Natural history of DMD/ BMD: What is clinically meaningful?
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1) There has been a changing natural history in Duchenne muscular dystrophy over the last 4 decades affecting both survival and loss of clinically meaningful functions (milestones).
What interventions have impacted the natural history of disease progression and survival in DMD?

1) Glucocorticoids

2) Management of spine deformity
   • Glucocorticoids
   • Timely spine surgery for curves > 30-40 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
1) There has been a changing natural history in Duchenne muscular dystrophy over the last 4 decades affecting *survival*

1960’s:
No treatment

1970-1990:
Spine Surgery & Ventilation

October; 31(2): 121–125.

DMD survival impacted primarily by ventilation

- Ventilation was recognized as a main intervention affecting survival

  - Ventilated median survival = 27.0 yrs
  - Without ventilation = 19.0 yrs

  - Ventilated mean survival = 27.9 yrs (range 23-38.6 yrs)
  - Without ventilation = 17.7 yrs (range 11.6-27.5 yrs)


1) There has been a changing natural history in Duchenne muscular dystrophy over the last 4 decades affecting survival. 

1980’s-present: Glucocorticoids / Steroids

- Schram et al. Journal of the American College of Cardiology
  Volume 61(9), 2013, 948 - 954

2000-present: Afterload reduction w/ ACE inhibitors

2) Loss of clinically meaningful milestones occurs in a predictable order in DMD

### Ambulatory Milestones
- Unable to jump, hop, and run
- Gowers sign with standing
- Loss of standing from the floor
- Loss of lie to sit
- Loss of stair climbing
- Loss of ability to stand from a chair
- Loss of ability to walk independently (10 meter walk/run; 6MWD)
- Loss of standing in place

### Non-ambulatory Milestones
- Loss of ability to reach overhead
- Loss of ability to reach the scalp
- 50% FVC (Cough Assistance; monitoring required)
- Loss of ability to self-feed without adaptations (hand to mouth)
- Loss of ability to place hands to table top
- Inability to sustain adequate overnight ventilation without support (>30% FVC)
- Loss of ability to use a computer (distal hand function)
3) Steroids affect disease progression in DMD over the entire course of the disease prolonging clinically meaningful functions (time to loss of milestones)
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Stand from the floor (supine)

Climb Stairs

Rise from a Chair

Henricson et al. Muscle & Nerve 2013
3) Steroids affect disease progression in DMD over the entire course of the disease prolonging clinically meaningful functional abilities (time to loss of milestones).

**Loss of Ambulation**

Steroids prolongs ambulation (50% still ambulating) by ~3 years

Henricson et al. Muscle & Nerve 2013
3) Steroids affect disease progression in DMD over the entire course of the disease prolonging clinically meaningful functional abilities (time to loss of milestones).

Ability to raise hand to the mouth and feed

Henricson et al. Muscle & Nerve 2013
FVC % Predicted

Henricson et al. Muscle & Nerve 2013

Cough Assistance: 50% FVC; ↓ Peak Cough Flow

Ventilation: 30-40% FVC
Key natural history concepts

4) Earlier functional abilities predict later functional abilities and timing of loss of clinically meaningful functions (milestones) predict when later milestones will be lost.
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Contemporary: with Steroids, Improved Cardiac Management, and Ventilation
4) Earlier functional abilities predict later functional abilities and timing of loss of clinically meaningful functions (milestones) predict when later milestones will be lost.

Loss of standing predicts loss of ambulation

Cooperative International Neuromuscular Research Group (CINRG) Data (McDonald et al. submitted): Correlation between age at loss of standing from supine and age at loss of ambulation is high (r=0.90).

Age at loss of rising from the floor and loss of ambulation r = 0.91

Humbertclaude et al. European J. of Paediatric Neurology 2012

CINRG Data (McDonald et al. submitted): On Kaplan Meier Survival analysis standing time predicts loss of ambulation. (Log rank P value < 0.0001)

43.3% lost ambulation at 12 mo.

PTC ataluren trial
If unable to stand at baseline:
14/30 (46.7%) lost Ambulation over 48 weeks
If able to stand at baseline
1/144 (0.7%) lost Ambulation over 48 weeks P < 0.0001
4) Earlier functional abilities predict later functional abilities and timing of loss of clinically meaningful functions (milestones) predict when later milestones will be lost.

CINRG Data (submitted):
Age at loss of ambulation predicts age at loss of ability to raise hand to mouth and feed self ($r = 0.76$)

France
Age at LOA correlated to age at loss of hands to head
$r = 0.60$

Humbertclaude et al.
European J. of Paediatric Neurology 2012
4) Earlier functional abilities predict later functional abilities and timing of loss of clinically meaningful functions (milestones) predict when later milestones will be lost.

Age at loss of ambulation predicts time to % predicted FVC of 30% (need for non-invasive ventilation)

Humbertclaude et al. European J. of Paediatric Neurology 2012
5) Higher baseline function or stabilization of baseline function over the short-term is almost always associated with slower long-term decline in DMD.
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6MWD as a measure of disease progression

Walking Function and Prediction of Loss of Ambulation

30 m ↓ from baseline → 10% worsening over 1 year → Loss of Ambulation (4 yrs)

5) Higher baseline function or stabilization of baseline function over the short-term is almost always associated with slower long-term decline in DMD.

Later age at loss of ambulation predicts higher peak FVC and slower rate of decline in FVC.

Humbertclaude et al. European J. of Paediatric Neurology 2012
Schematic Natural History of Duchenne Muscular Dystrophy

Contemporary: with Steroids and Improved Cardiac Management

Motor Function
- Delays
- Functional Gains (slower than typically developing)
- Functional Decline of Ambulation
- Functional Decline of Upper Limb Function
- Growth
- Decline in FVC
- Decline in % FVC / %FEV1
- Decline in MIP, MEP
- Decline in Cardiac MRI

Respiratory Function
- Decline in FVC
- Decline in % FVC / %FEV1
- Decline in MIP, MEP
- Decline in Cardiac MRI

Cardiac Function
- Decline in Cardiac MRI

Loss of Standing
Loss of Ambulation
Loss of Self Feeding
Ventilation
Death
Schematic Natural History of Duchenne Muscular Dystrophy

5 Years  9 Years  14 Years  20 Years

Contemporary: with Steroids, Improved Cardiac Management, and Ventilation

Clinical Endpoints with Validation and Existing Longitudinal Data
Griffiths

- Bayley III
- Northstar Ambulatory Assessment (NSAA)
- Timed Function Tests
  - 6MWT
- Strength: Manual muscle testing
- Strength: Quant. Lower limb
- Strength: Quant. Upper limb (proximal and distal)
- Pulmonary Function Testing
- Performance of Upper Limb Scale (PUL)
- Patient Reported Outcomes (PROs): PODCI, PROM
Schematic Natural History of Duchenne Muscular Dystrophy

5 Years | 9 Years | 14 Years | 20 Years

Contemporary: with Steroids, Improved Cardiac Management, and Ventilation

Loss of Standing

Loss Ambulation

Loss of Self Feeding

Ventilation | Death

Promising Exploratory Clinical Endpoints

Motor Function Measure (MFM)

Skeletal muscle MRI

Cardiac MRI

Myotools

ActiMyo

ActiMyo

Tri-axial Accelerometers; StepWatch™ Step activity monitor

Reachable Workspace (Kinect)

Electrical Impedance Myography (EIM)

Patient Reported Outcomes (PROs): NeuroQoL; PedsQL NM Module
### Decision Framework for Inclusion of Clinical Outcome Measures in Trials

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Griffiths locomotor</th>
<th>Bayley III Gross Motor</th>
<th>North Star Amb. Ass. (NSAA)</th>
<th>Timed Function Tests</th>
<th>6MWT</th>
<th>Strength MMT</th>
<th>Strength Quant.</th>
<th>Pulmonary Function Tests</th>
<th>Perf Upper Limb (PUL)</th>
<th>PROs - PODCI</th>
<th>PROs-PROM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical subgroups</td>
<td>0-8 years</td>
<td>1-42 mo.</td>
<td>3.5 years until non-amb</td>
<td>4 years until non-amb</td>
<td>5 years until non-amb</td>
<td>4 years to grade 2-</td>
<td>LE: 5-12</td>
<td>UE:5-20+</td>
<td>7 – 20+ years</td>
<td>7 – 20+ years</td>
<td>3 – 21 years</td>
</tr>
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#### Supports mechanism of action
- ✔ Specific to the therapeutic agent under investigation

#### Conceptual framework fits DMD

#### Reliability

#### Validation with other measures

#### Normative ranges

#### Ongoing natural history Studies

#### Multicenter studies

#### Responsiveness to treatment
- ? or (-) if age ≥ 10

#### Clinical meaningfulness
- ?
Schematic Natural History of Becker Muscular Dystrophy
(Adapted from Bushby and Connor Clin Investig (Lond). 2011; McDonald et al. Muscle & Nerve 2013)

Becker Early Onset
- Loss of Standing
- Loss of Ambulation
- Cardiomyopathy
- Loss of Self Feeding
- Death

Becker Later Onset
- Loss of Standing
- Loss of Ambulation
- Cardiomyopathy
- Loss of Self Feeding
- Death

DMD
Median survival is 27 yrs

BMD
Median survival is 67 yrs
Conclusions regarding the natural history of disease progression as it relates to clinical trials

• **Standards of care** and improved respiratory and cardiac management have led to improvements in survival and outcome;

• **Steroids** have led to improved survival and long-term improvements in clinically meaningful functional activities (milestones) in the ambulant and non-ambulant;

• Extrapolation: There are new data that **link the clinically meaningful milestones to each other** from the ambulatory stages to the non-ambulatory stages;

• Specific changes in **6MWT** predict 10% worsening and loss of ambulation; Age at loss of ambulation predict later milestones and disease progression.
CINRG Clinical Sites
Duchenne Natural History Study
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
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