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

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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

- **Developmental Delay**
- **Impaired Standing**
- **Progressive Ambulatory Changes**
- **Wheelchair Onset – skeletal deformity**
- **Very limited use of arms**
- **Ventilation at night**
- **Ventilation 24 hours**
- **Death**
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.

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

Craig McDonald, MD

www.cinrgresearch.org
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
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

Definition of GC Status

Current User

Prior Use => 1 month

Naïve = < 1 month and discontinued, or never

*This presentation combines Prior/Naïve*
Effect of Glucocorticoids / Steroids

Stand

Climb Stairs

Rise from a Chair
Effect of Glucocorticoids /Steroids on Loss of Ambulation

Ability to Ambulate Independently by GC Status

Age Group

- GC-Naive
- GC-Treated

Logrank test P-value < 0.0001
12-18 Month Risk of Loss of Ambulation based on 10-Meter Walk Time

- McDonald et al. 1995

>12 seconds (No Steroids)

Log rank P value < 0.0001

McDonald et al. 1995
Timed Function Testing in 4-6 Year Olds with DMD

- **NO Steroids**
  - >12 sec: 10%
  - 8-12 sec: 10%
  - 6-8 sec: 80%
  - <6 sec: 10%

- **+ Steroids**
  - >12 sec: 10%
  - 8-12 sec: 10%
  - 6-8 sec: 80%
  - <6 sec: 10%
DMD Care Considerations (2009)

Non-ambulatory and any of the following:
- Suspected hypoventilation
- **FVC < 50% predicted**
- Current use of assisted ventilation

Awake end-tidal CO₂ level by capnography*

At least annually

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Baseline FVC < 40% predicted
and/or awake baseline blood or ETCO₂ > 45 mm Hg and/or awake baseline SpO₂ < 95%

FVC < 1.25 L
(in any teenage or older patient)

Assessment of gas exchange during sleep*
(home or laboratory setting)
Glucocorticoids / Steroids and Spine Deformity


- 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

Ability to Raise a Hand to the Mouth by GC Status

Age Group

- 4-6 Years
- 7-9 Years
- 10-12 Years
- 13-18 Years
- >18 Years

% Able to Raise Hand to Mouth

- GC-Naive
- GC-Treated

[Bar chart showing the ability to raise a hand to the mouth by GC status across different age groups.]
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

<table>
<thead>
<tr>
<th>Core Measures (Clinic)</th>
<th>Clinical Trials</th>
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<tbody>
<tr>
<td>Standing Time (from supine)</td>
<td>6MWD</td>
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<tr>
<td>4 Stair Climb</td>
<td>Northstar</td>
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<td>10 meter walk /run</td>
<td>Patient reported Outcome measures</td>
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<td>PFTs</td>
<td>Novel Upper Extremity measures</td>
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Natural History of 6MWT Findings in DMD

Observational Study

Ataluren trial N=57
Natural History of 6MWT Findings in DMD

Observational Study

Ataluren trial N=57

Maturational Issues

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

- **Stand**
  - Log rank P value < 0.0001

- **Ability to Ambulate**
  - Log rank P value < 0.0001

- **Climb Stairs**
  - Log rank P value < 0.0001
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

Log rank P value < 0.0001
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

Velocity on 10 Meter Walk/Run, m/sec

6 sec

6MWD (m)

r = 0.80
6MWD as a Predictor of Loss of Ambulation (PTC ataluren trial)

Baseline 6MWD in DMD subjects who lost ambulation:
- 14/15 patients who lost ambulation:
  - 6MWD < 300 m (all < 315 m)
  - Percent Predicted 6MWD < 50%

Baseline 6MWD in DMD subjects who lost ambulation
12-18 Month Risk of Loss of Ambulation based on 10-Meter Walk Time

McDonald et al. 1995

356 Meters 6MWD

<6 Seconds (N = 73)

6 - 12 Seconds (N = 94)

> 12 Seconds (N = 16)

>12 seconds (No Steroids)

McDonald et al. 1995

Log rank P value < 0.0001
Percent Predicted 6MWD to Account for Maturational Influences

% 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 2\textsuperscript{nd} decade phenomenon
Usually occurs about 3 years after transition to wheelchair (in those not on steroids)

Posterior Spine Fusion for Scoliosis $> 30^\circ$

Optimally performed when $\% \text{FVC} > 40%$
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 $p = 0.0001$. 
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 vs the 5th and 95th percentiles for the normal population. The bold line represents the LOWESS regression for height.

Figure 2. Scatterplot of weight gain (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)

• Is short stature a biologic signal for corticosteroid activity?

• Are there biomechanical advantages to short segment lever arms?

(CINRG DMD Natural History Study)
Cardiomyopathy in DMD

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

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.
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
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
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
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
Clinical Trial Endpoints

• FDA Clinical Endpoint Qualification Process

• “Clinically Meaningful”

• Related to Patient-reported Outcomes
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 Questionnaire
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).
Quality-of-Life Measures in Children With Neurological Conditions: Pediatric Neuro-QOL

Jin-Shei Lai, PhD, Cindy Nowinski, MD, PhD, David Victorson, PhD, Rita Bode, PhD, Tracy Podrabsky, Natalie McKinney, Don Straube, PhD, Gregory L. Holmes, MD, Craig M. McDonald, MD, Erik Henricson, PhD, R. Ted Abresch, MS, Claudia S. Moy, PhD, and David Cella, PhD
Pediatric NeuroQOL Domains (based on PROMIS items)
Framework for Item Banks and Targeted Scales

**PHYSICAL**

- **Function/Health**
  - Mobility/Ambulation
  - ADL's/UE's

- **Symptoms**
  - Pain
  - Fatigue

**MENTAL**

- **Emotional Health**
  - Depression
  - Anxiety
  - Stigma

- **Cognitive Health**

**SOCIAL**

- **B=Bank**
- **T=Targeted Scale**
Strength: QMT Knee Extension*

Baseline Distribution
(Shows differences in steroids, non-steroids)

* Previously shown to have the highest correlation with Vignos leg functional grade.
Quantitative Isometric Knee Extension Strength vs. Walking Velocity

Walking Velocity

Isometric Knee Extension Strength (NM/Kg)
PRO measures and Strength
(McDonald et al. Child Neurology 2010)
Shriners Hospitals Study: PI M. Sussman

PODCI: Sports & Physical Functioning

Knee Extension Strength (N-M/kg)
Strategic Directions for the Next Action Plan to End Duchenne

A Parent Project Muscular Dystrophy Report & Recommendations from the One Voice Summit
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
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
• 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
## 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
Thank You!

UC Davis Neuromuscular Disease Clinical Research Team