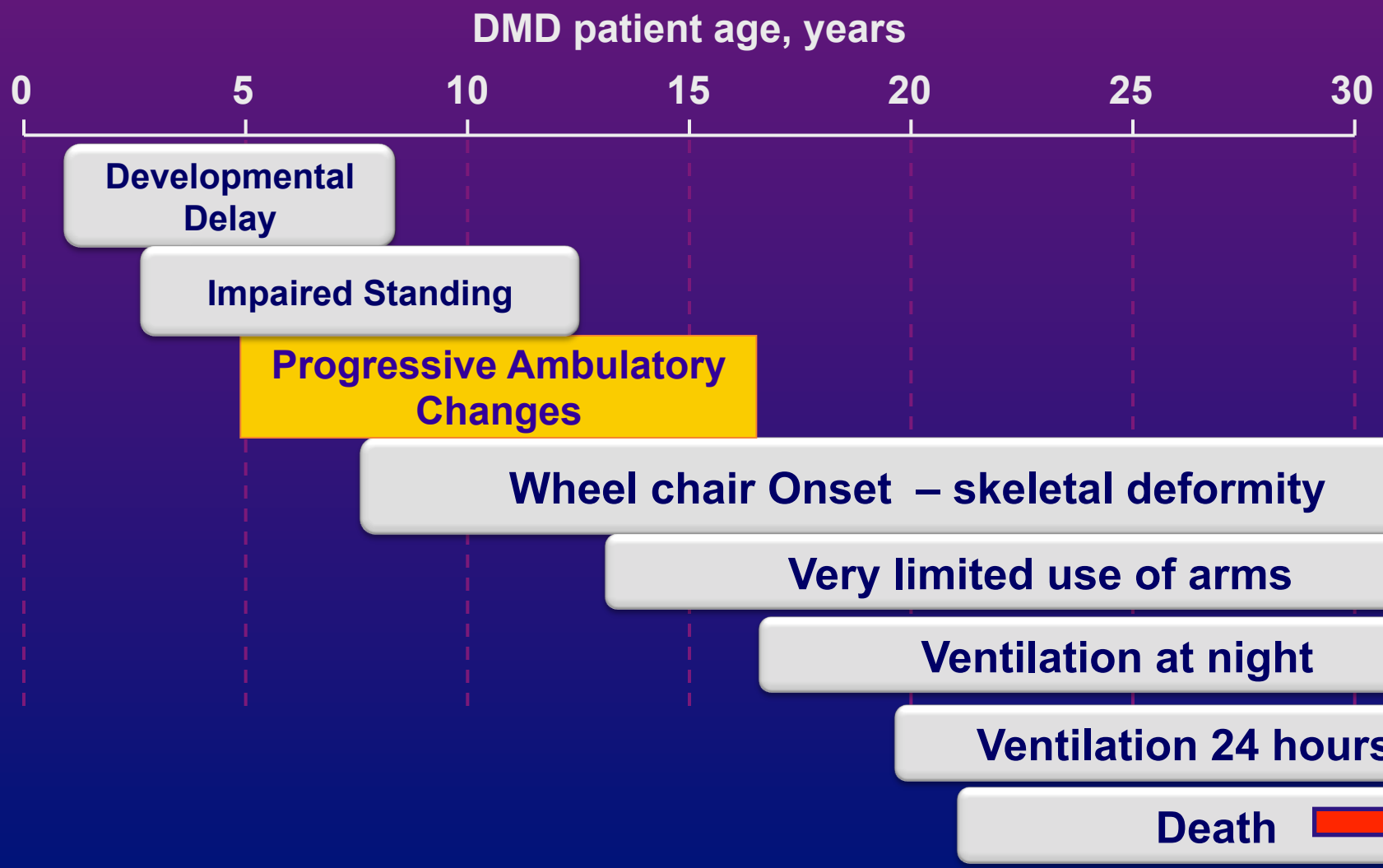
Disclosures

- Dr. McDonald has served on Advisory Committees for:
  - PTC Therapeutics
  - Acceleron / Shire
  - Prosensa
  - GSK
  - AVI Biopharma
  - Novartis
  - Halo Therapeutics

DMD Disease Progression



What Interventions have Impacted the Natural History of Disease Progression in DMD?

1) Glucocorticoids
2) Management of spine deformity
   - Glucocorticoids
   - Timely spine surgery for curves > 30 degrees
3) Pulmonary Management
   - Airway clearance strategies / Mech. Cough Assistance
   - Non-invasive ventilation
4) Cardiac Management
   - Early afterload reduction (e.g. ACE inhibitors)
   - Recognition and management of heart failure

Requires:

5) Communication and Coordination

Steroids, Spine Surgery for Scoliosis, and Ventilation in DMD has long-term benefits and is standard of care.

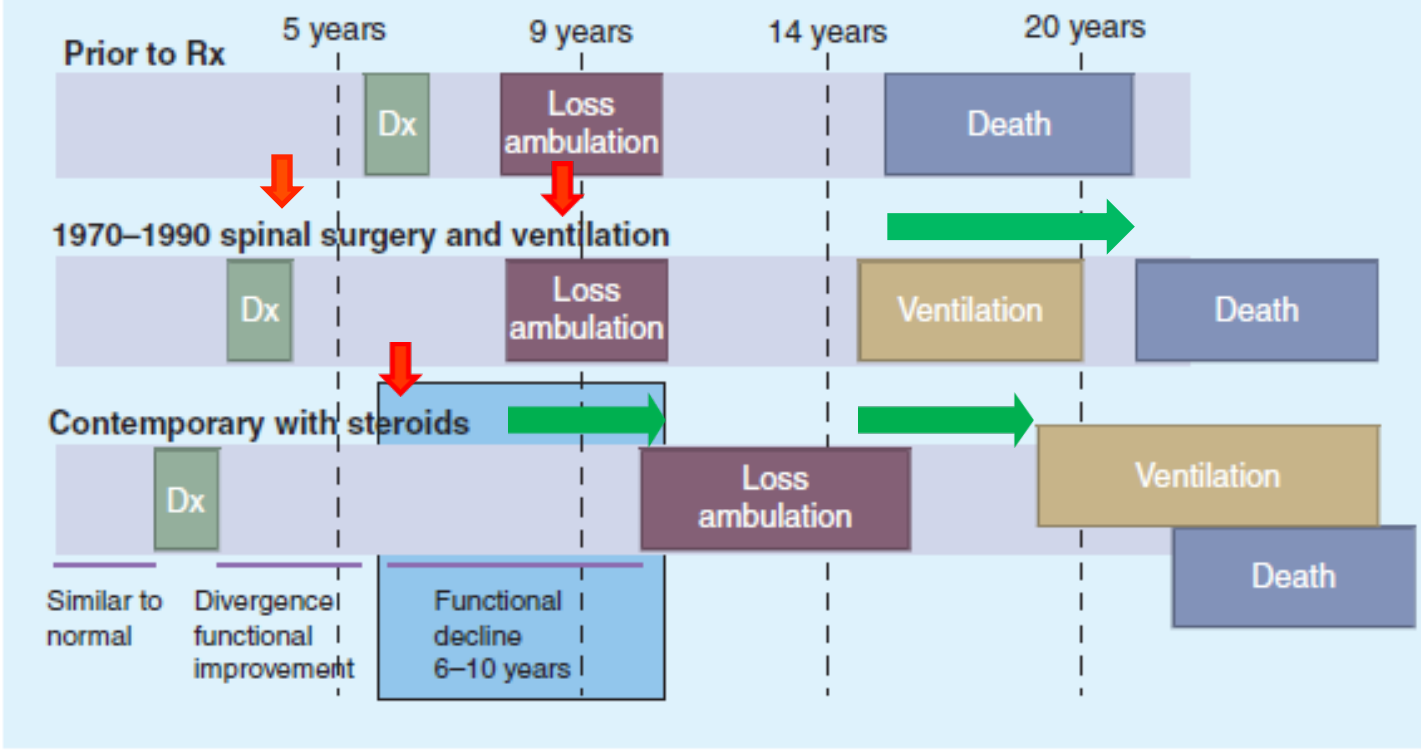


Figure 11. Natural history of Duchenne muscular dystrophy.

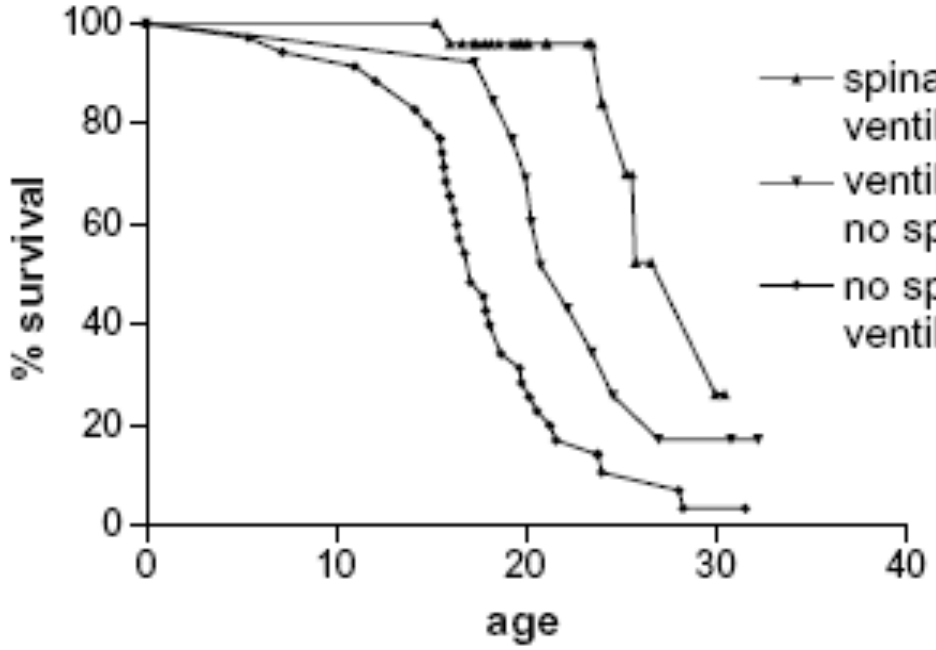


Fig. 3. Kaplan–Meier survival plot to show the impact of spinal surgery and ventilation on survival. Survival curves are significantly different $p = 0.0001$.

- Eagle M, et al. Managing Duchenne muscular dystrophy--the additive effect of spinal surgery and home nocturnal ventilation in improving survival.
- Neuromuscul Disord. 2007 Jun;17(6):470-5.

"Clinical Outcome Measures"

- Clinical Trials of Therapeutics

- Measure *Efficacy* — whether the treatment works or not.

- Trial Endpoints
- Primary: 6MWD, PFTs
- Secondary: TFTs, 9-HPT
- HrQOL
- Exploratory Endpoints: MRI, biomarkers

- Quality of Care
- *Comparative Effectiveness Research*

- Measure *Effectiveness* — benefits the treatments produce in routine clinical practice.

- Quality of Care Indicators
- Process Measures: Use of Steroids, PFTs, Spine X-Ray, Spine Surgery Offered, use of Airway Clearance strategies, NIPPV
- Outcomes: Spine surgery Complication rates, Survival

Loss of Clinically Meaningful Milestones (Predictable Order)

- Loss of standing from supine
- Loss of stair climbing
- Loss of the ability to rise from a chair
- Loss of ability to walk (Inability to walk 10 m)
- Loss of the ability to raise a hand to the mouth

Cooperative International Neuromuscular Research Group

CINRG Natural History Study and Development of Clinical Endpoints in Duchenne Muscular Dystrophy

Craig McDonald, MD

www.cinrgresearch.org

Cooperative International Neuromuscular Research Group

CINRG Clinical Sites

Cooperative International Neuromuscular Research Group

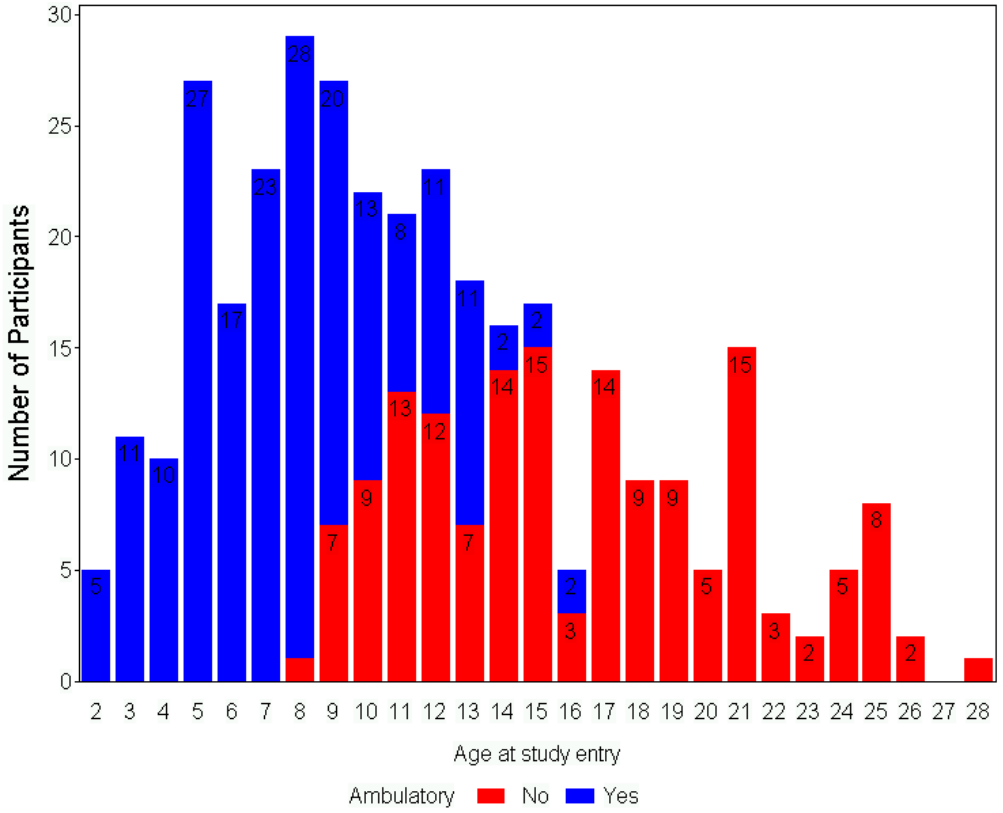
Methods

- **Design:** Multicenter, international "accelerated" longitudinal observational study

- **Assessments:** Conducted at **Baseline**, **Months 3**, **6**, **9**, **12:**
  - Clinical History / Review of Systems
  - Anthropometrics / Goniometry
  - MRC MMT / Isometric Strength (CINRG CQMT)
  - Timed Motor Performance Testing (Stand, Stairs, 10M walk)
  - Brooke / Vignos functional assessment scales
  - Pulmonary Function (FVC, FEV1, PEFR, MIP, MEP)
  - Health-Related Quality of Life

- **Continuation** of assessments annually to at least 5Y will yield ~1700 person-years of data from early childhood to adulthood.

Enrollment by Age and Ambulatory Status



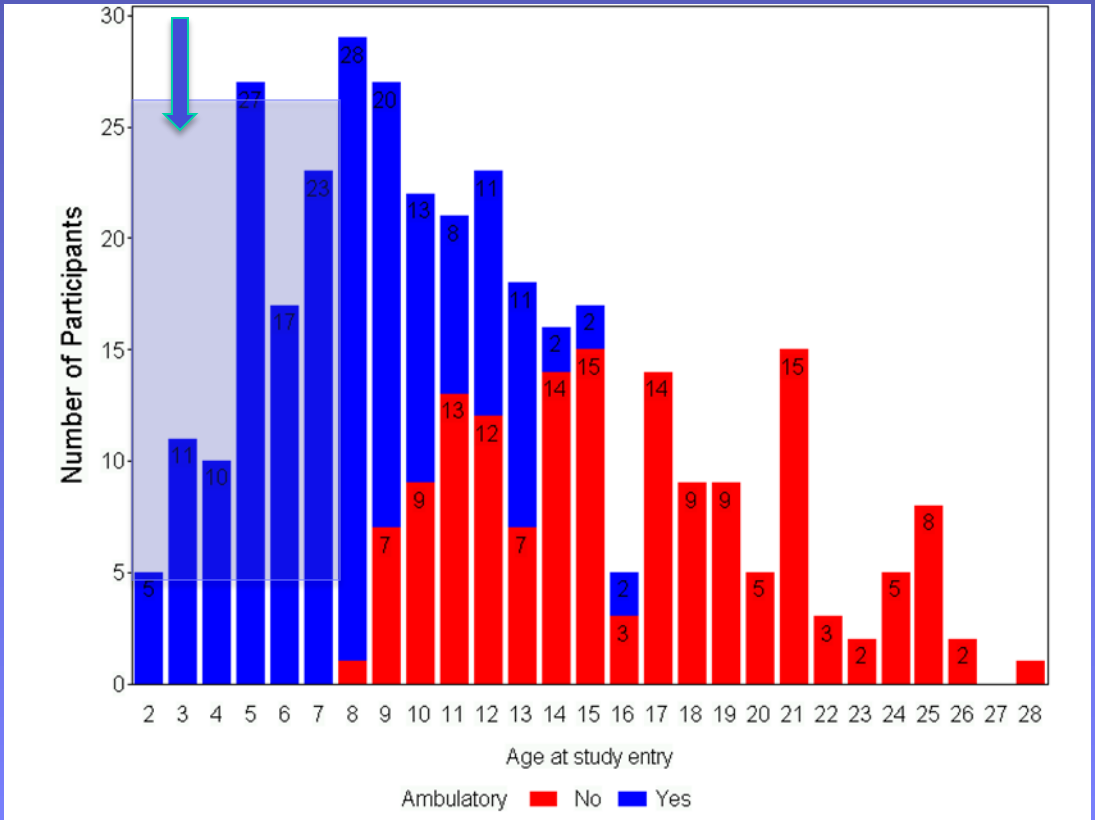
Ambulatory = Able to walk independently, judged by investigator

Cutoff for strength evaluation = able to do 1-person assisted stand-pivot transfer

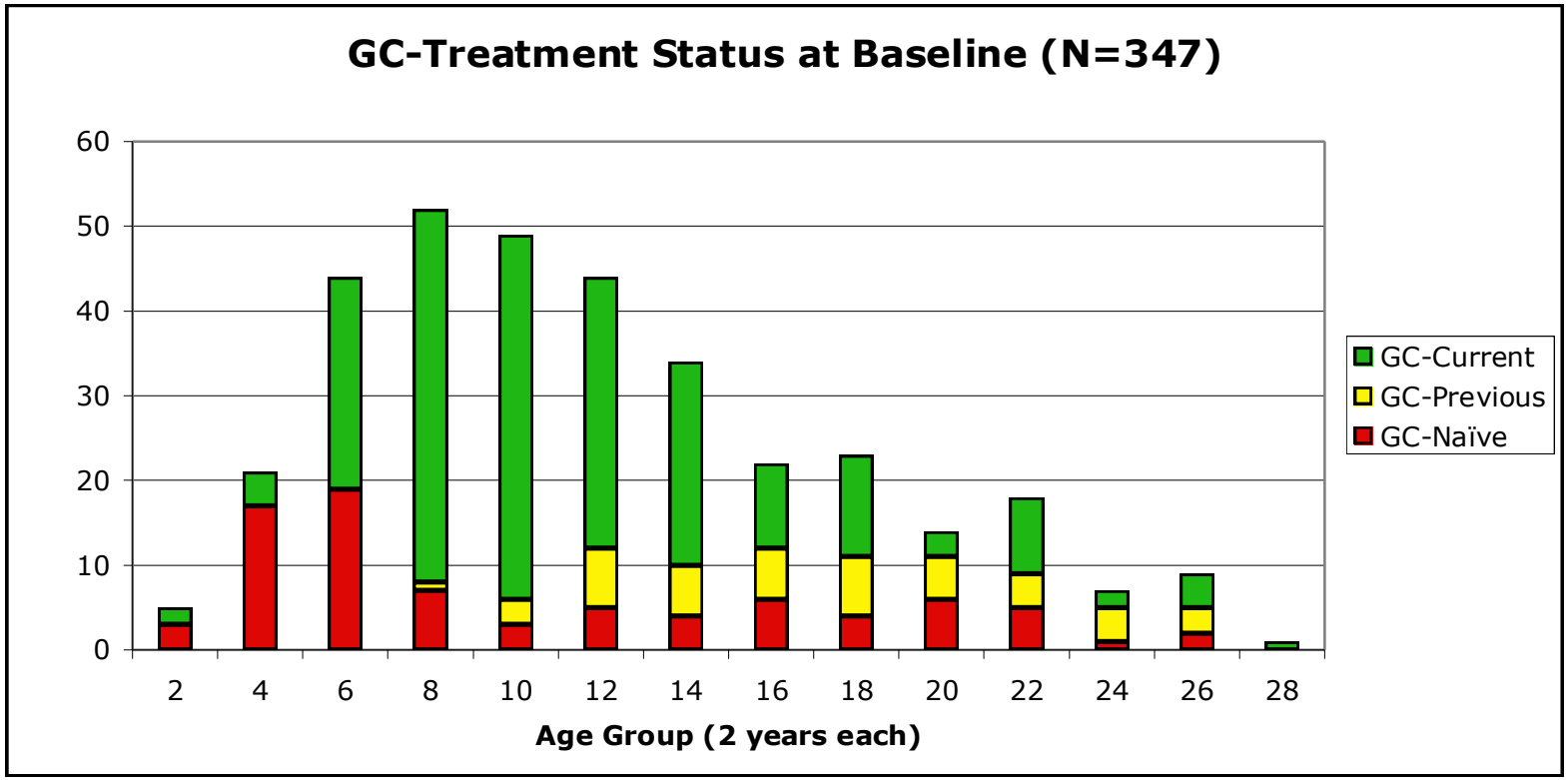
Cooperative International Neuromuscular Research Group

Plans for Natural History Study

- NIDRR, NIAMS and PPMD funded
- Reopen enrollment to all newly diagnosed patients with DMD (or age < 5-6)



Glucocorticoid Status at Study Entry



<u>Definition of GC Status</u>

Current User

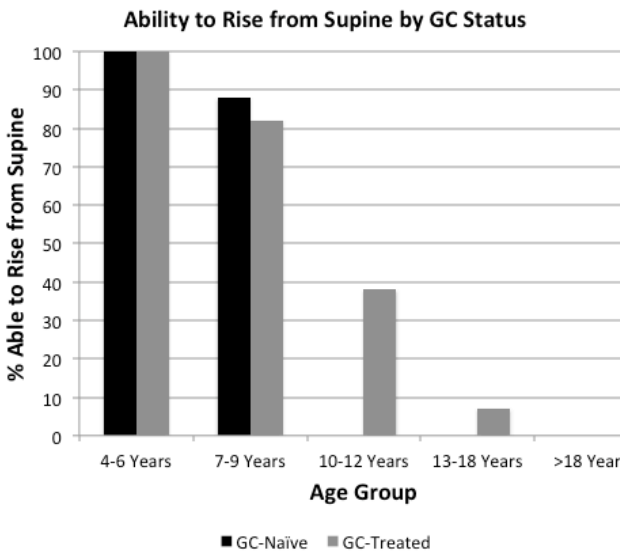
Prior Use = > 1 month

Naïve = < 1 month and discontinued, or never

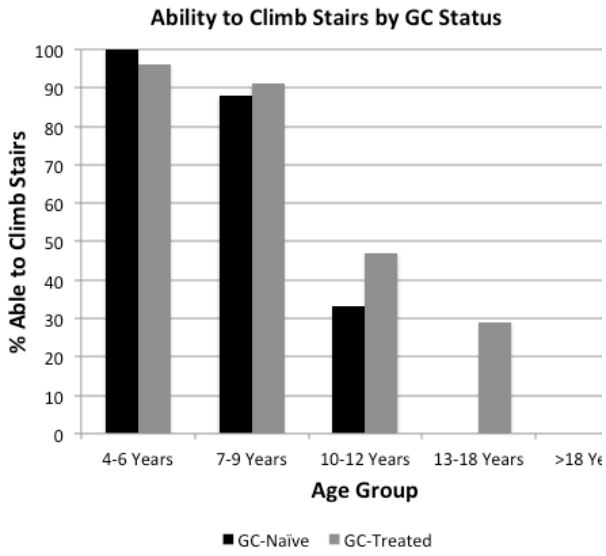
This presentation combines Prior/Naive

Effect of Glucocorticoids / Steroids

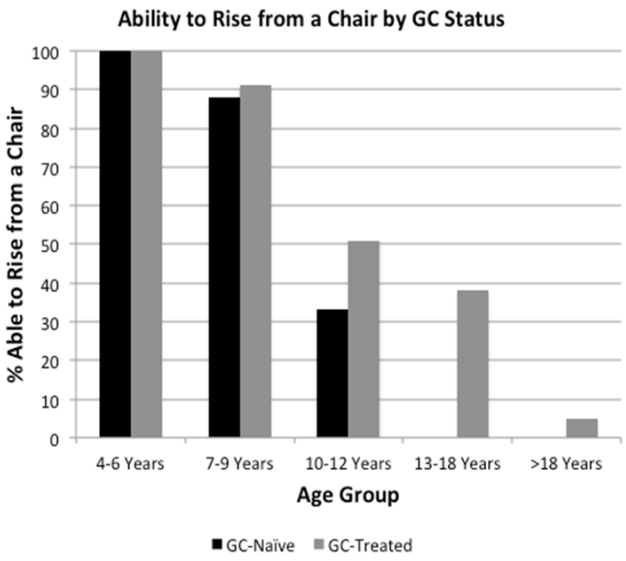
Stand



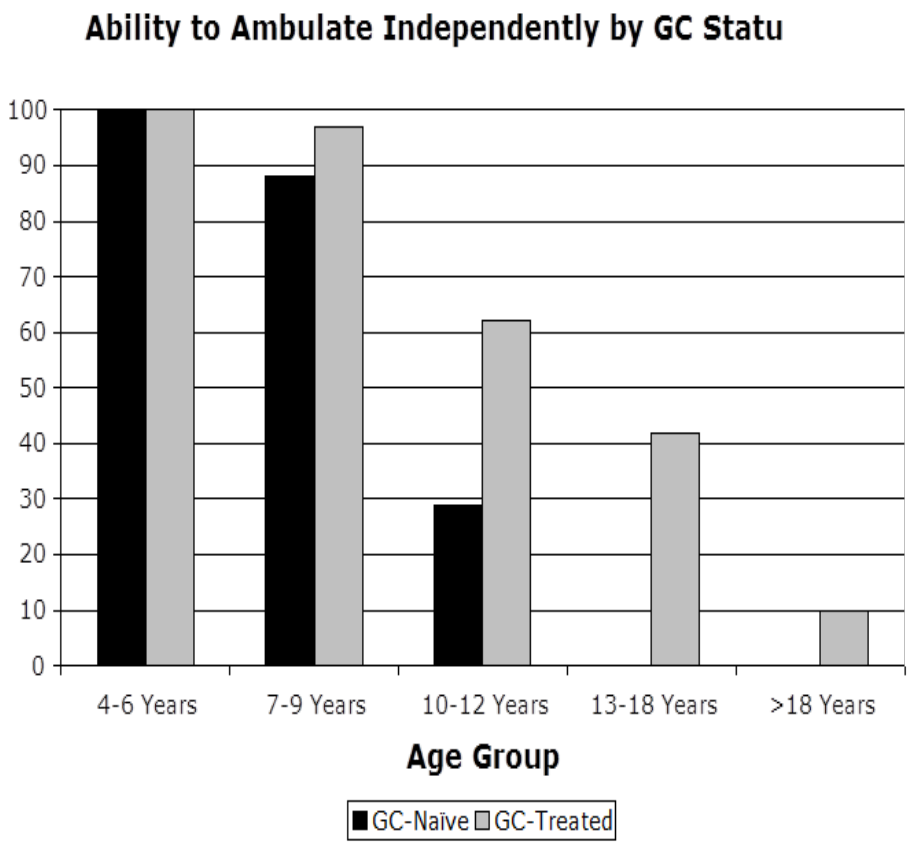
Climb Stairs

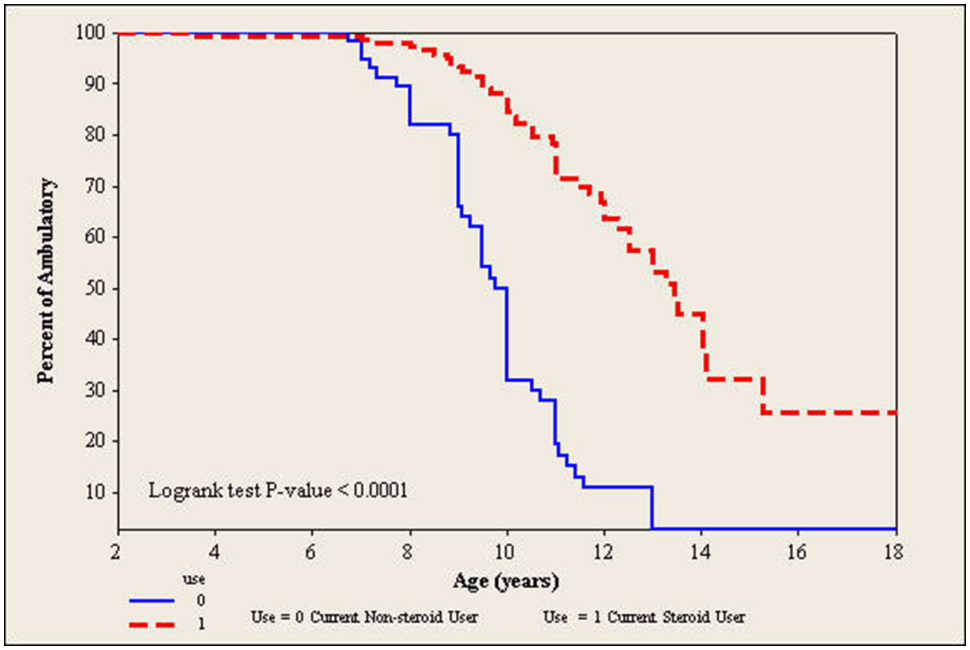


Rise from a Chair

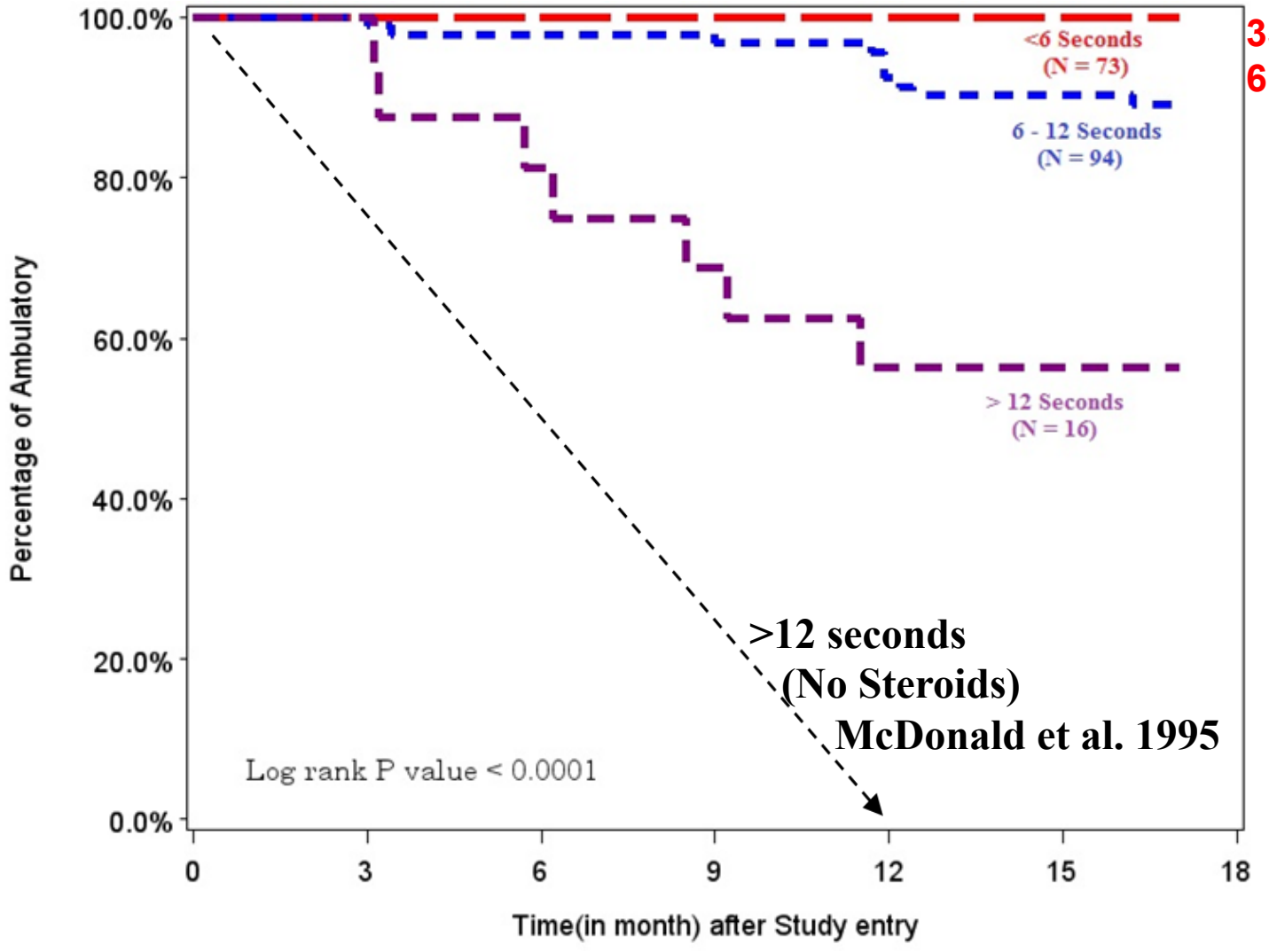


Effect of Glucocorticoids /Steroids on Loss of Ambulation



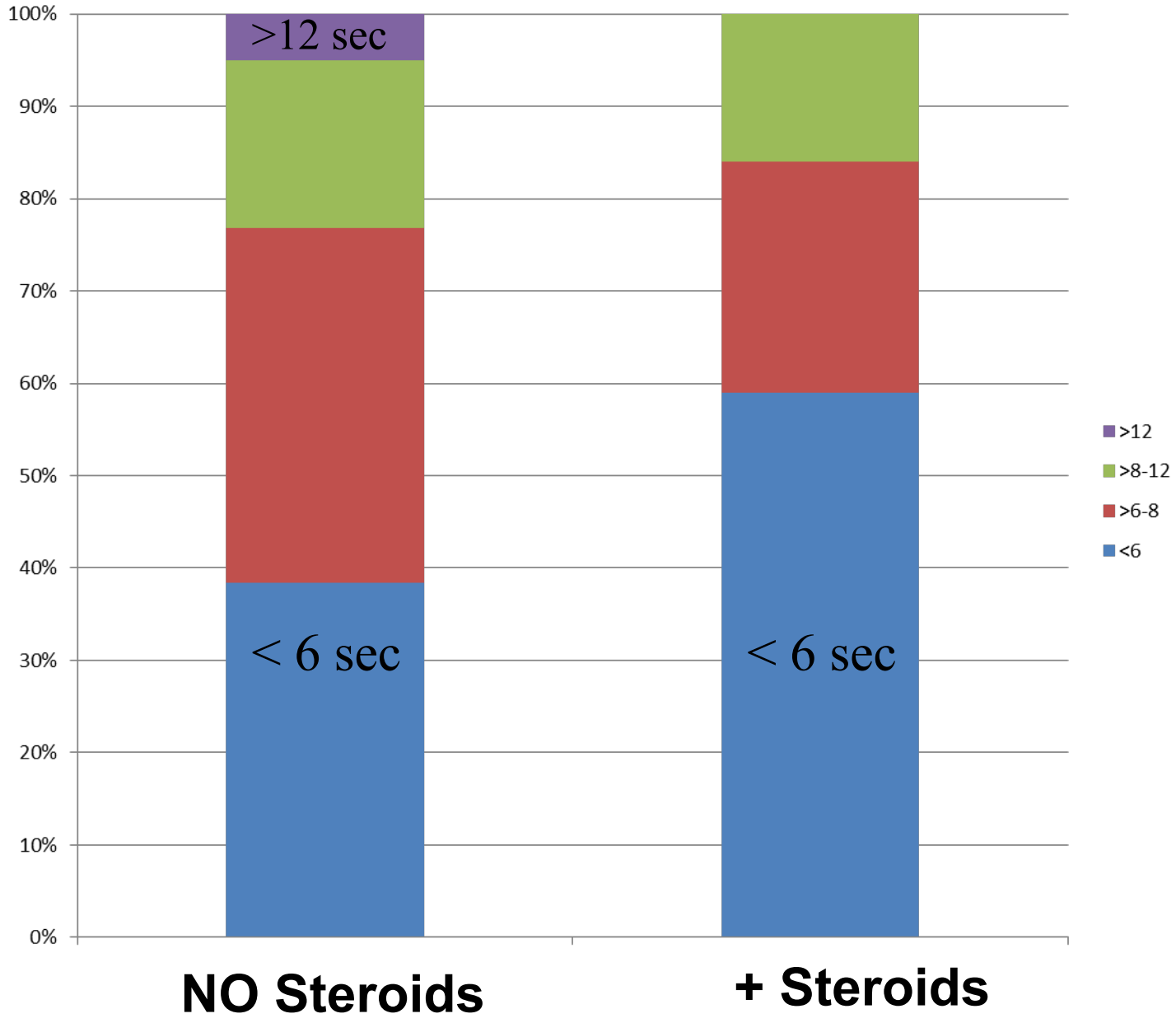


12-18 Month Risk of Loss of Ambulation based on10-Meter Walk Time

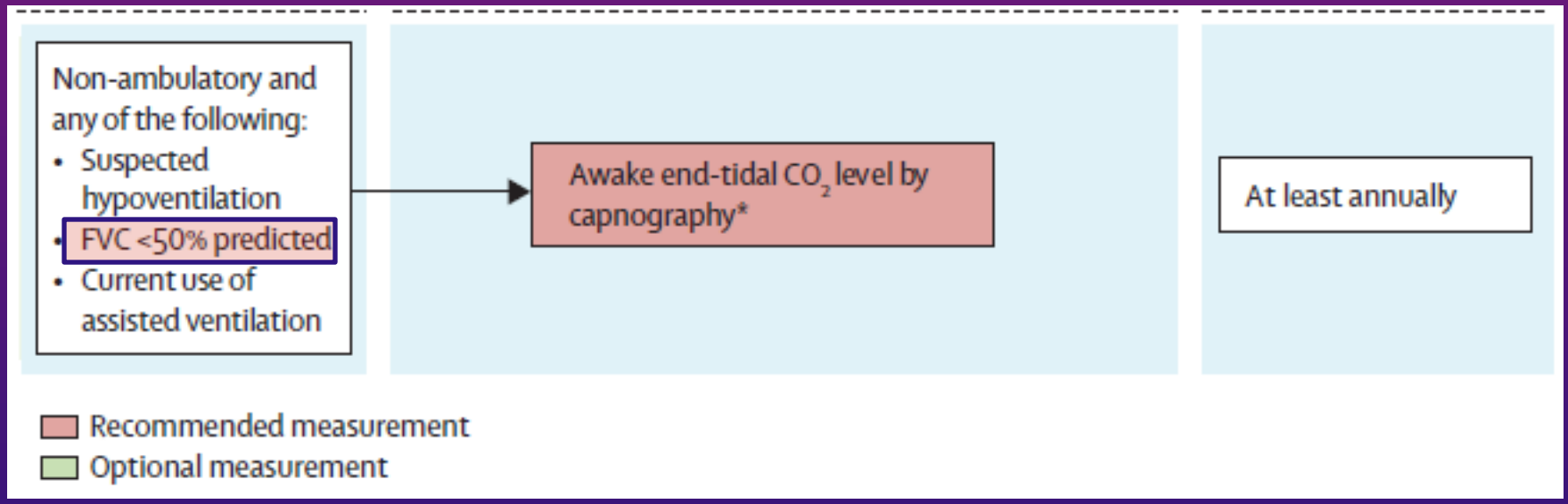


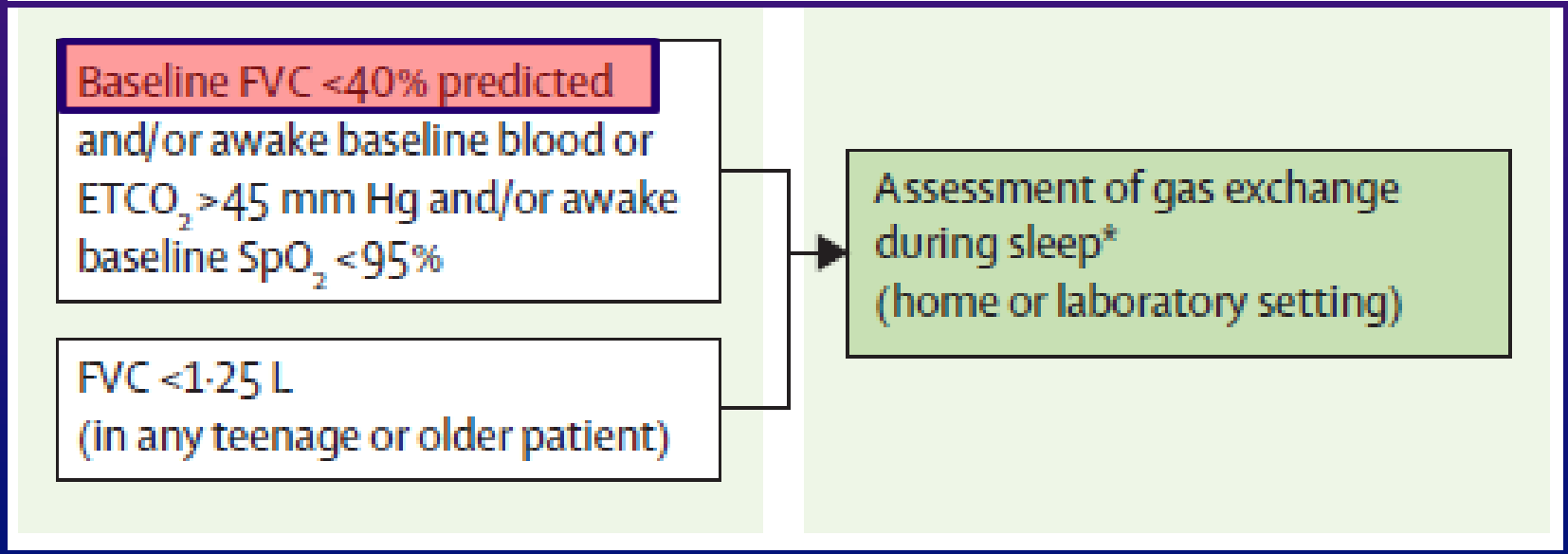
356 Meters
6MWD

Timed Function Testing in 4-6 Year Olds with DMD

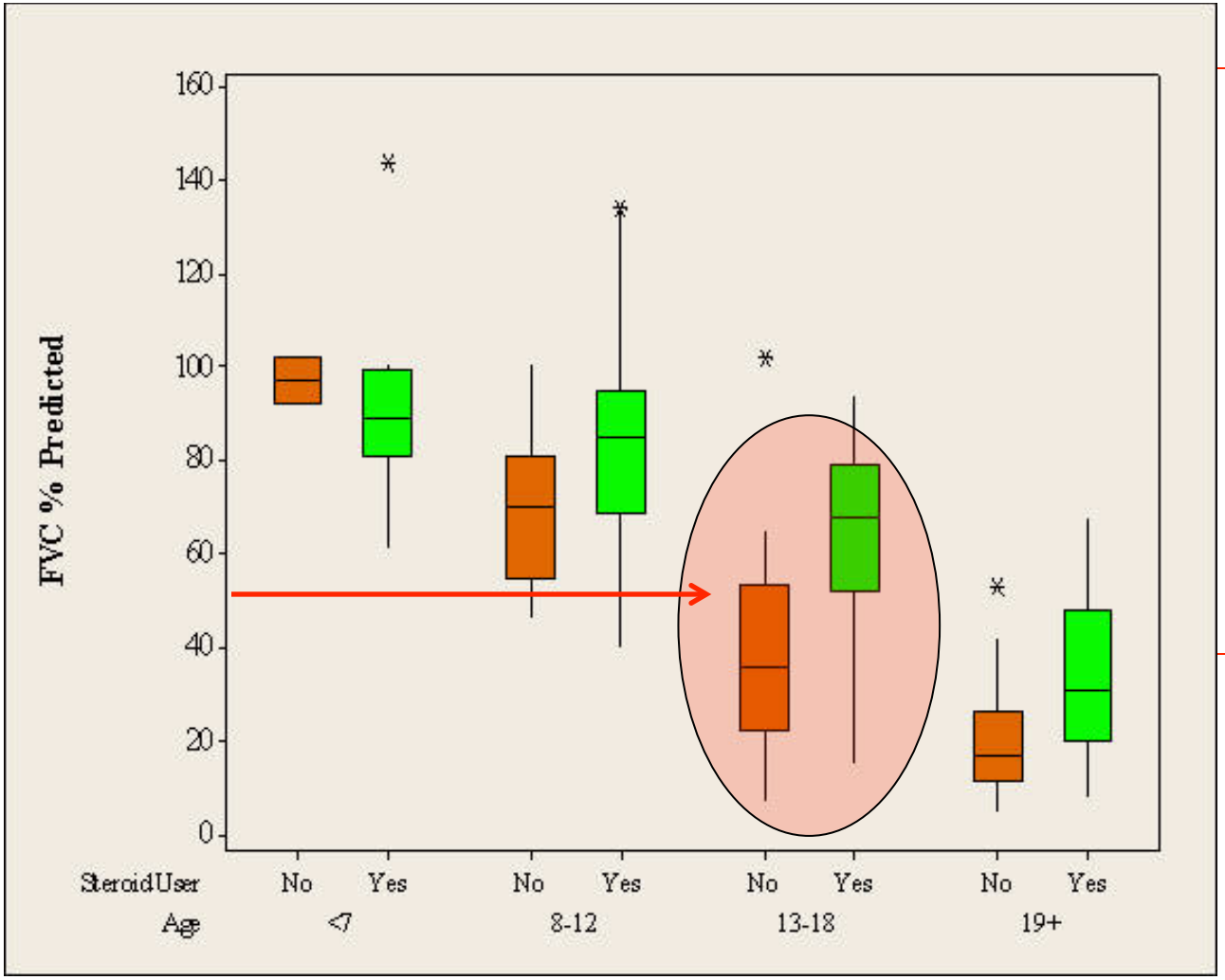


American Thoracic Society Consensus Statement (2004) DMD Care Considerations (2009)





FVC % Predicted



Glucocorticoids / Steroids and Spine Deformity

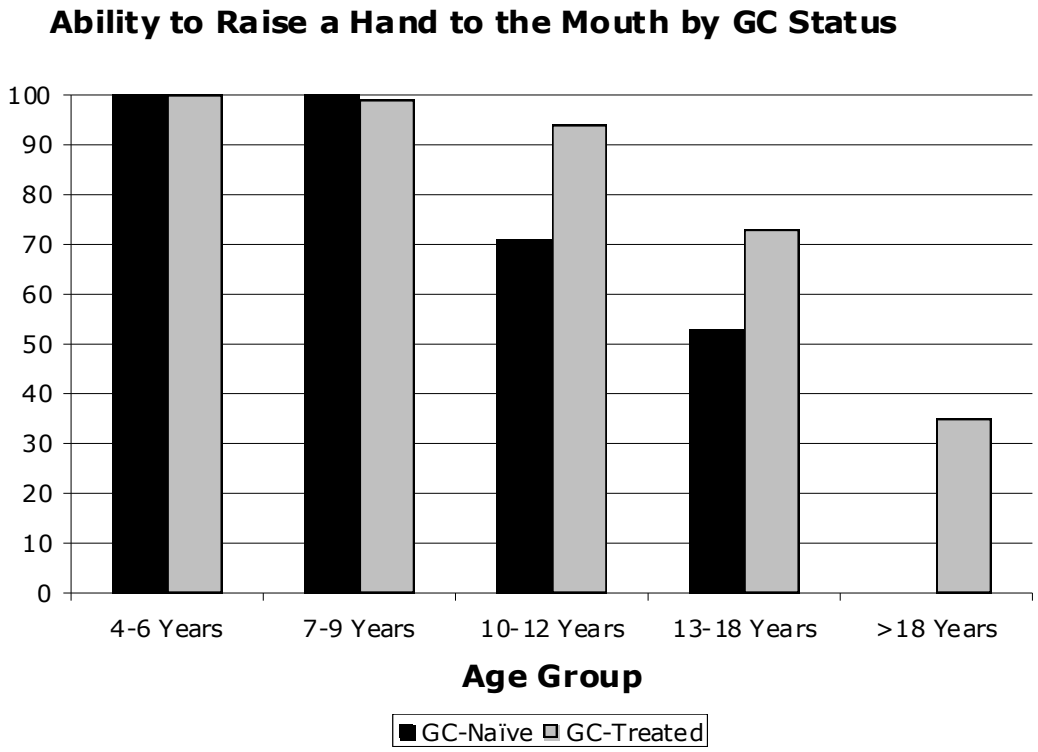
- Deflazacort in DMD: a comparison of two different protocols. Biggar, et al. Neuromuscular Disorders. 14(8-9):476-82, 2004

- 0.9 mg/kg/d
  - 77% ambulatory at 15 years vs. 0% (no steroids)
  - 16% developed scoliosis vs. 90% (no steroids)

  - 30% asymptomatic cataracts

-

Preserving Upper Extremity Function



Interventions to Maximize Independence in Children with DMD

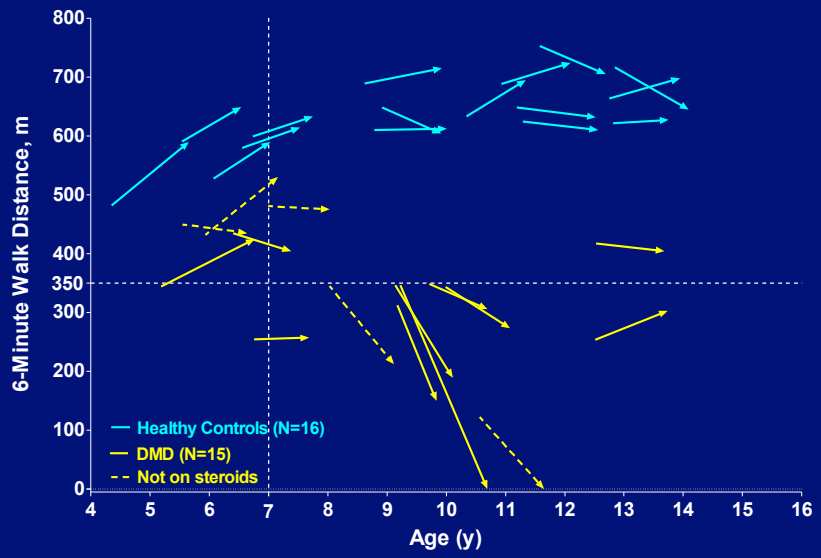
Assess patients objectively (using core clinical measures) to:

- determine prognostic features
- assess response to therapeutic interventions
- plan for the future and provide anticipatory guidance to families

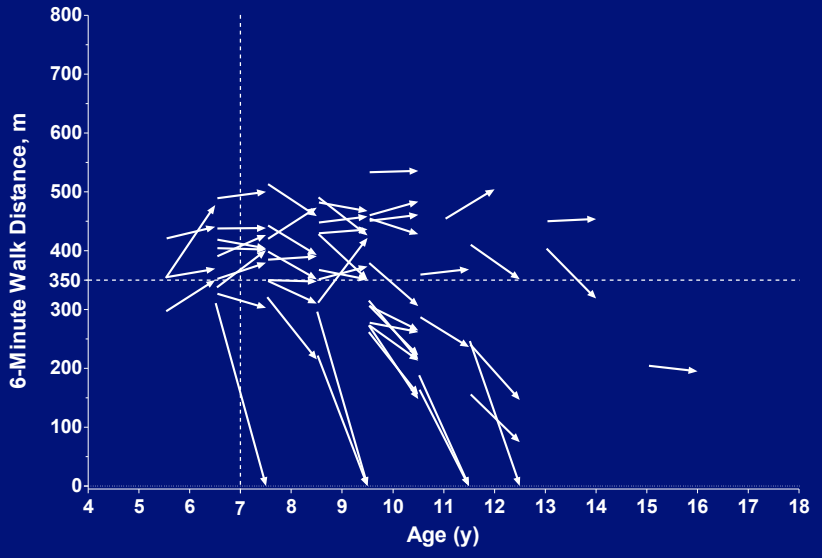
Core Measures (Clinic)	Clinical Trials
Standing Time (from supine)	6MWD
4 Stair Climb	Northstar
10 meter walk /run	Patient reported Outcome measures
PFTs	Novel Upper Extremity measures

Natural History of 6MWT Findings in DMD

Observational Study



Ataluren trial N=57



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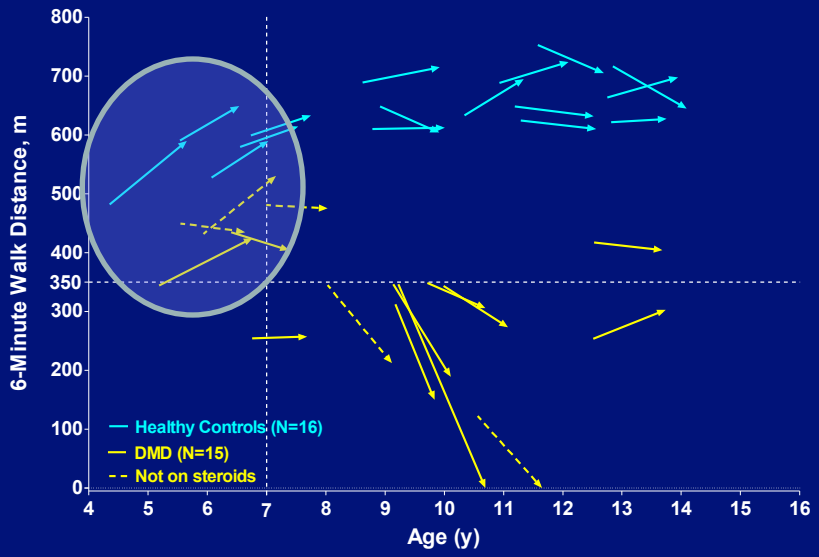
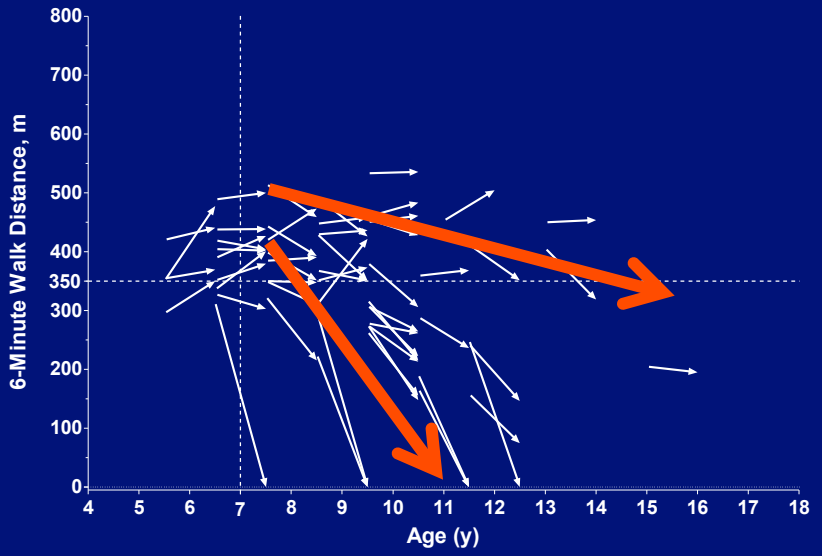


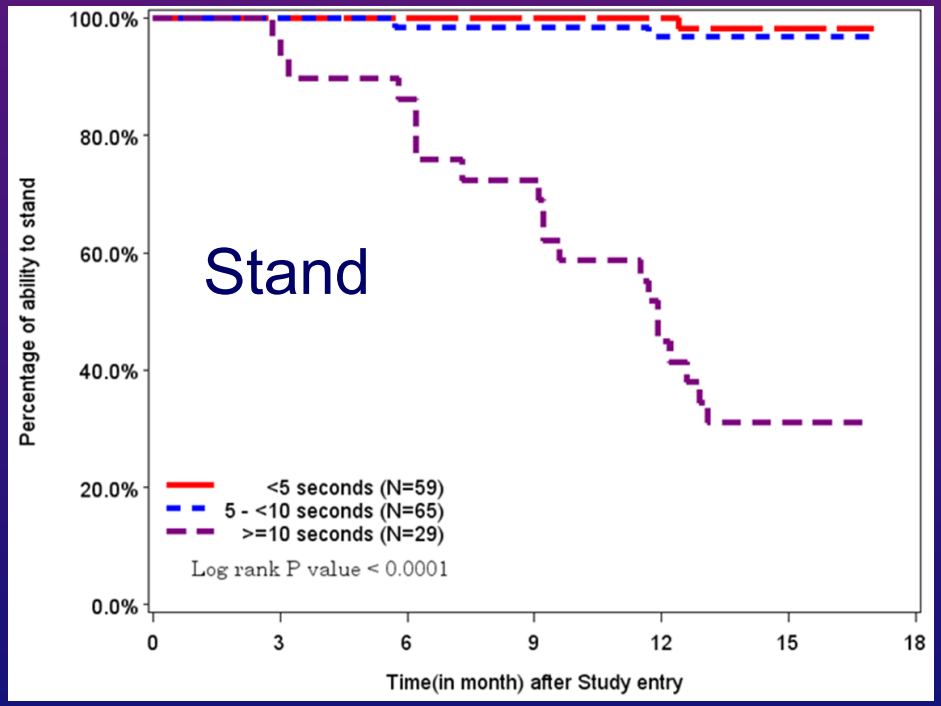
Maturational Issues

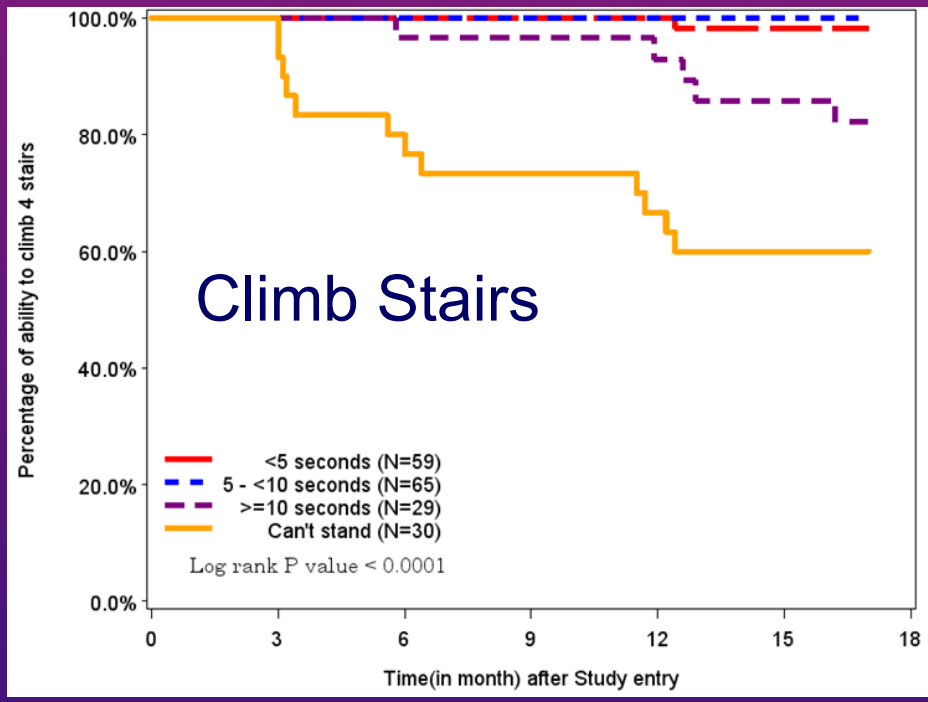
Ataluren trial N=57

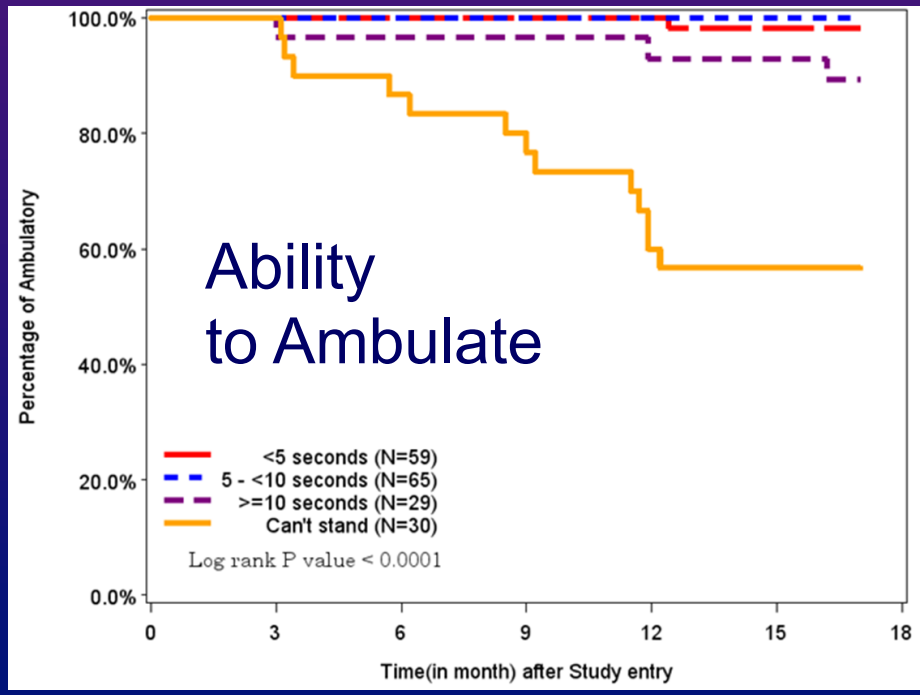


Variability Issues

Time to Stand Predicts Loss of ability to Stand Climb Stairs and Walk independently in DMD





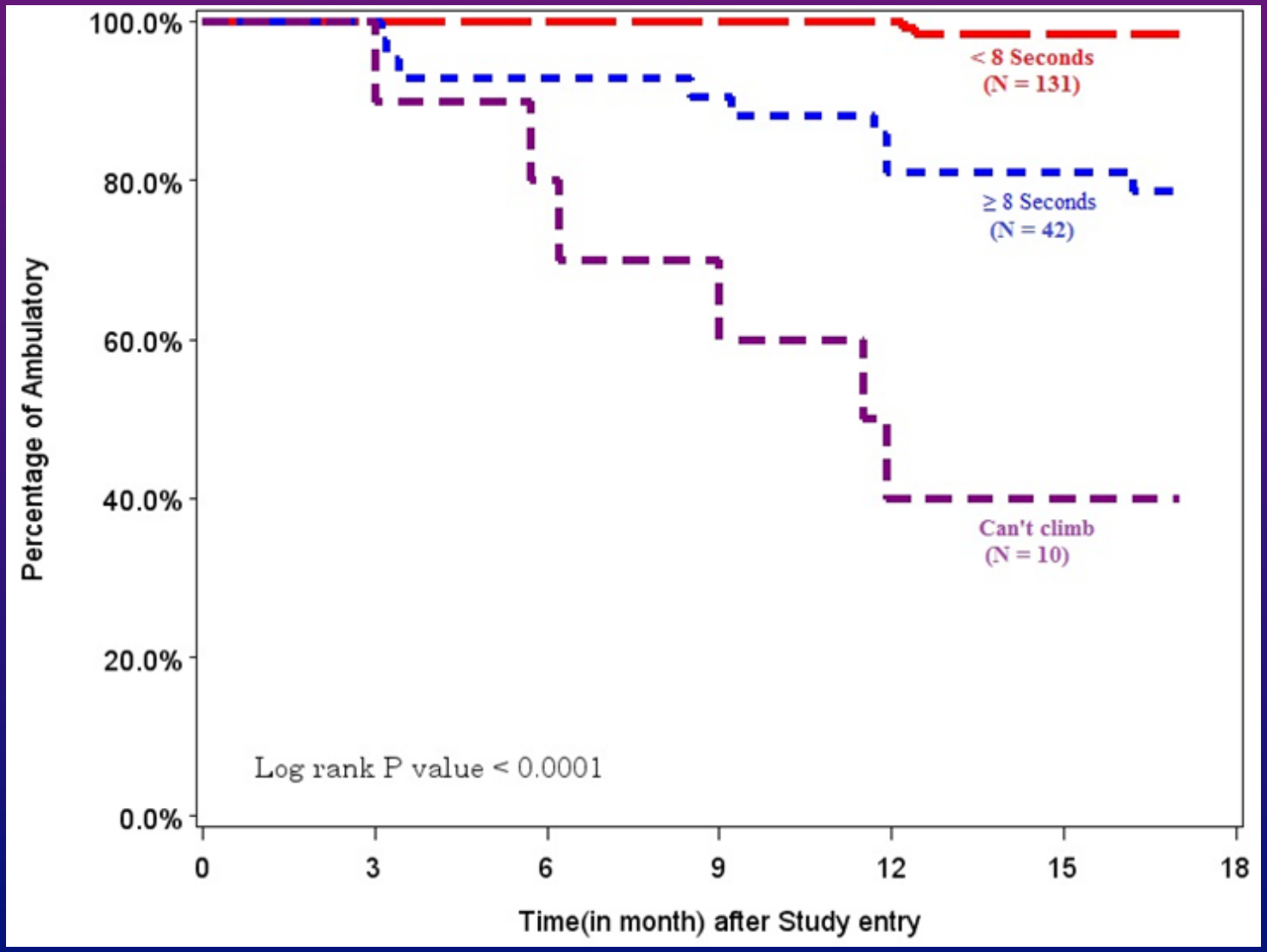


Ability to Stand as a Predictor of Loss of Ambulation (PTC Ataluren Trial)

- Lost Standing at baseline → 14 / 30 (46.7%) Lost Ambulation over 48 weeks
- Able to stand at baseline → 1 / 144 (0.7%) Lost Ambulation over 48 weeks

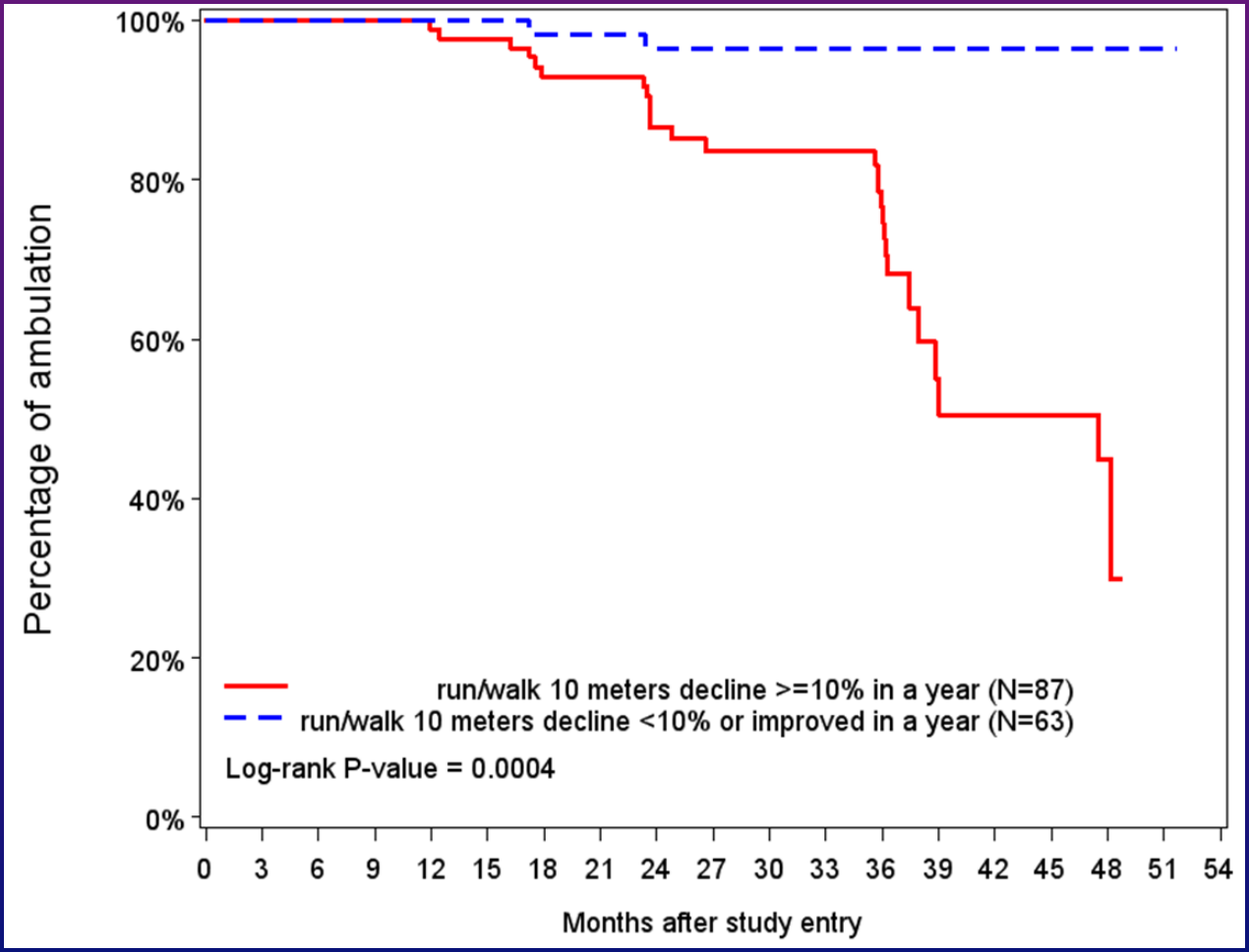
$P < 0.0001$

Time to Climb 4 Stairs predicts Loss of Ambulation in DMD

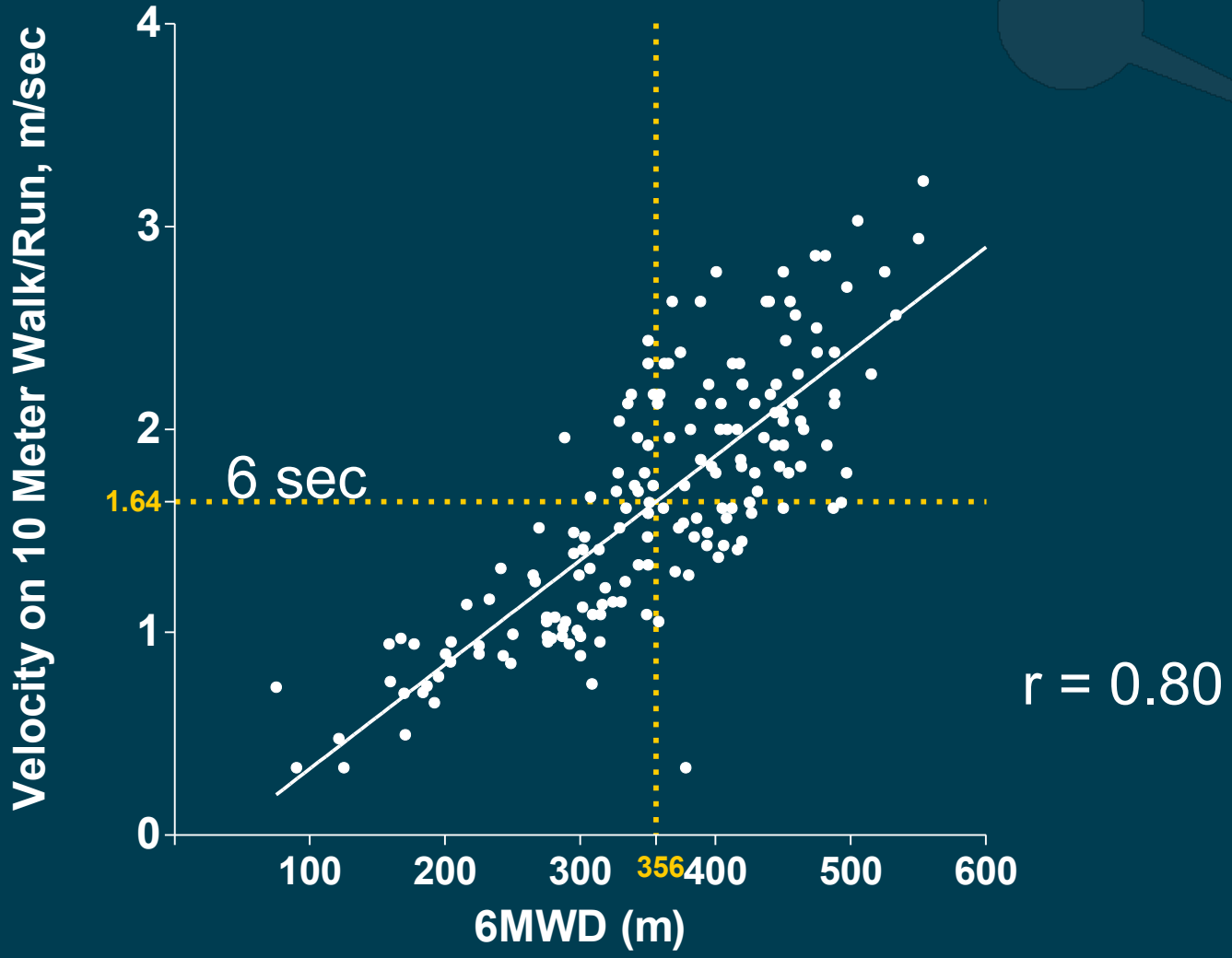


Magnitude of loss of walking ability over 1 year predicts the loss of ambulation over 4 years:

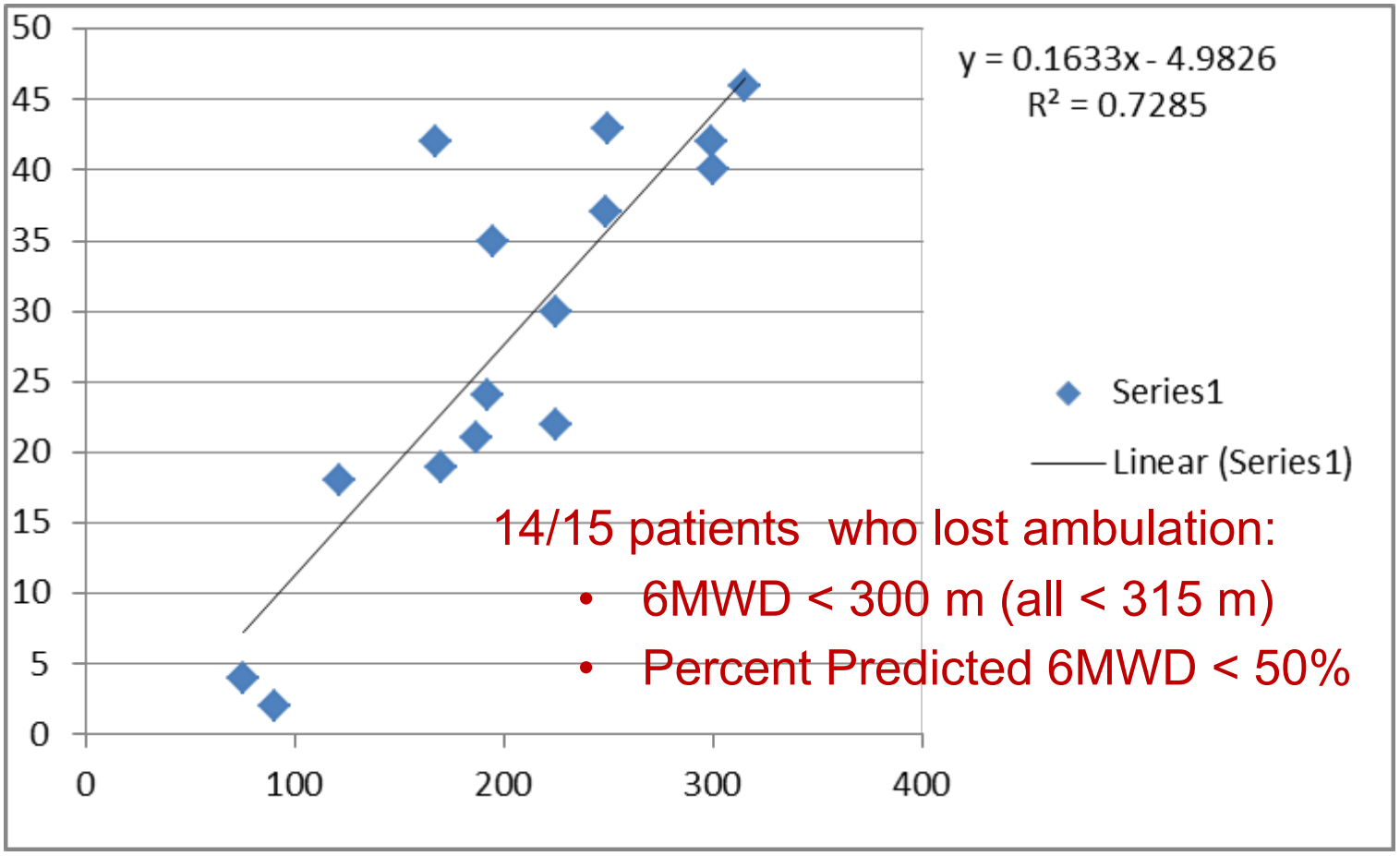
< 10% decline versus ≥ 10% decline in one year



Velocity During 10-Meter Walk/Run vs 6MWD at Baseline

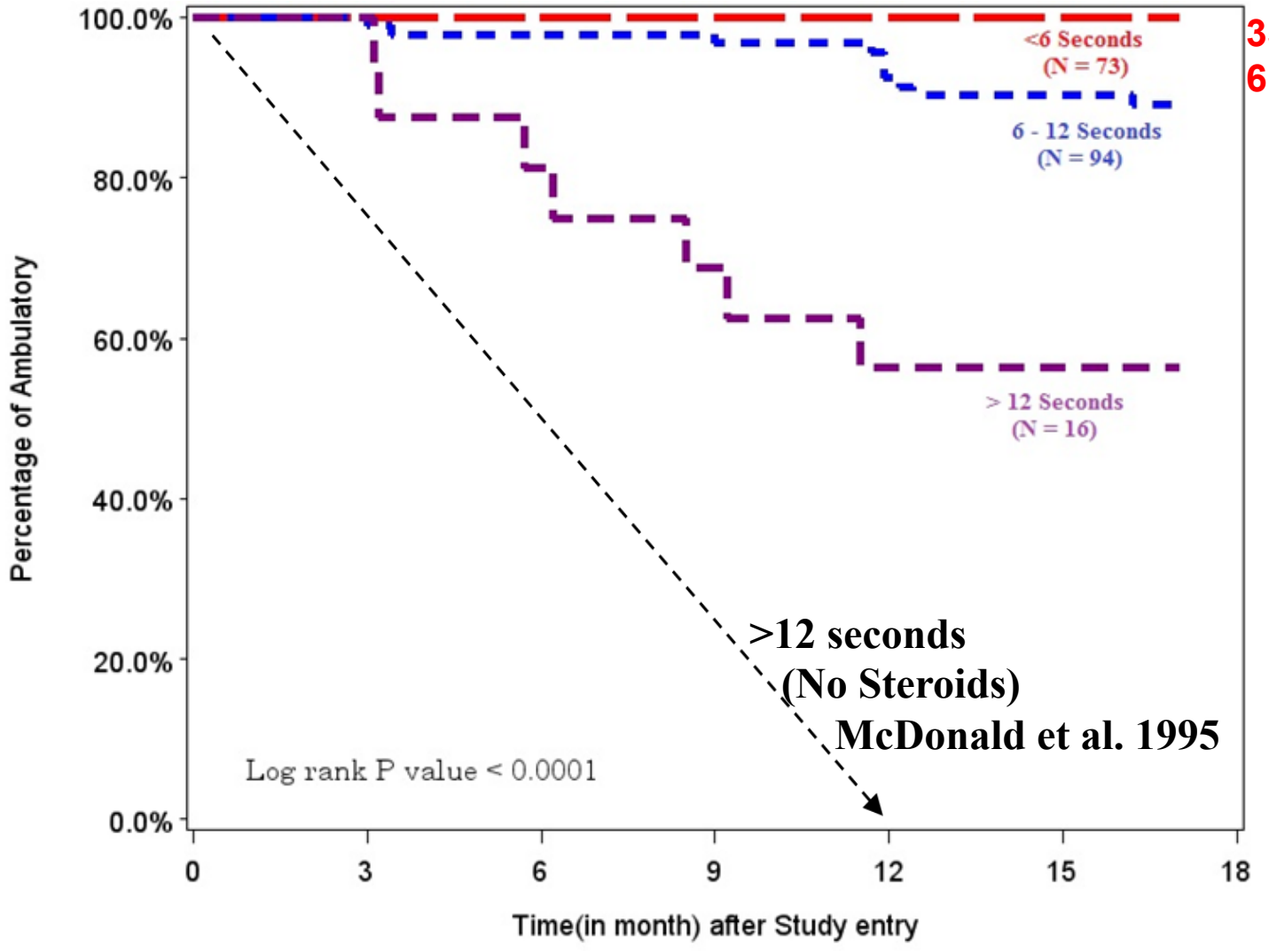


6MWD as a Predictor of Loss of Ambulation (PTC ataluren trial)



Baseline 6MWD in DMD subjects who lost ambulation

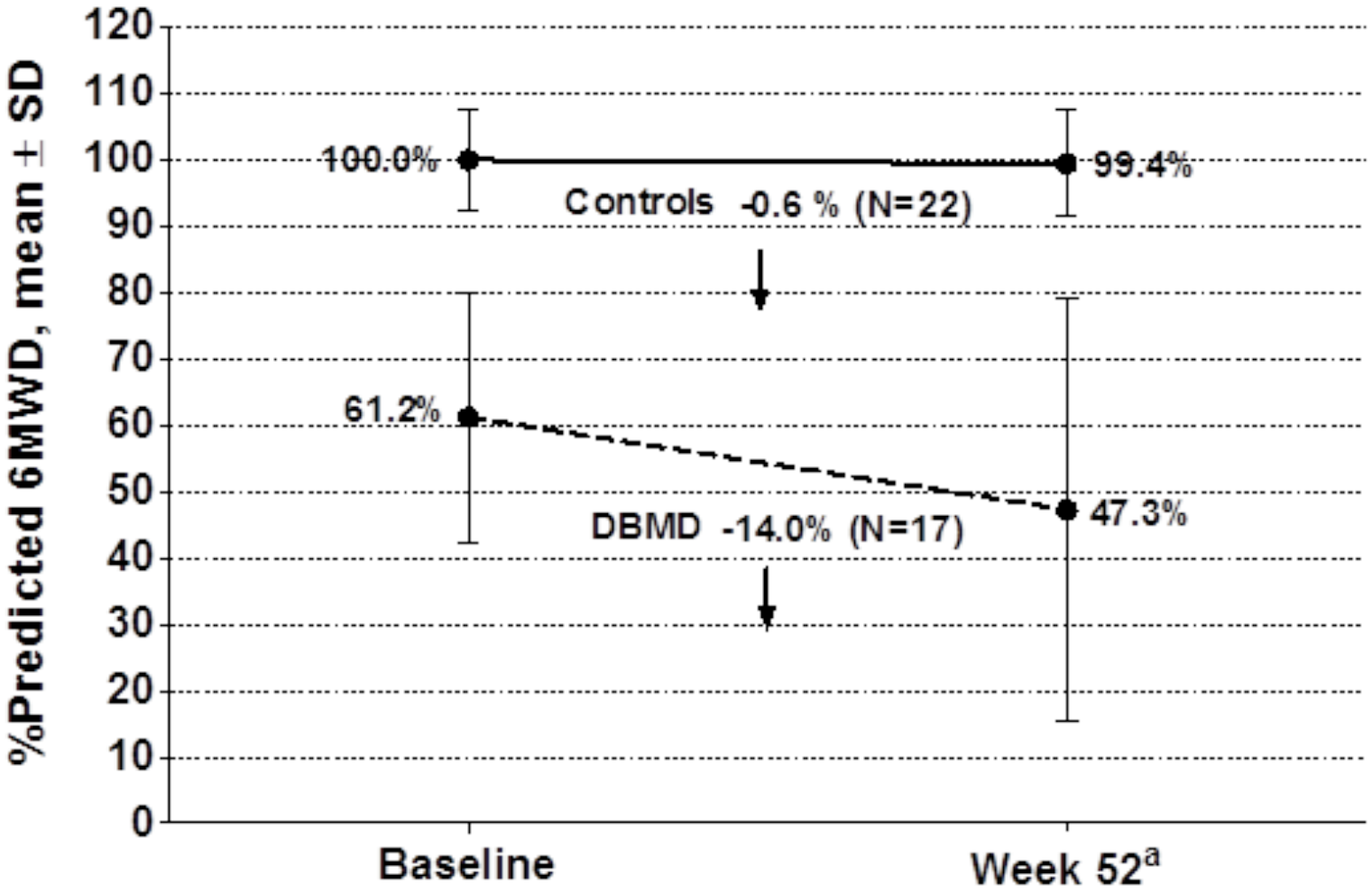
12-18 Month Risk of Loss of Ambulation based on10-Meter Walk Time



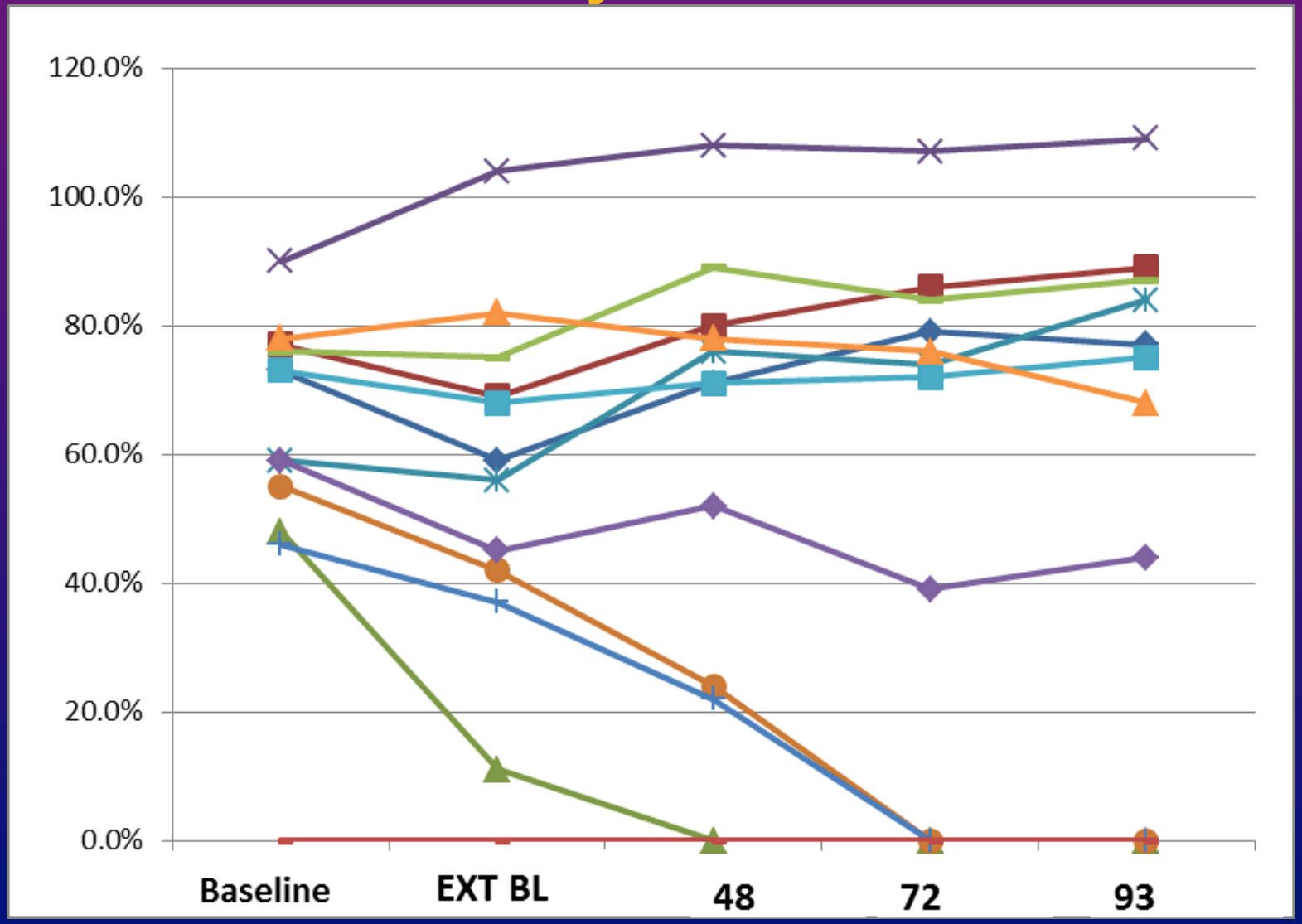
356 Meters
6MWD

Percent Predicted 6MWD to Account for Maturational Influences

(Henricson et al. PLoS Curr. 2012 Jan 25;3:RRN1297)



% Predicted 6MWD in Prosensa Extension Study (PRO 051 X 93 weeks)

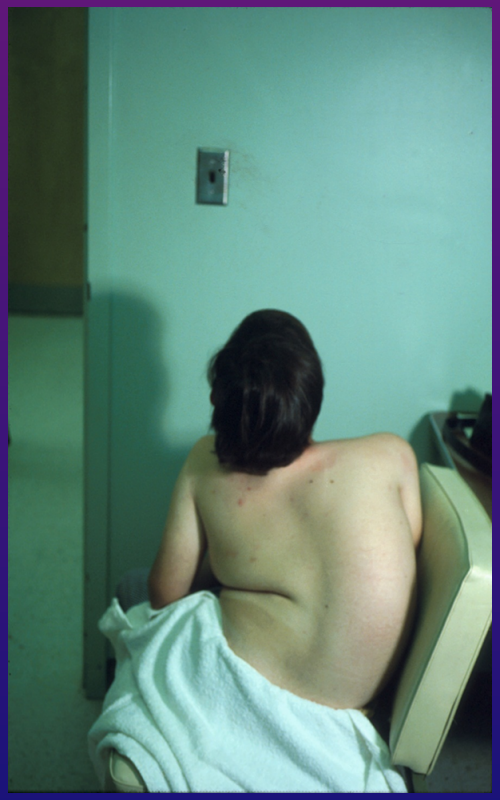


6MWT: Meaningful Clinical trial Endpoint in DMD

- Randomized studies of other FDA approved agents have shown baseline mean 6MWDs in drug-treated patients relative to placebo-treated patients increased by 8-13%

- What is "clinically meaningful" for Duchenne:
  - Approximately 30 meter improvement in 6MWD
  - Prevention of 10% decline in 6MWD over 1 year
  - 5% effect size in % predicted 6MWD
  - Time to 50% Predicted 6MWD

Prevention and management of spine deformity determined by Natural history



DMD

Scoliosis is a 2nd decade phenomenon
Usually occurs about 3 years after transition to wheelchair (in those not on steroids)

Posterior Spine Fusion for Scoliosis > 30 °

Optimally performed when % FVC > 40%
May be done for those with FVC below 30% with pulmonary interventions

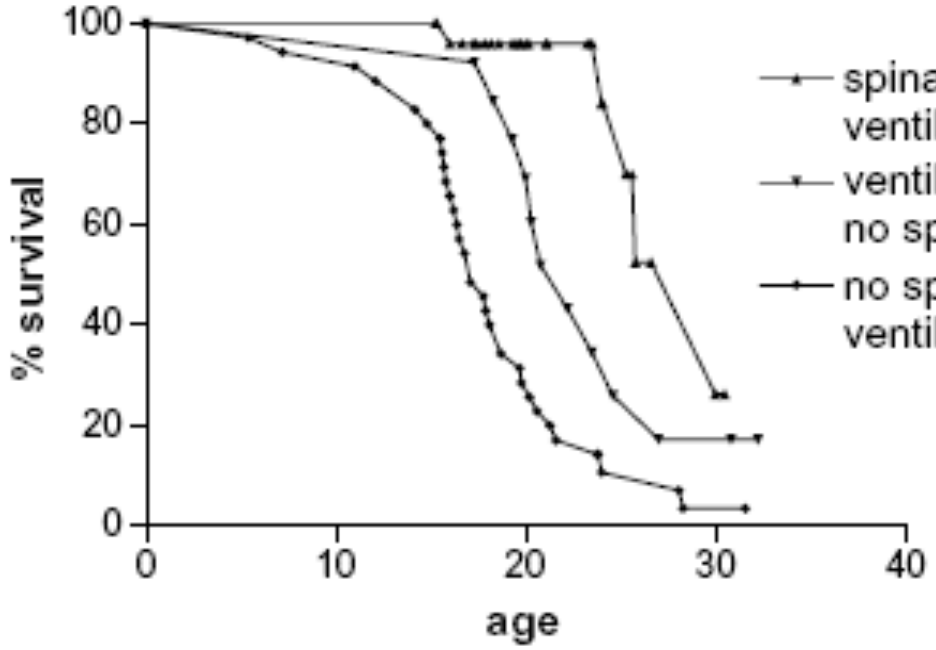


Fig. 3. Kaplan–Meier survival plot to show the impact of spinal surgery and ventilation on survival. Survival curves are significantly different $p = 0.0001$.

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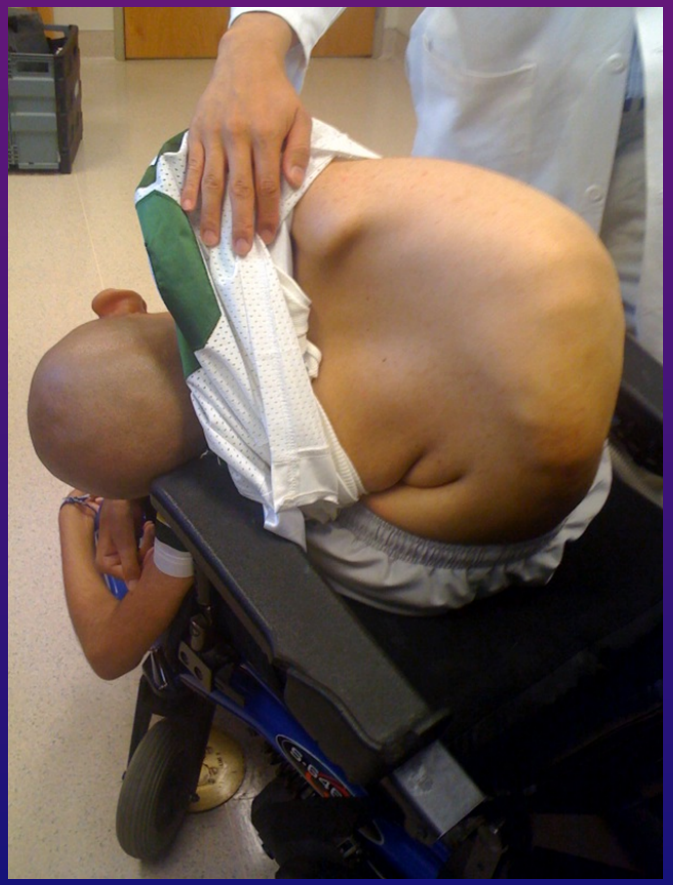
- Neuromuscul Disord. 2007 Jun;17(6):470-5.

Rationale for Spine fusion in DMD

- Preservation of Thoracic Lung Volumes
- Sitting balance
- Comfort / Pain
- Ability to sit in power wheelchair long-term

- Quality of life



20 y.o. Hispanic spanish-speaking patient referred to UC Davis in 2011 from Southern California.

Growth and Weight Gain in DMD

Short Stature and weight gain in DMD due to disease and corticosteroids

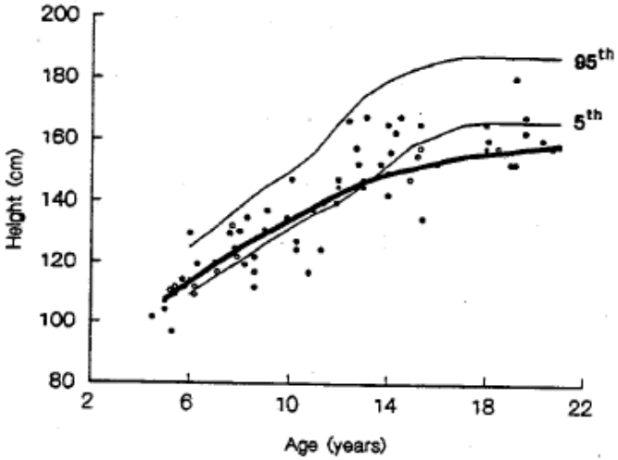
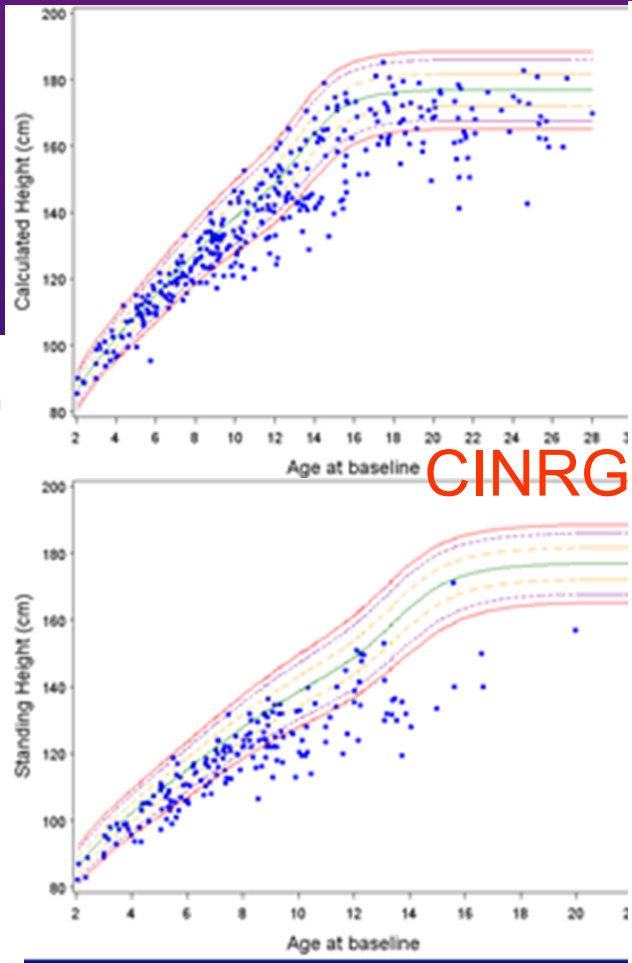
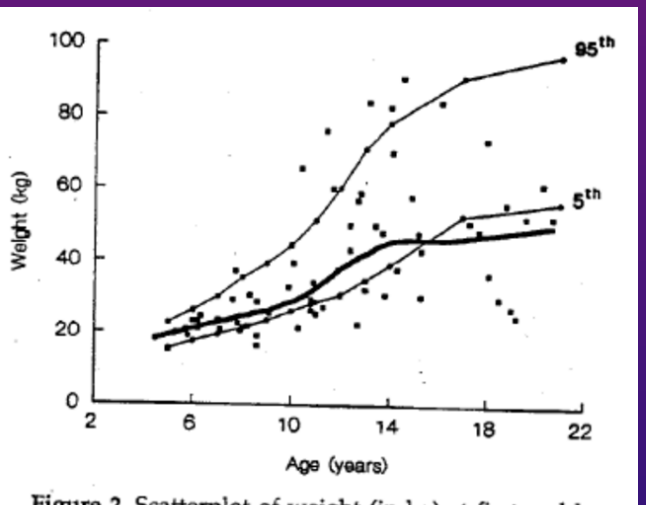


Figure 1. Scatterplot of height (in cm) at last examination by age in DMD *v* the 5th and 95th percentiles for the normal population. The *bold line* represents the Lowess regression for height.



CINRG



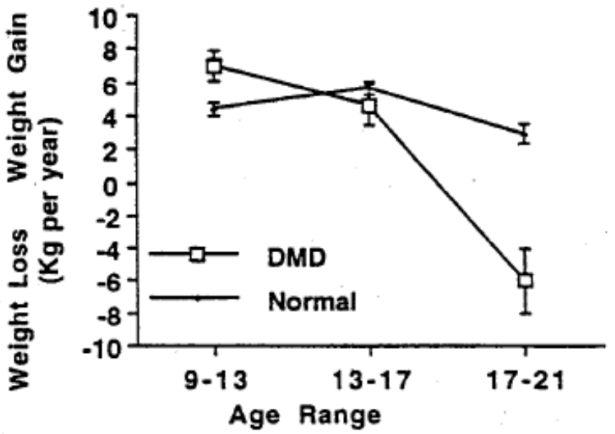


Figure 3. Average rates of weight gain or weight loss (in kg per year) for DMD (*open squares*) and normal controls from ages 9-13, 13-17, and 17-21.

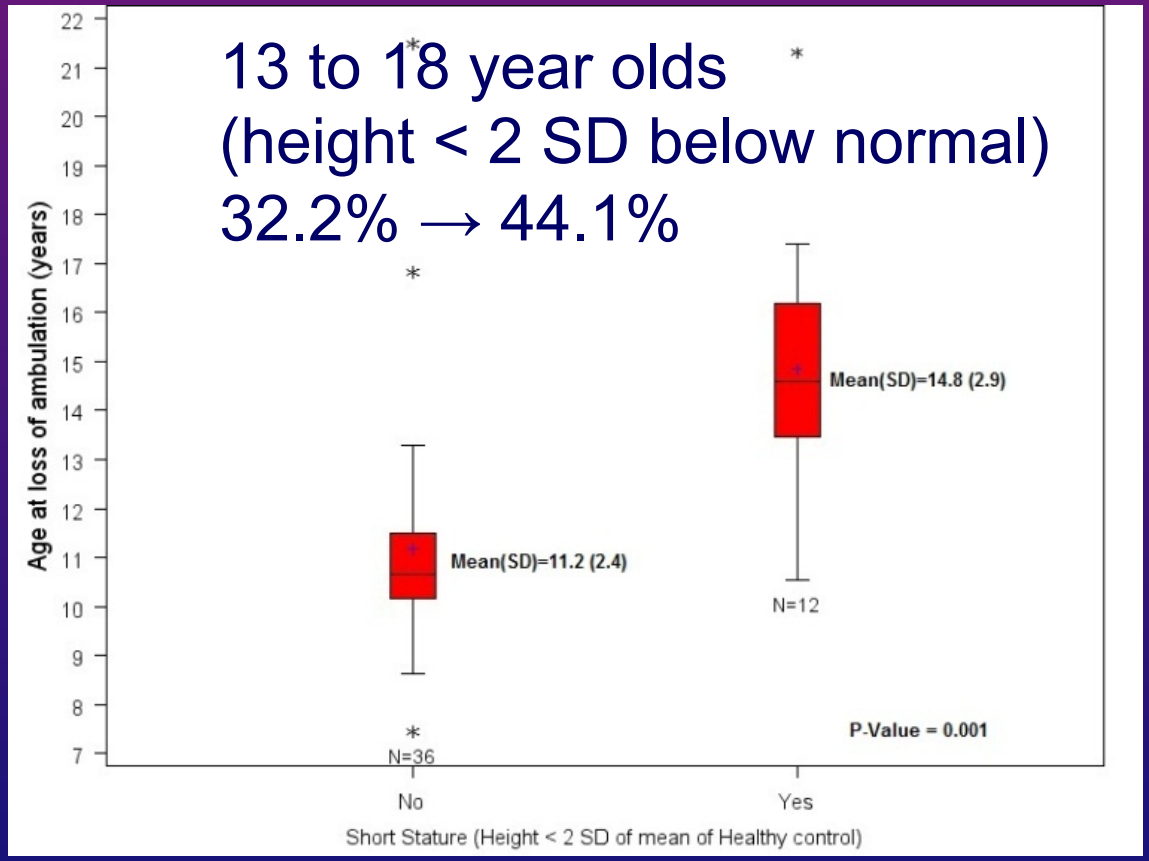
Steroid Naive + Steroid

When to start Corticosteroids in DMD?
Merlini et al. (in press Muscle & Nerve)

- Prospective long-term, open label study of low-dose, alternate-day, corticosteroids starting in boys aged 2-4 years old with Duchenne muscular dystrophy (DMD).
- 4 out of 5 boys started early on corticosteroids (ages 2.4 to 4.0 years) did better than those whose families opted for later initiation or no treatment.
- 4 of 5 continued ambulation beyond age 16 years
- Permanent linear growth retardation
  (3.01-4.77 S.D. below population-based normative data)

Loss of Ambulation and Short Stature

(defined as standing or calculated height less than two standard deviation below normal)



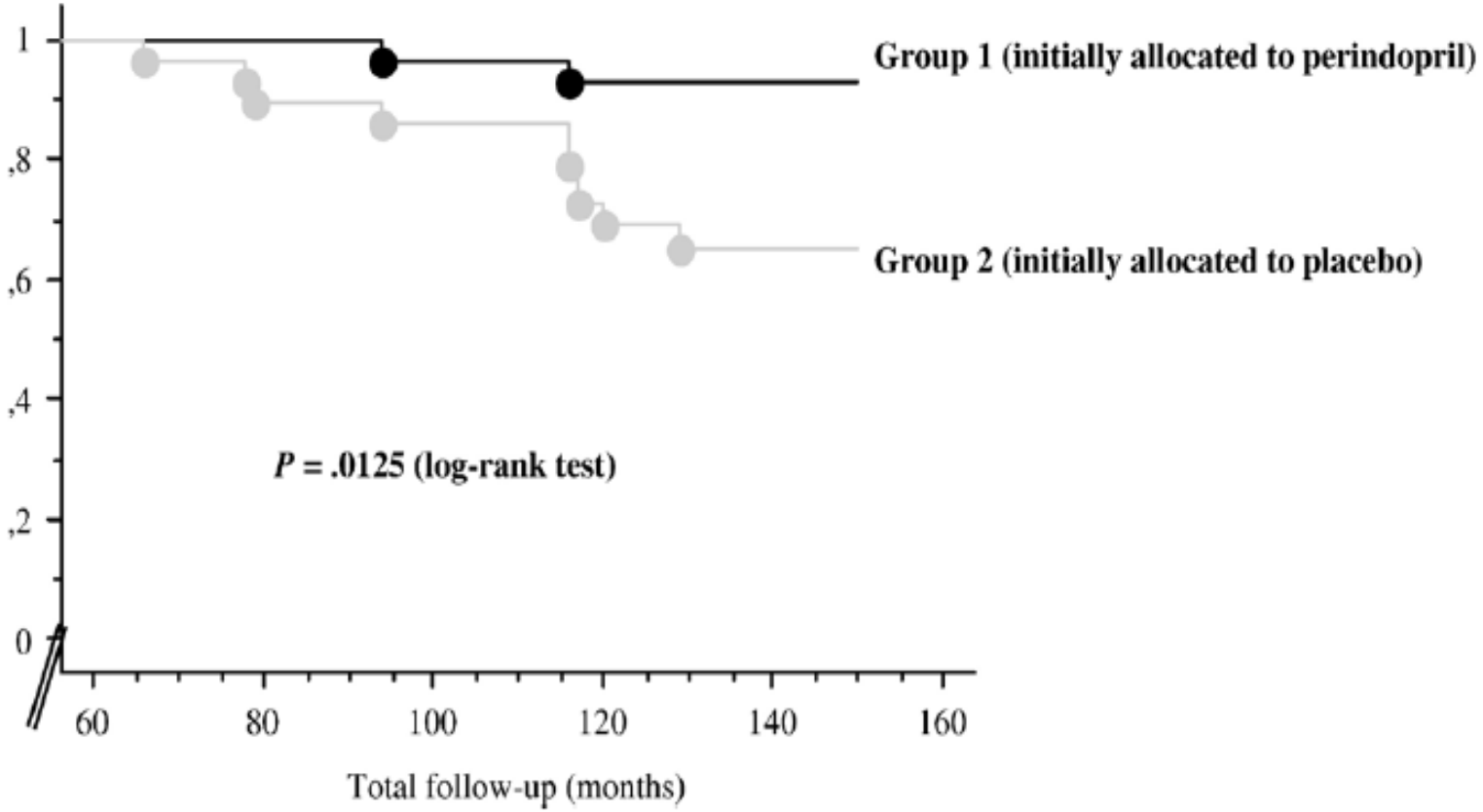
(CINRG DMD Natural History Study)

- Is short stature a biologic signal for corticosteroid activity?
- Are there biomechanical advantages to short segment lever arms?

Cardiomyopathy in DMD

- Clinically significant cardiomyopathy rare before age 10; MRI changes common
- Fibrosis posterior wall left ventricle
- Myocardium exhibits abnormal contractility
- Arrythmias

- Treatment: Early ACE Inhibitors; Evidence Class Ia
  - enalapril, lisinopril, perindopril
- ? ARBs (Losartan)
- ? Beta Blockers (metoprolol, carvedilol)
- ? Aldosterone receptor antagonists (Spironolactone)
- ? Diuretics (Furosemide, Thiazides)



- Perindopril preventive treatment on mortality in Duchenne muscular dystrophy: 10 years' follow-up.
- Duboc D, et al. Am Heart J. 2007 Sep;154(3):596-602.

Measuring Effective Care in DMD

- Quality of Care
- *Comparative Effectiveness Research*

- Measure *Effectiveness* — benefits the treatment produces in routine clinical practice.
- Quality of Care Indicators
- Process Measures: Use of Steroids, PFTs, Spine X-Ray, Surgery Offered, use of Airway Clearance, NIPPV
- Outcomes: Spine surgery Complication rates, Survival

Interventions have Impacted Natural History

1) Corticosteroids

2) Spine Management

3) Pulmonary
   Airway Clearance
   Noninvasive Ventilation

4) Cardiac Management

Key:
Communication & Coordination

Measuring Effective Care in DMD

1) Glucocorticoids

Process: % treated > Age 6 (70% benchmark)

Appropriate monitoring for complications (e.g. DEXA, Ophthalmology?)

Discontinued after loss of ambulation?

2) Spine Care:

Process: Spine radiographs obtained at recommended interval?

Fusion offered if Cobb > 30 degrees?

Outcomes: Survival / discharge home without ventilation

Measuring Effective Care in DMD

3) Pulmonary: Airway Clearance

Process: PFTs, Static Airway Pressures, Peak cough flow?

Respiratory infections? If yes:

Pulse Oximetry if Peak cough flow < 270

End tidal CO2 if FVC < 50%

Use of Mechanical Cough Assistance?

Baseline peak cough flow <160 L/min
MEP <40 cm water

Baseline FVC <40% predicted or <1.25 L

Measuring Effective Care in DMD

3) Pulmonary: Noninvasive ventilation

Process:

Serial FVCs, baseline SpO_2; blood or end-tidal CO_2

Proportion with %FVC < 30% on Nocturnal Non-invasive ventilation

Measuring Effective Care in DMD

4) Cardiac management

Process:

- Regular Cardiac Echo, EKG, Holter done?
- Percent of patients > 9 years on ACE inhibitors

5) Communication / Coordination

Process: Communication with PMDs

Meaningful Use / EHR

Data sharing with patient / family

Emergency Preparedness

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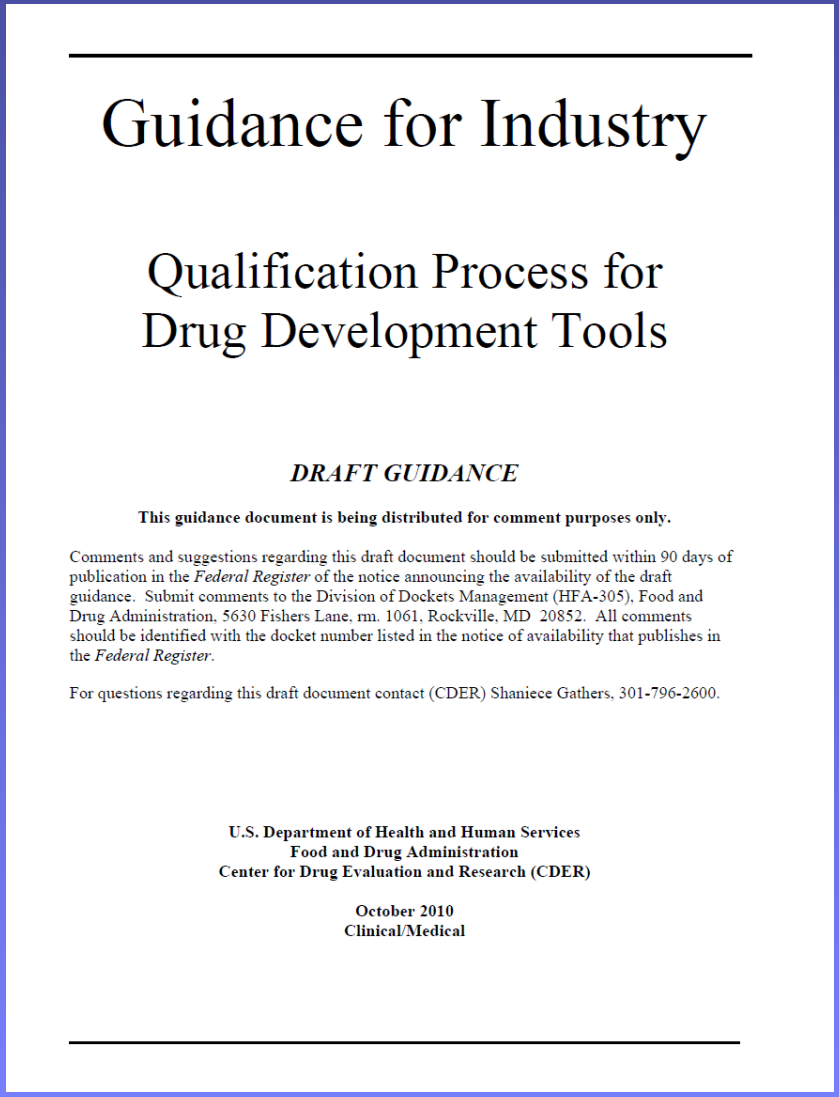
Clinical Trial Endpoints

- FDA Clinical Endpoint Qualification Process
- "Clinically Meaningful"
- Related to Patient-reported Outcomes



Guidance for Industry

Qualification Process for Drug Development Tools

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Shaniece Gathers, 301-796-2600.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2010
Clinical/Medical

Clinically Meaningful Milestones

- Ambulatory
- Stand from the floor
- Climb stairs
- Stand from a chair
- Walk independently (10 meter walk /run; 6MWD)
- Non-ambulatory
- Time to 50% FVC / 40% FVC (Cough Assistance; monitoring required)
- Reach overhead
- Reach the scalp
- Roll self in bed
- Self-feed without adaptations (hand to mouth)
- Hands to table top
- Computer use (distal hand function)
- Sustain adequate overnight ventilation without support (30% FVC milestone places patient at risk)
- Cardiac (Echo vs. Cardiac MRI)

Secondary Endpoints for Ambulatory DMD

- Timed function tests
- Northstar (Eagle, Mazzone)
- Strength testing
- Fall assessment
- MR imaging (Fishbeck, Vandenborne)
- Patient-reported outcomes (NeuroQoL, PODCI)
- Dystrophin / utrophin expression

- Lesson Learned: Limit the number; avoid exploratory endpoints that may be insensitive

CINRG Natural History Patient-Reported (PRO) instruments

- NeuroQOL
- PedsQL
- Neuromuscular Module PedsQL
- POSNA / PODCI
- Life Satisfaction Index
- Pittsburgh Sleep Quality Index
- SF-36
- WHO QOL-BREF
- NIFD Health Services Questionaire

Non-ambulatory endpoints in DMD

- PFTs
  - FVC, FEV1, PEFR, Peak Cough Flow, MIP, MEP
- Grip and Pinch Strength
- 9 Hole Peg Test

- Model change in PFTs with
  - Time to 50% / 40% predicted FVC
  - Time to 30% predicted FVC
  - Time to Peak Cough Flow (270 L/min; 160 L/min)

Volume of Reachable Workspace (UC Davis)

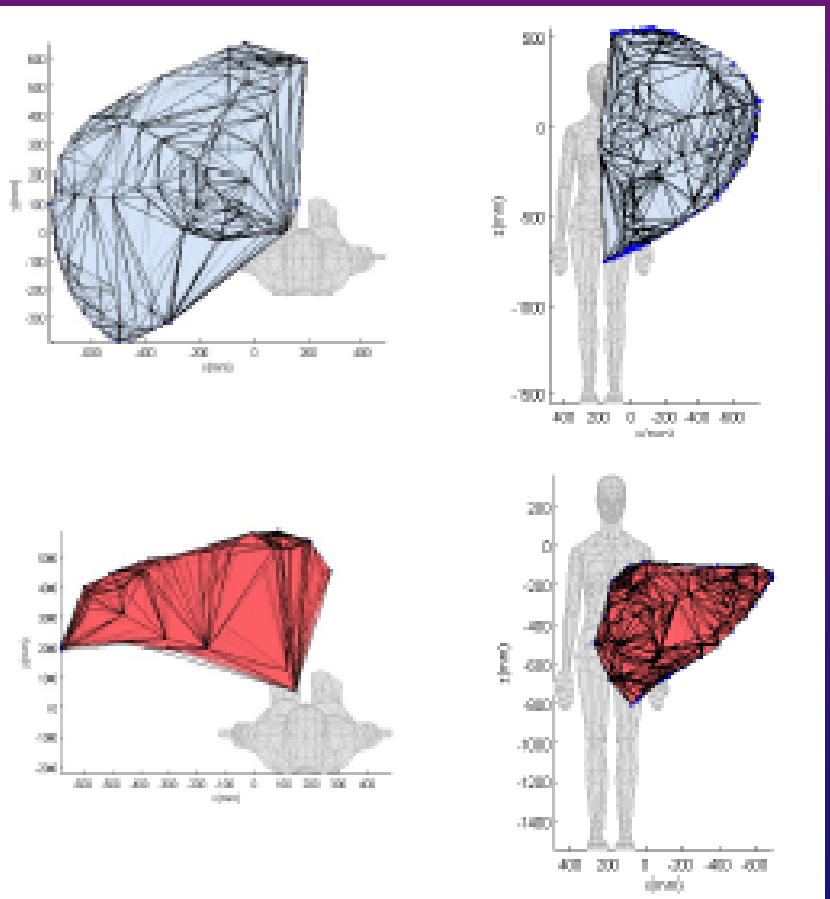


Figure 2: Measured reachable workspace in a healthy person (top) and a person with neuromuscular condition (bottom).

Clinical Research Articles

Quality-of-Life Measures in Children With Neurological Conditions: Pediatric Neuro-QOL

Neurorehabilitation and
Neural Repair
26(1) 36–47

DOI: 10.1177/1545968311412054
http://nnr.sagepub.com
SAGE

Jin-Shei Lai, PhD[1], Cindy Nowinski, MD, PhD[1], David Victorson, PhD[1], Rita Bode, PhD[1], Tracy Podrabsky[1], Natalie McKinney[1], Don Straube, PhD[2], Gregory L. Holmes, MD[3], Craig M. McDonald, MD[4], Erik Henricson, PhD[4], R. Ted Abresch, MS[4], Claudia S. Moy, PhD[5], and David Cella, PhD[1]

Pediatric NeuroQOL Domains (based on PROMIS items) Framework for Item Banks and Targeted Scales

PHYSICAL

Function/Health

- Mobility/Ambulation — B
- ADL's/UE's — B

Symptoms

- Pain — T
- Fatigue — T

MENTAL

Emotional Health

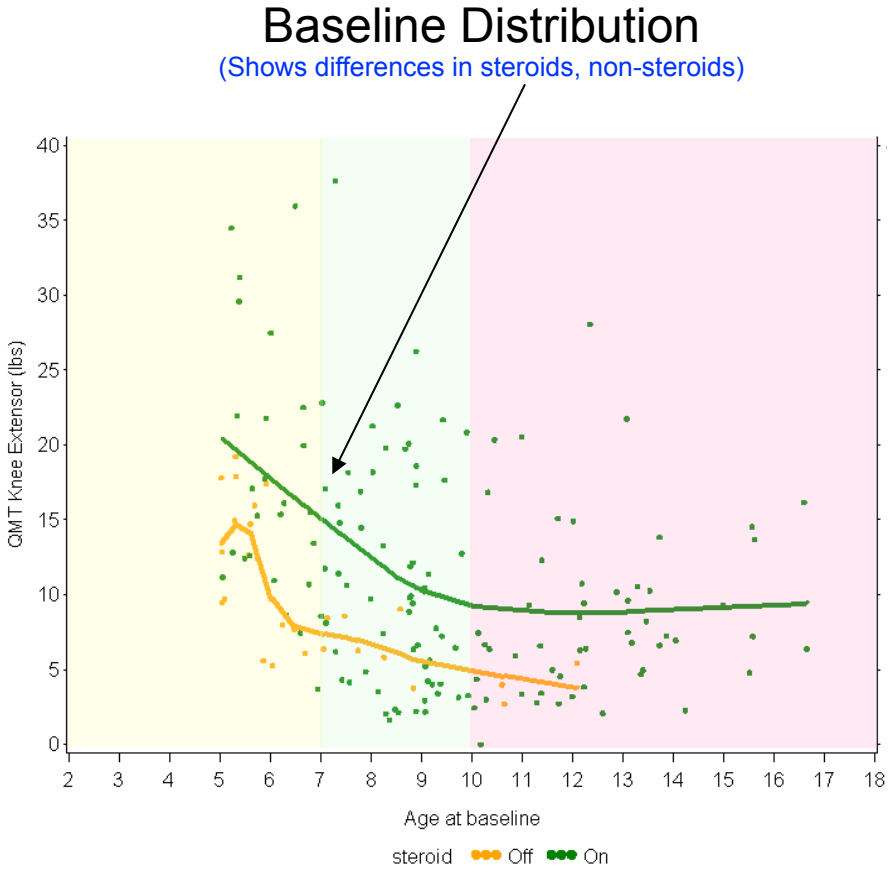
- Depression — B
- Anxiety — B
- Stigma — T

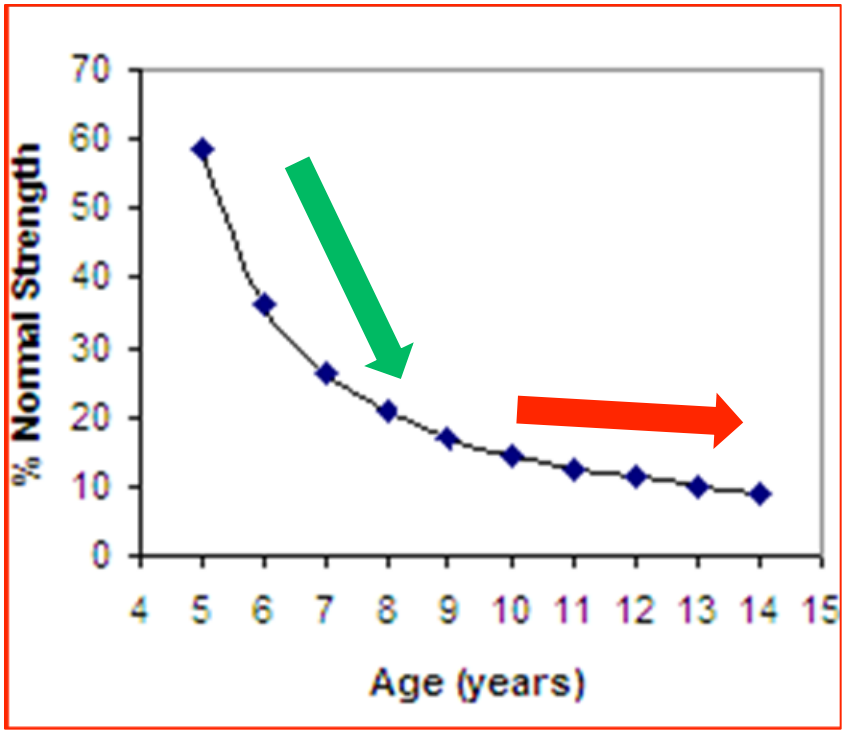
Cognitive Health — T

SOCIAL — B

B=Bank
T=Targeted Scale

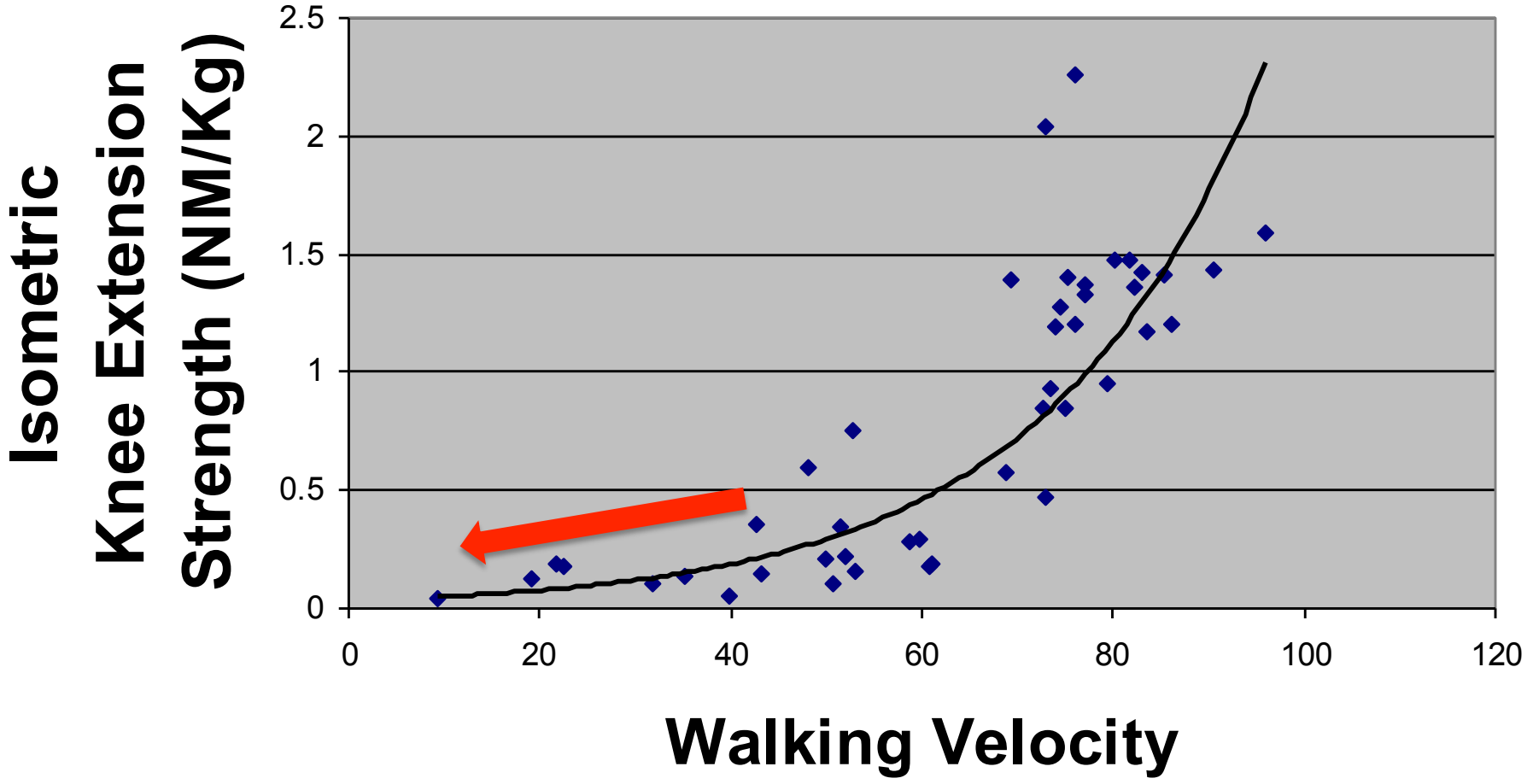
Strength: QMT Knee Extension*





* Previously shown to have the highest correlation with Vignos leg functional grade.

Quantitative Isometric Knee Extension Strength vs. Walking Velocity



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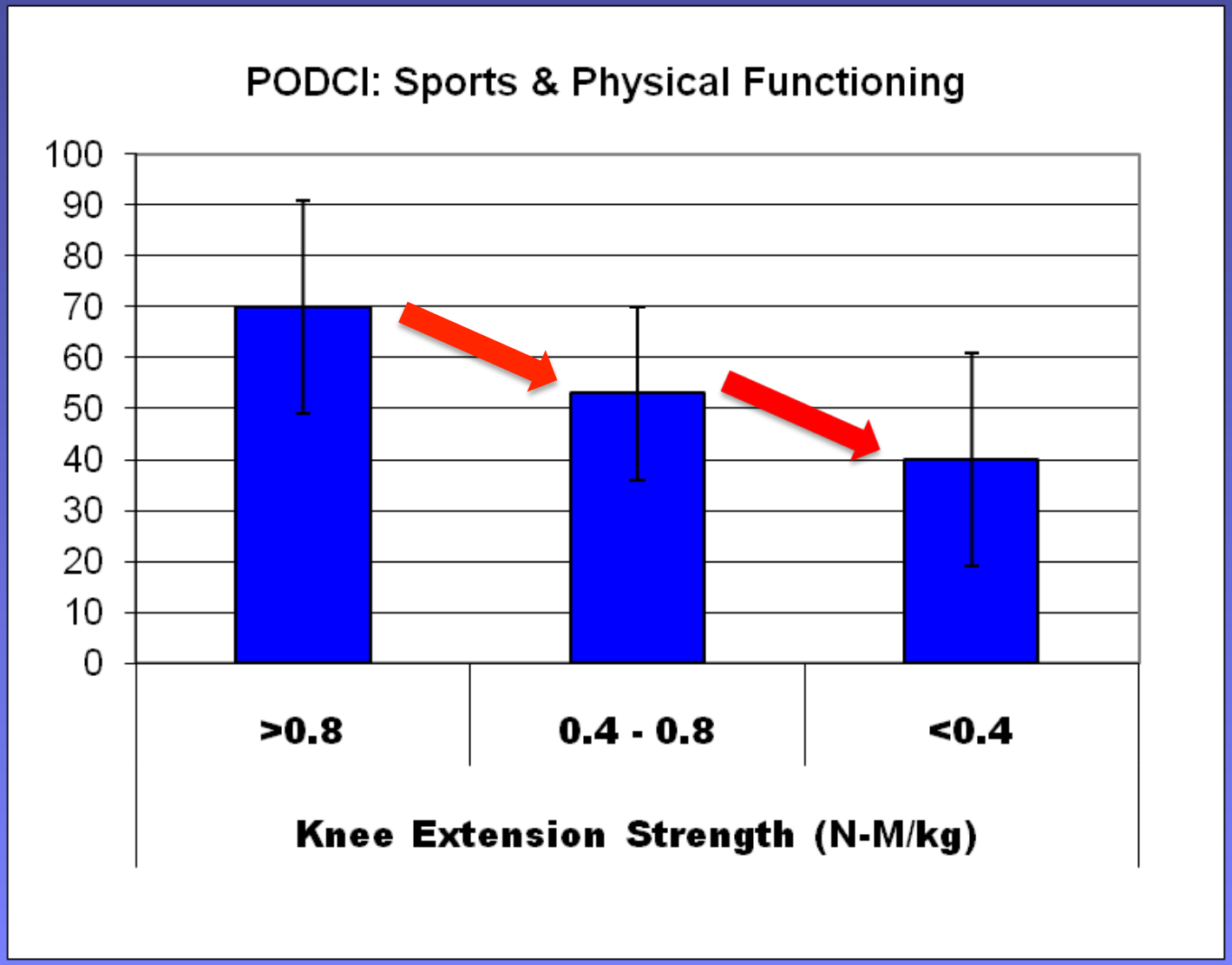
PRO measures and Strength

(McDonald et al. Child Neurology 2010)

Shriners Hospitals Study: PI M. Sussman



Strategic Directions for the Next Action Plan to **End Duchenne**

A Parent Project Muscular Dystrophy Report &
Recommendations from the One Voice Summit

Parent Project
Muscular Dystrophy
LEADING THE FIGHT TO END DUCHENNE

Executive Summary: Recommendations from the Duchenne Community for the Next Action Plan

- "NIH should provide funding for natural history and similar studies that examine the efficacy of certain care standards."

- $1.4 million NIAMS grant will add clinically meaningful endpoints to existing CINRG Natural History study including:
  - Northstar
  - 6MWT
  - Quality of Life measures (NM-PedsQL; NeuroQoL)
  - Non-ambulatory upper limb measures

  - Normative data for all endpoints

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NIH Ancillary Study

- Serum Biomarker discovery in DMD
- N=425 subjects (100 new subjects)
- Pre-Post initiation of steroids (n=100)
- Annual serum samples (n=425, ages 4 to adult)
  - micro RNA profiling
  - nanoparticle proteomics
  - metabolomics profiling
  - cytokine bead-arrays
- Create integrated molecular/clinical database (G-DOC) with the Georgetown University CTSA Biomedical Informatics Core

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- Minimally Important Differences
- Clinically Meaningful Milestones (RASCH)
- Patient Reported Outcomes

Needs for Natural History Studies / Clinical trials

- Normative data from CINRG will help
- Better Clinical Measures of Fibrosis (? MRI)
- Development of milestone-based measures for infants and Toddlers
- Development of novel upper extremity measures
- Validation of patient-reported QOL measures
- Imaging Biomarkers (Vandenborne)
- Serum biomarker discovery studies
- Cardiac interventions / natural history
- Genotype / polymorphisms

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CINRG Clinical Site Locations

US Sites

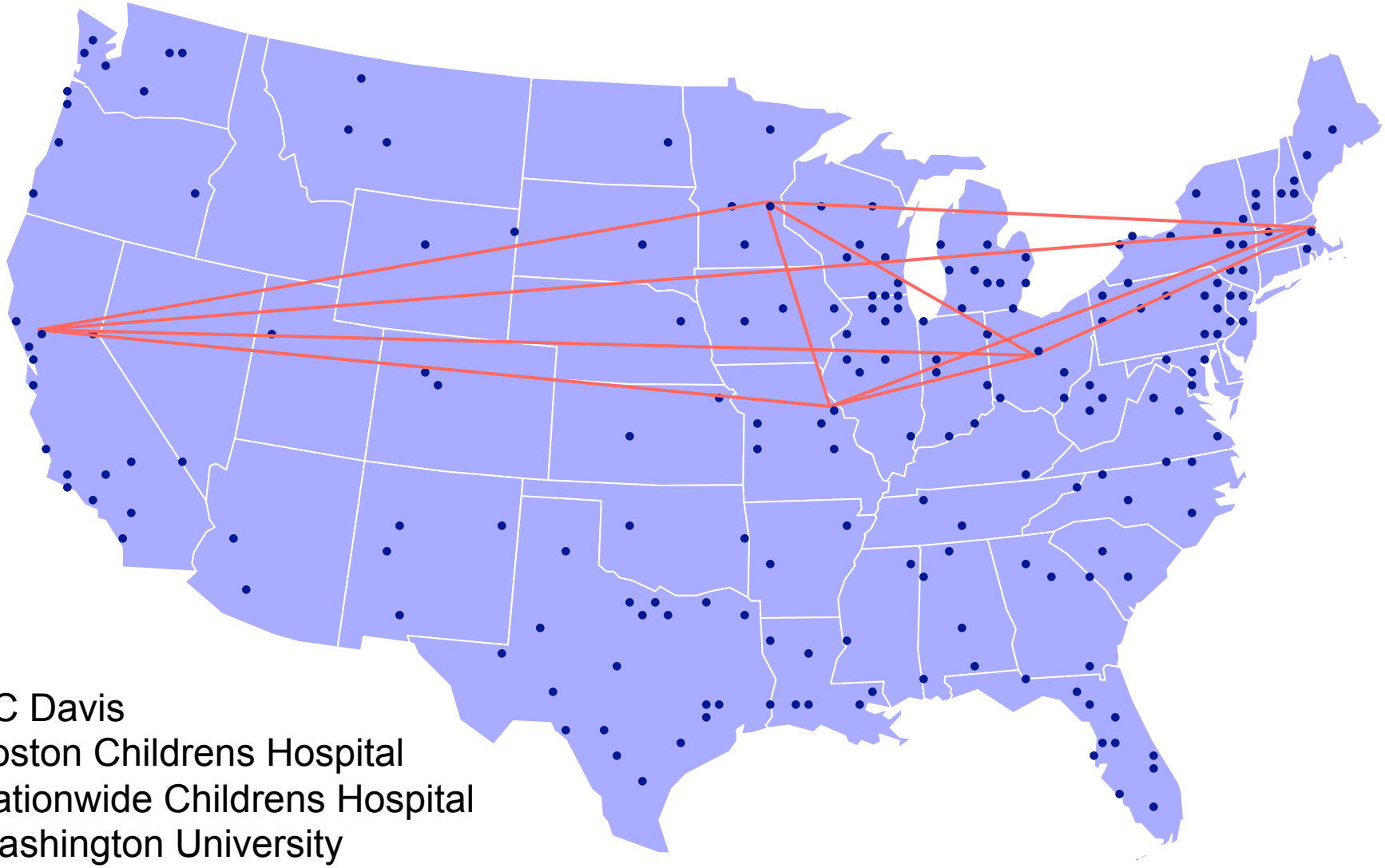
- Children's National Medical Center, Washington, DC
- Children's Hospital, Richmond, VA
- Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA
- University of Tennessee, Memphis, TX
- University of Puerto Rico, San Juan, PR
- Washington University - St. Louis, MO
- Mayo Clinic, Rochester, MN
- University of California - Davis, Sacramento, CA
- Texas Children's Hospital, Houston, TX
- University of Minnesota, Minneapolis, MN
- Carolinas Medical Center, Charlotte, NC
- Children's Memorial Hospital, Chicago, IL

International Sites

- University Hospitals, Leuven, Belgium
- Hadassah, Hebrew University Hospital, Jerusalem, Israel
- Bloorview Kids Rehab, Toronto, Canada
- Sundaram Medical Foundation, Chennai, India
- Royal Children's Hospital, Melbourne, Australia
- Fundacion Favaloro, Buenos Aires, Argentina
- Queen Silvia Children's, Göteborg, Sweden
- The Children's Hospital at Westmead, Sydney, Australia
- Alberta Children's Hospital, Calgary, Canada
- University of Alberta, Edmonton, Canada
- Centro Clinico NeMO Hospital, Milan, Italy
- National Center of Neurology and Psychiatry, Tokyo, Japan

200 MDA Clinics Nationwide

5 networked DMD clinical research centers



UC Davis
Boston Childrens Hospital
Nationwide Childrens Hospital
Washington University
University of Minnesota

MDA® Muscular Dystrophy Association

MDA MUSCULAR DYSTROPHY ASSOCIATION

Thank You!

SCHOOL OF MEDICINE · UC DAVIS

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LEADING THE FIGHT TO END DUCHENNE

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National Institute of Arthritis and Musculoskeletal and Skin Diseases
NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke
National Institutes of Health

Congressionally Directed Medical Research Programs
CDMRP
Department of Defense

NATIONAL INSTITUTE ON DISABILITY AND REHABILITATION RESEARCH
NIDRR

Shriners Hospitals for Children™

UC Davis Neuromuscular Disease Clinical Research Team