Diagnostic, Management and Treatment Strategies for DMD

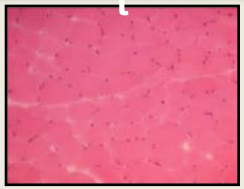
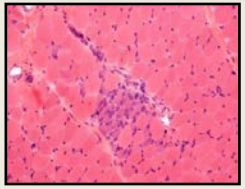
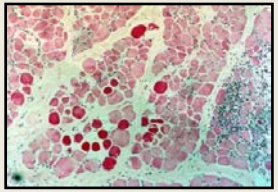
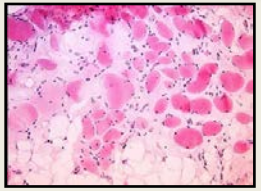
Craig McDonald, MD

Professor and Chair of PM&R
Professor of Pediatrics
Study Chair CINRG Duchenne Natural History Study
University of California Davis Health
Sacramento, CA

UCDAVIS CHILDREN'S HOSPITAL

Neuromuscular Research Center — Discovering Creates Hope

Duchenne is a X-linked Rare, Relentless and Fatal Disease of Boys and Young Men

	Newborn/Infant	3-7 years	7 years	Early Teens	Early 20s
Muscle Biopsies					
Clinical Course					

Progressive paralysis, respiratory failure, cardiomyopathy and premature death

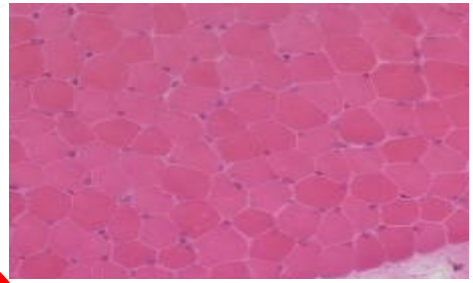
DMD pathomechanism

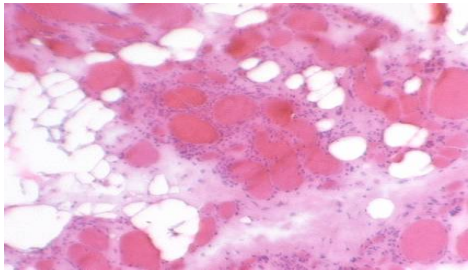
Gene abnormality at Xp21 loci

↓

Absence of dystrophin

Structural defect





Membrane instability

Apoptosis / Necrosis

Satellite Cell Activation
Muscle Fiber Regeneration

Activation of NF-kB *Inflammation*

Fibrosis

Fiber Death

Adapted from
Engvall & Wewer (2003) FASEB 17:1579

CK vs. Age (3 to 17 years)

CK values may be 10-fold higher in younger patients with DMD
(e.g. 25,000 vs 2,500 in a 3 year old vs. 12 year old)

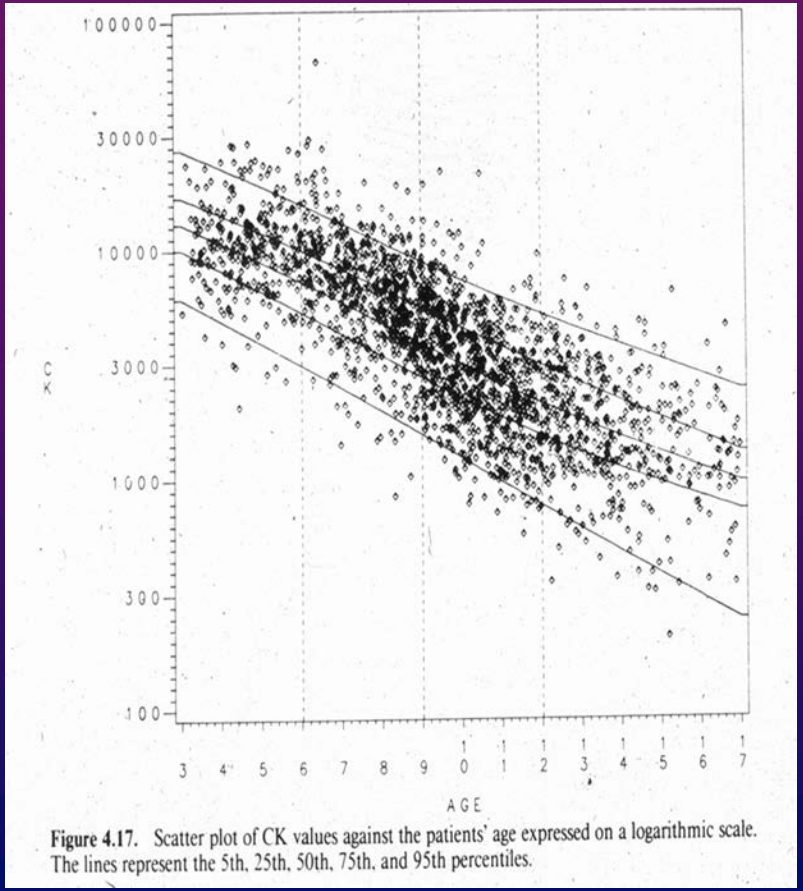


Figure 4.17. Scatter plot of CK values against the patients' age expressed on a logarithmic scale. The lines represent the 5th, 25th, 50th, 75th, and 95th percentiles.

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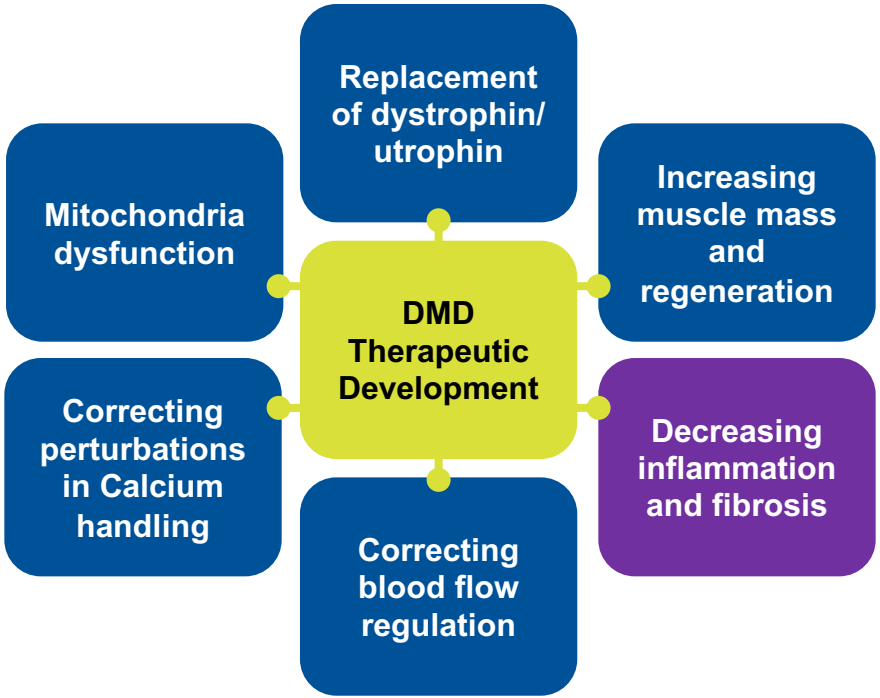
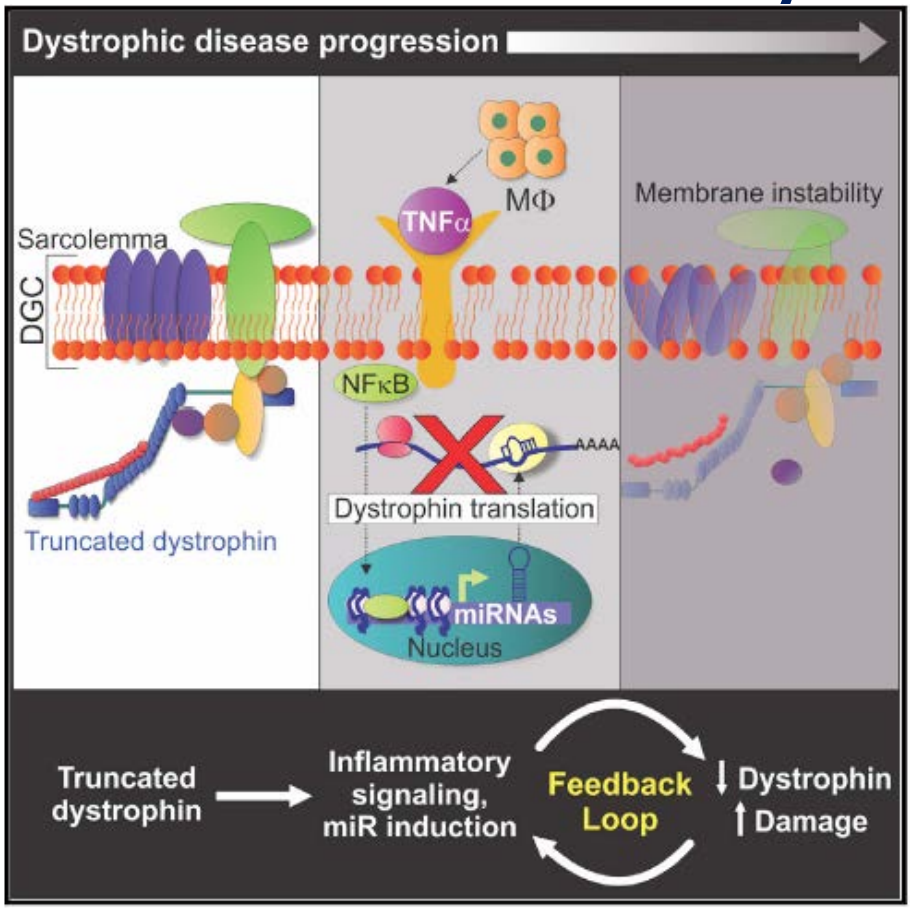
Development of State-of-the-Art Combination Therapies for Duchenne Muscular Dystrophy

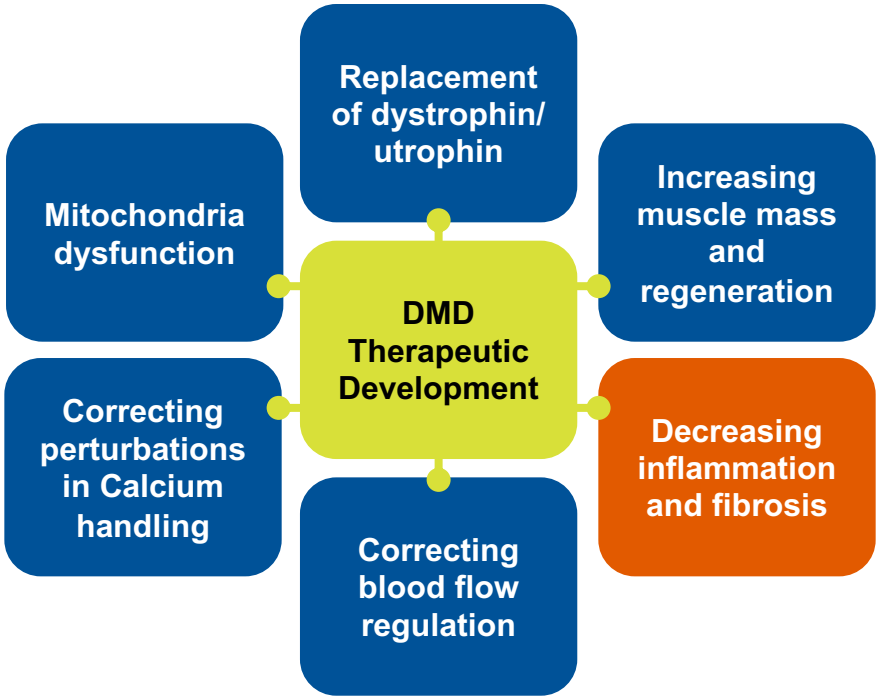


- Six main categories for therapeutic targets for DMD
- One addresses primary genetic defect; rest address downstream aspects of the pathogenesis
- Targeting any single pathway may be an approvable mono-therapy
- Future treatment paradigm may involve targeting multiple pathways to have greater patient impact

Glucocorticoids target NF-κB which is Chronically Activated in DMD



- miRNAs in muscle microenvironments cause variable dystrophin in muscular dystrophy
- miRNAs are elevated in dystrophic myofibers and increase with age and disease severity (use as a biomarker)
- Inflammatory cytokines induce miRNAs, and antiinflammatories block their expression
- miRNAs provide a precision medicine target in dystrophy



- **NF-κB Is Chronically Activated in DMD**
- Prednisone / Prednisolone
- Deflazacort (Emflaza, PTC)

- Current Trials:
- Vamorolone (ReveraGen)
  - Dissociative steroids (decreased AEs)
- Edasalonexent (Catabasis)
  - covalently linked salicylic acid (ASA) and docosahexaenoic acid (DHA),
  - synergistically leverages the ability of both compounds to intracellularly inhibit activated NF-κB

Contemporary Treatments that have Affected the Natural History of Disease Progression and Survival in DMD

1. **Glucocorticoids**
2. **Management of spine deformity**
   - Glucocorticoids
   - Timely spine surgery for curves >30 to 40 degrees
3. **Pulmonary management**
   - Airway clearance strategies/mechanical cough assistance
   - Noninvasive ventilation
4. **Cardiac management**
   - Early afterload reduction (e.g., ACE inhibitors)
   - Recognition and management of heart failure

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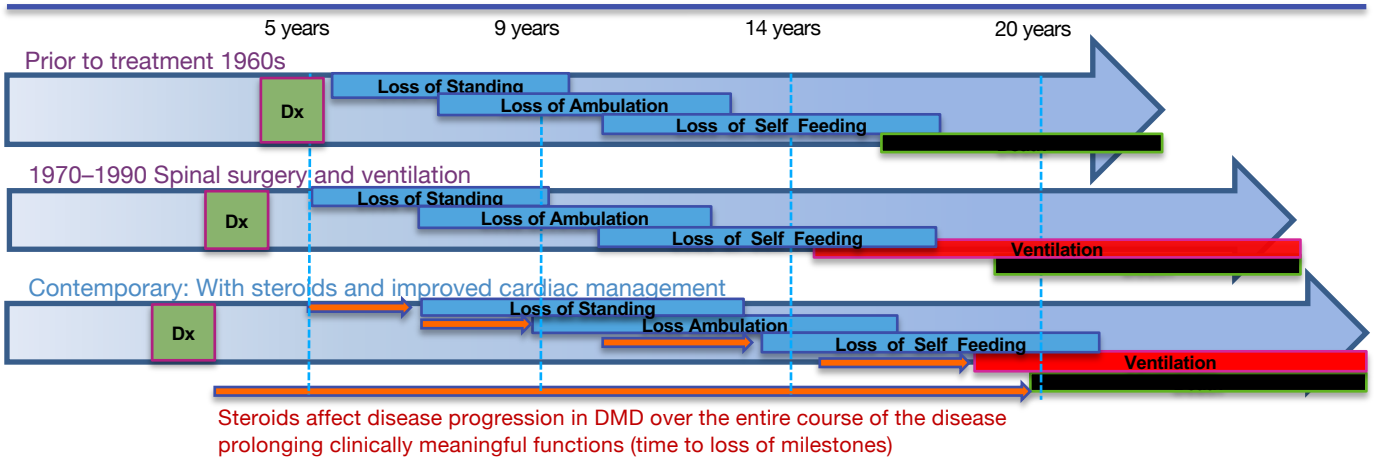
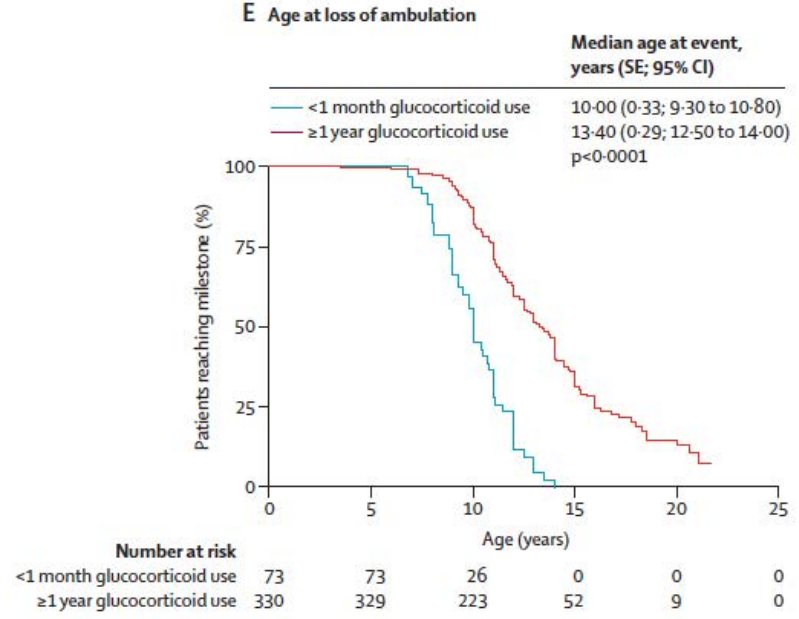
Natural History of DMD

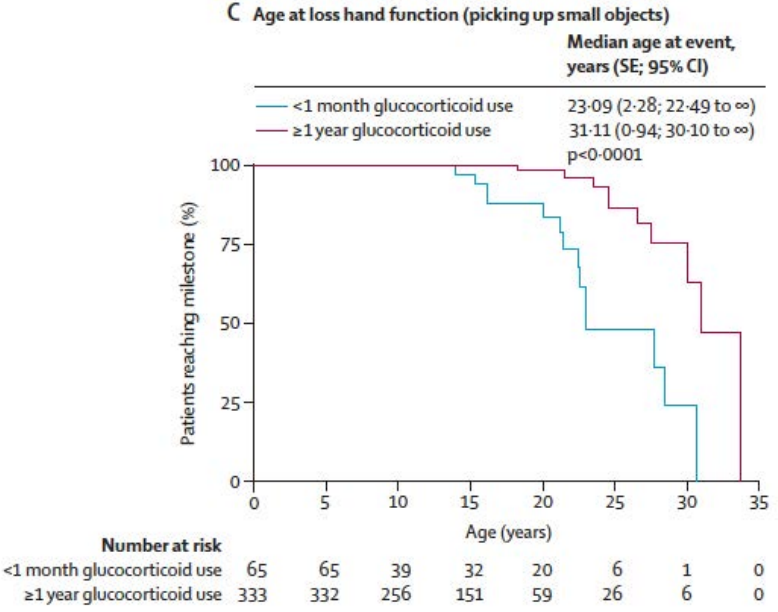


Adapted from Bushby K, Connor E. Clin Investig (Lond). 2011;1:1219–1235. 2. McDonald CM, et al. Muscle Nerve 2013;48:32–54.

THE LANCET

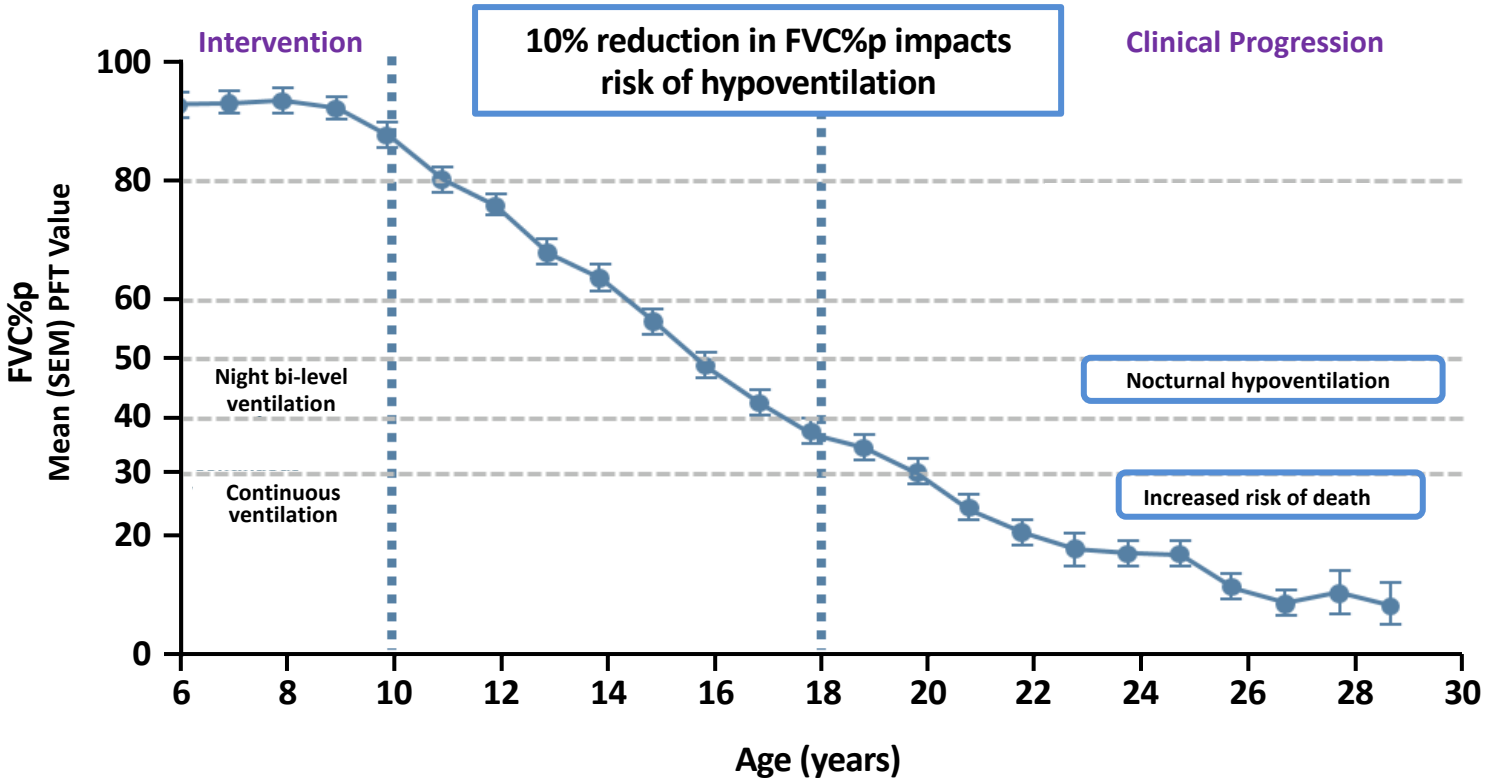
Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study





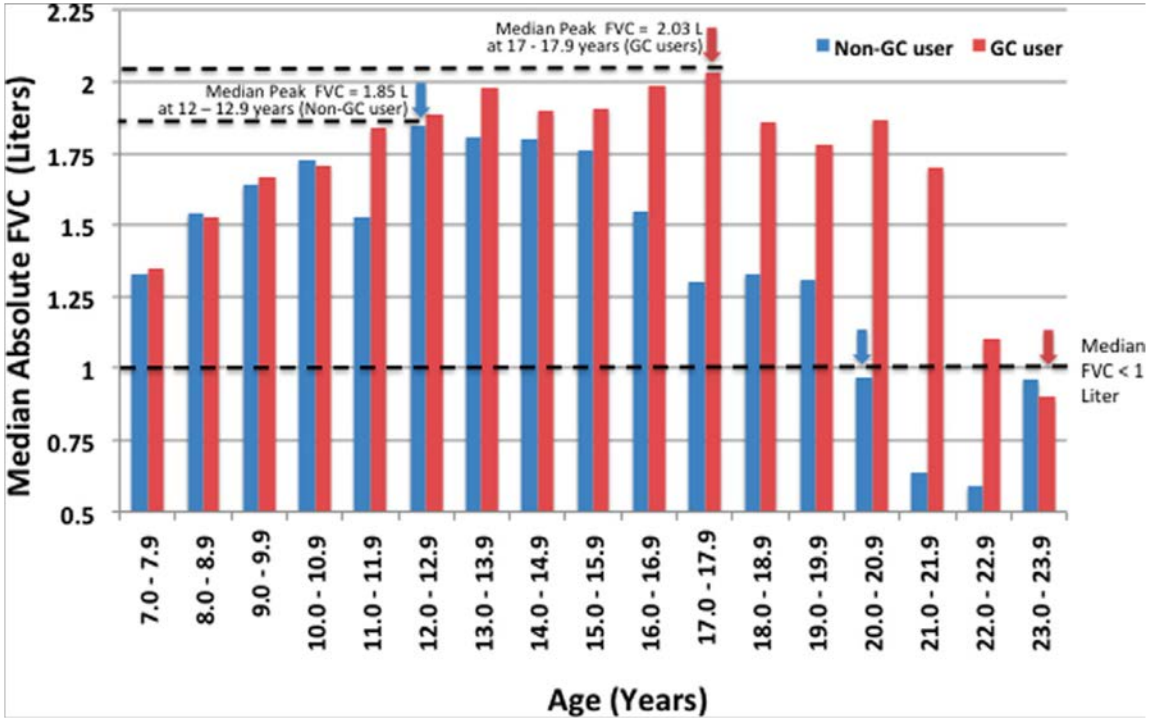
McDonald et al. Lancet. 2018 Feb 3;391(10119):451-461.

Declining FVC%p Linked to Clinically Meaningful Thresholds and Risk of Death (Based on CINRG Data)



Modified from † Mayer, et al. 2017; CINRG Data: McDonald CM, et al. 2018.

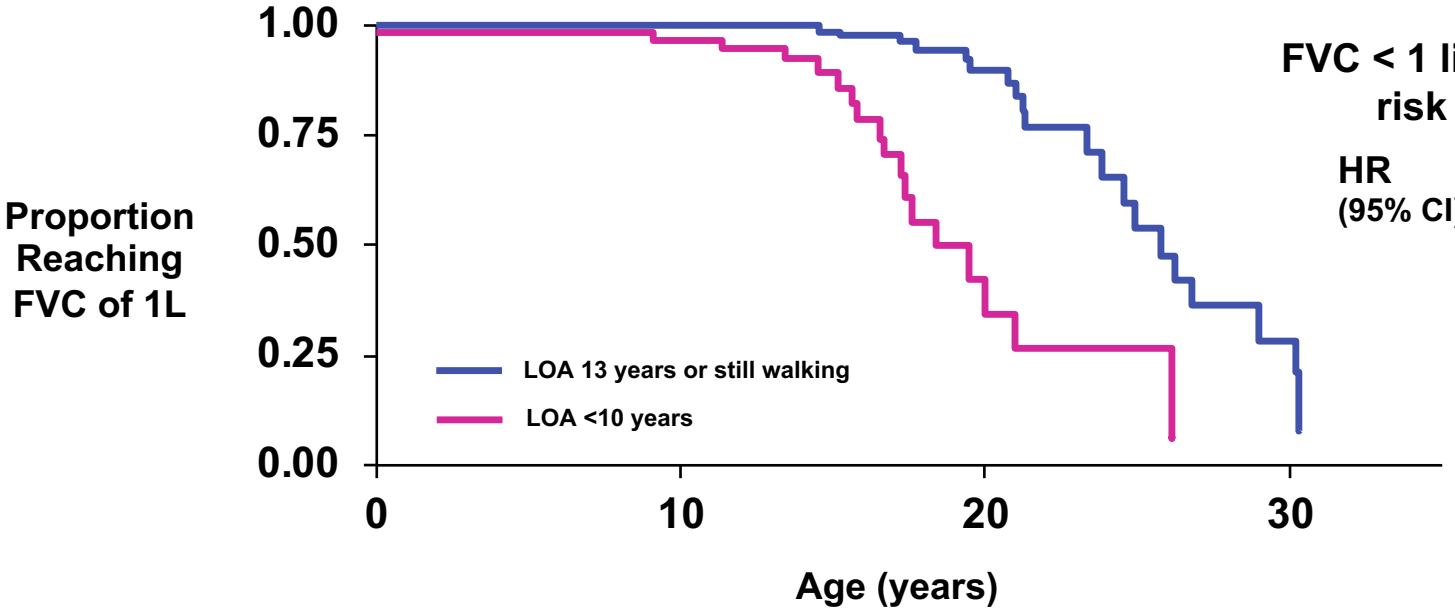
Median Absolute FVC (Liters) by Age and GC use in DMD



Peak in median FVC is shown and the point at which the median absolute FVC value drops below 1 l.

McDonald et al. Lancet. 2018 Feb 3;391(10119):451-461.

Age at Loss of Ambulation Predicts Age at Onset of 1 liter FVC (CINRG Data)



FVC < 1 liter increases risk of death

HR (95% CI)	4.1 (1.3, 13.1)

Number at Risk

LOA <10 years	53	53	46	22	3	1	0	0
LOA 13 years or still walking	208	208	132	71	27	7	0	0

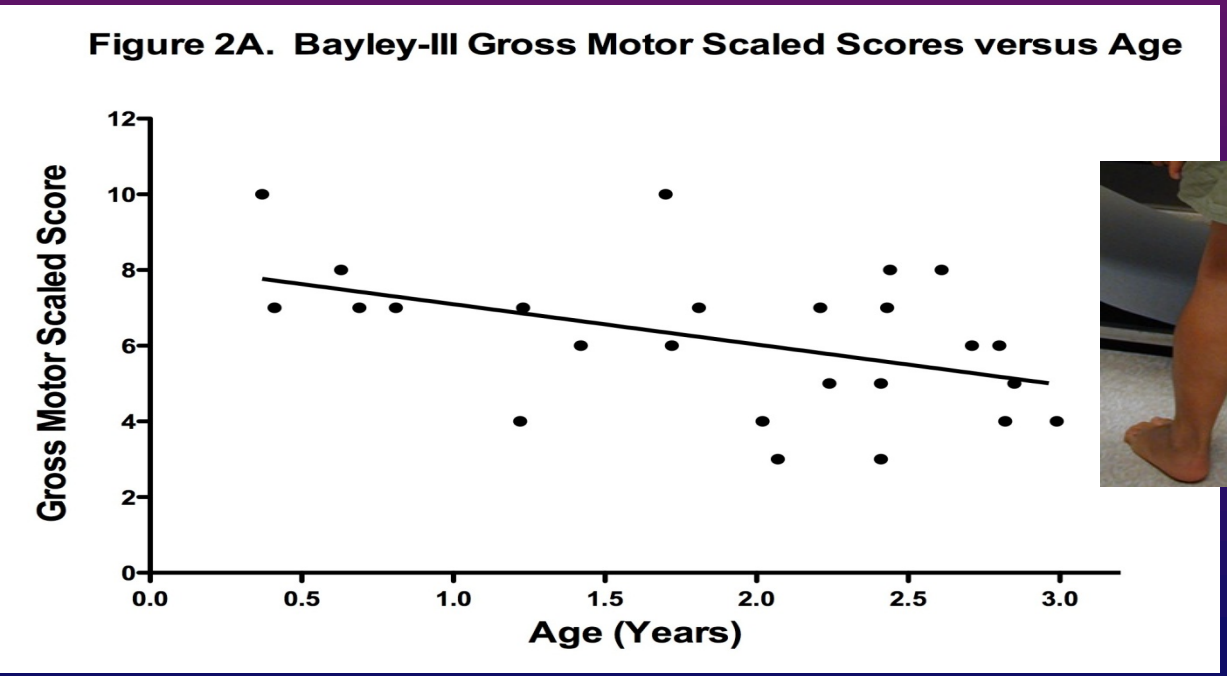
Ambulatory patients age 9-18 at study entry

McDonald et al. Lancet, 2018

Motor and Cognitive Assessment of Infants and Young Boys with Duchenne Muscular Dystrophy:

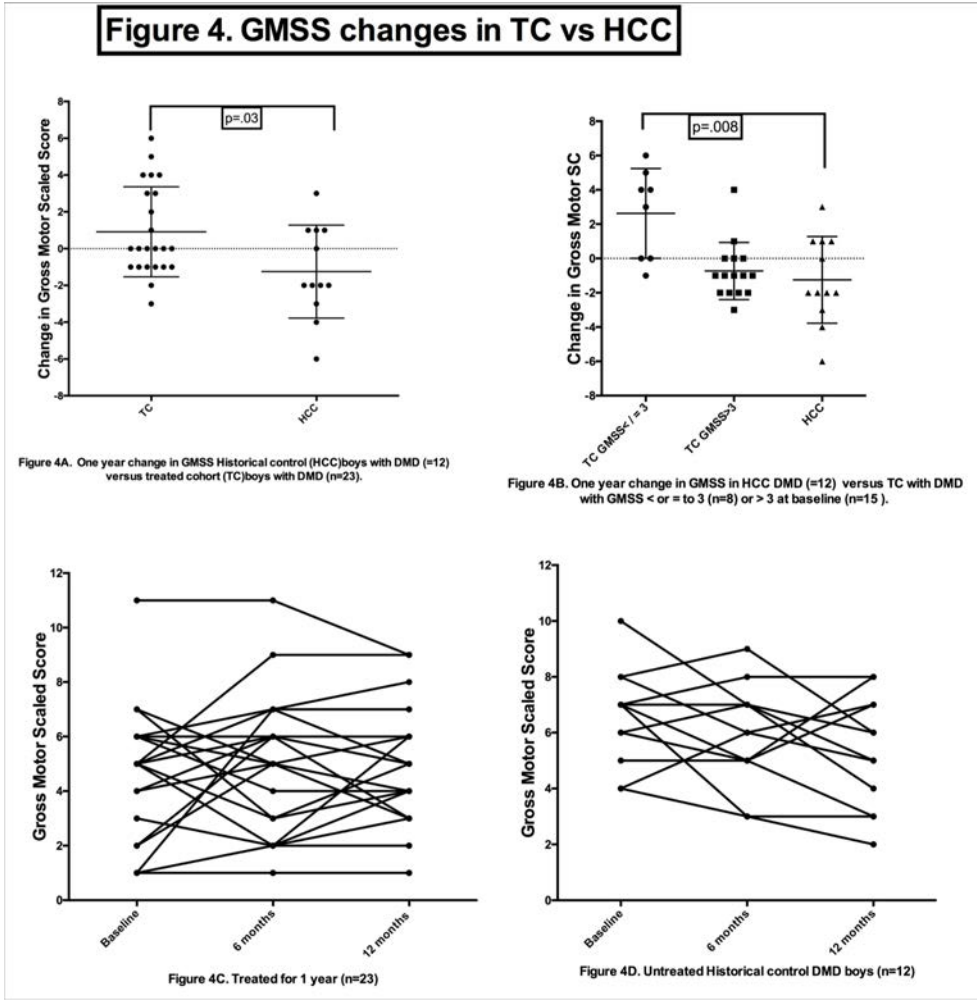
Results from the Muscular Dystrophy Association DMD Clinical Research Network. Connolly et al.

(n=25; 1.8±0.8 years)



- **Twenty-five steroid naive boys four to 30 months of age with genetically confirmed DMD were enrolled.**
- **Treated boys gained an average of 0.5 points on the Bayley-III gross motor scaled score (GMSS) compared to the Historical Control Cohort who, on average, declined 1.3 points (p=0.03)**

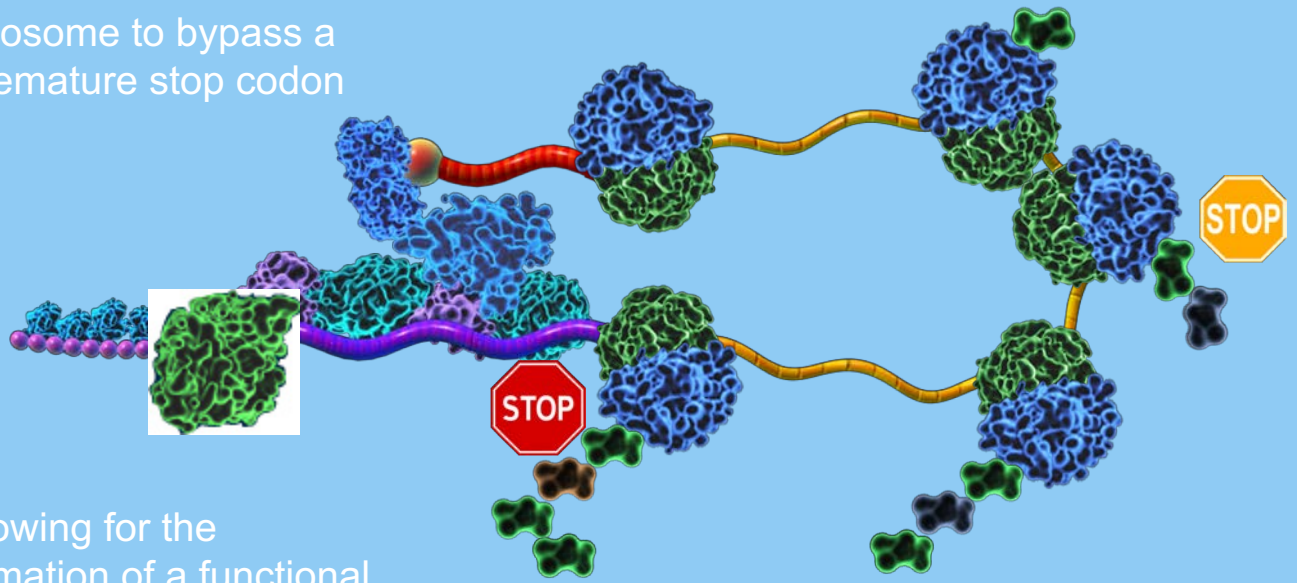
Connolly et al. submitted 2018



Advancements in RNA Therapy & Exon Skipping in DMD

Ataluren enables the ribosome to bypass a nonsense mutation and produces a functional protein

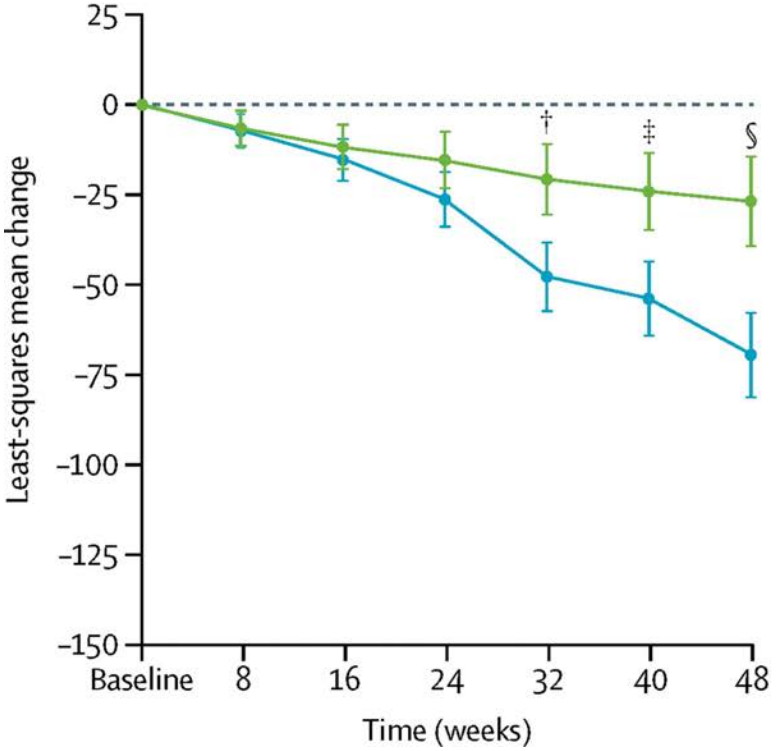
Ataluren causes the ribosome to bypass a premature stop codon



Allowing for the formation of a functional protein

- Orally bioavailable compound
- High specificity for nonsense readthrough without affecting normal termination codons
- Mechanism of action is distinct from exon-skipping drugs

Ataluren slows progression measured by 6MWT in subgroup where measure can be responsive in a 1-year trial



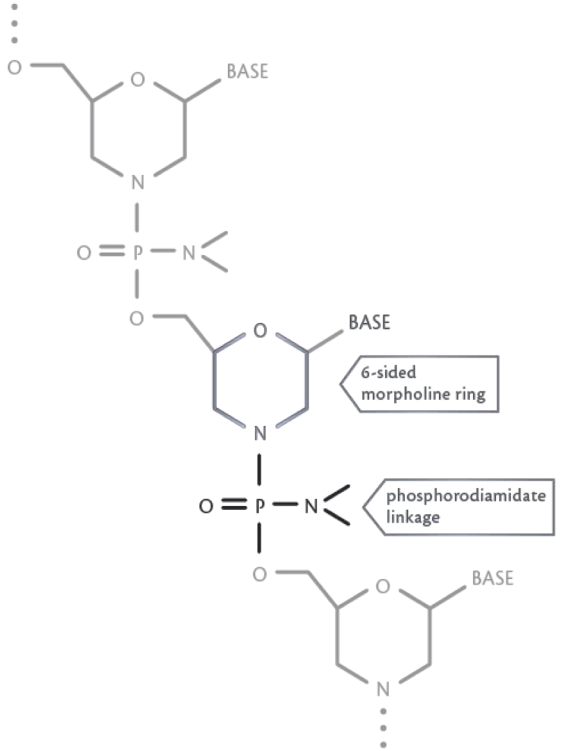
6MWD
difference = 42·9 m
95% CI 11·8–74·0;
p=0·007

McDonald et al. Lancet. 2017 Sep 23;390(10101):1489-1498.

Phosphorodiamidate Morpholino Oligomer (PMO)

- Bind sequence-specifically to RNA targets[1]
- Chemically modified nucleic acid analog[2]
- Stable in serum and intracellularly[3]
- Uncharged backbone[4]

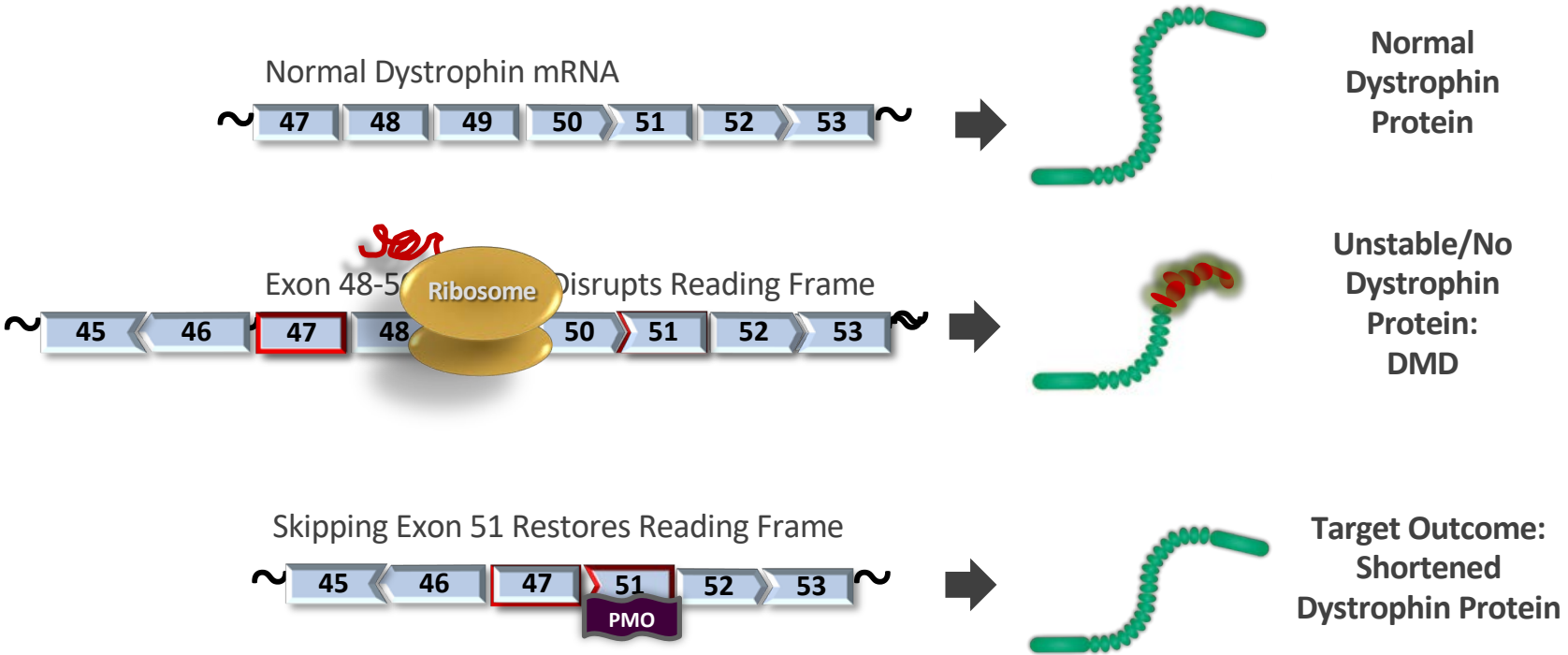
PMO Structure



1. Summerton J, Weller D. *Antisense Nucleic Acid Drug Dev*. 1997;7(3):187-195. 2. Kole R, Leppert BJ. *Discov Med*. 2012;14(74):59-69.
3. Popplewell LJ, et al. *Mol Ther*. 2009;17(3):554-561. 4. Wilton SD, Fletcher S. *Curr Gene Ther*. 2011;11(4):259-275.

2
1

Exon Skipping Proposed Mechanism of Action e.g. Exon-51–Amenable DMD Patients

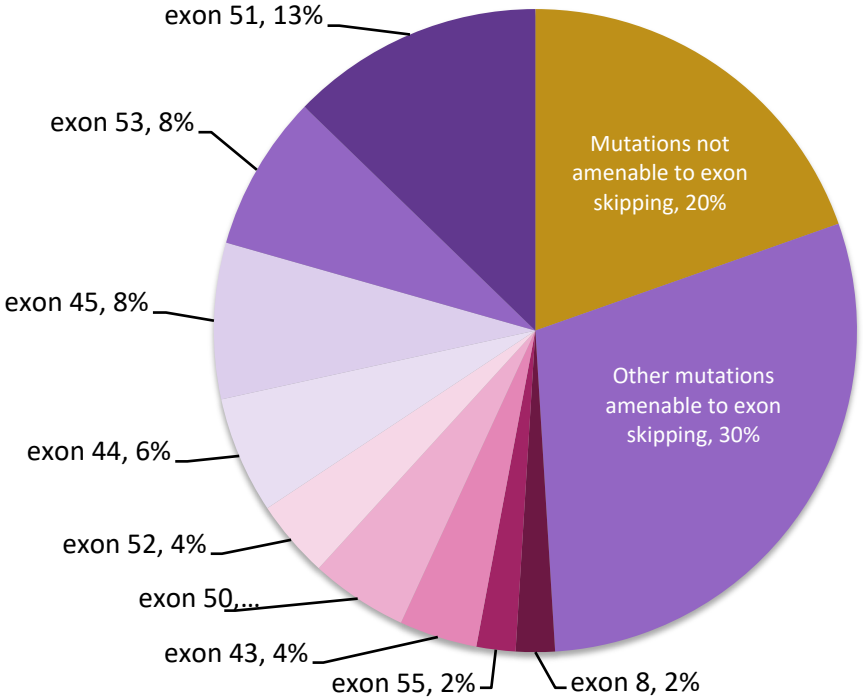


Exon Skipping PMOs in late stage clinical development programs to address up to ~30% of all DMD Patients

Eteplirsen (FDA approved):
PMO for skipping of Exon 51

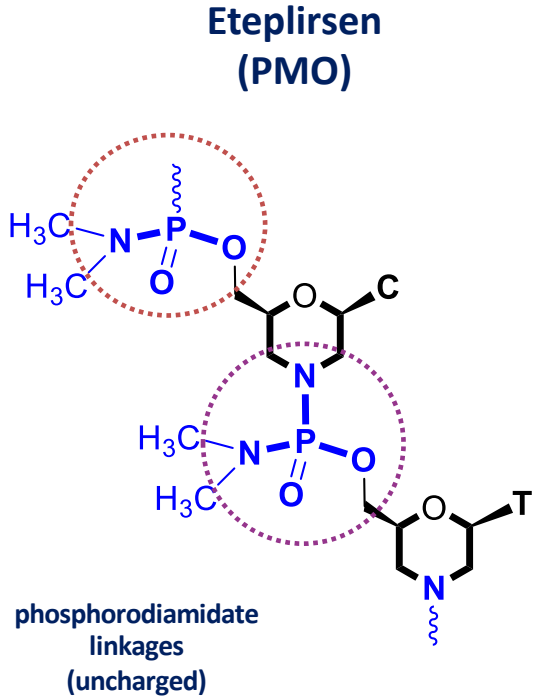
Golodirsen; Viltolarsen:
PMO for skipping of Exon 53

Casimersen:
PMO for skipping of Exon 45



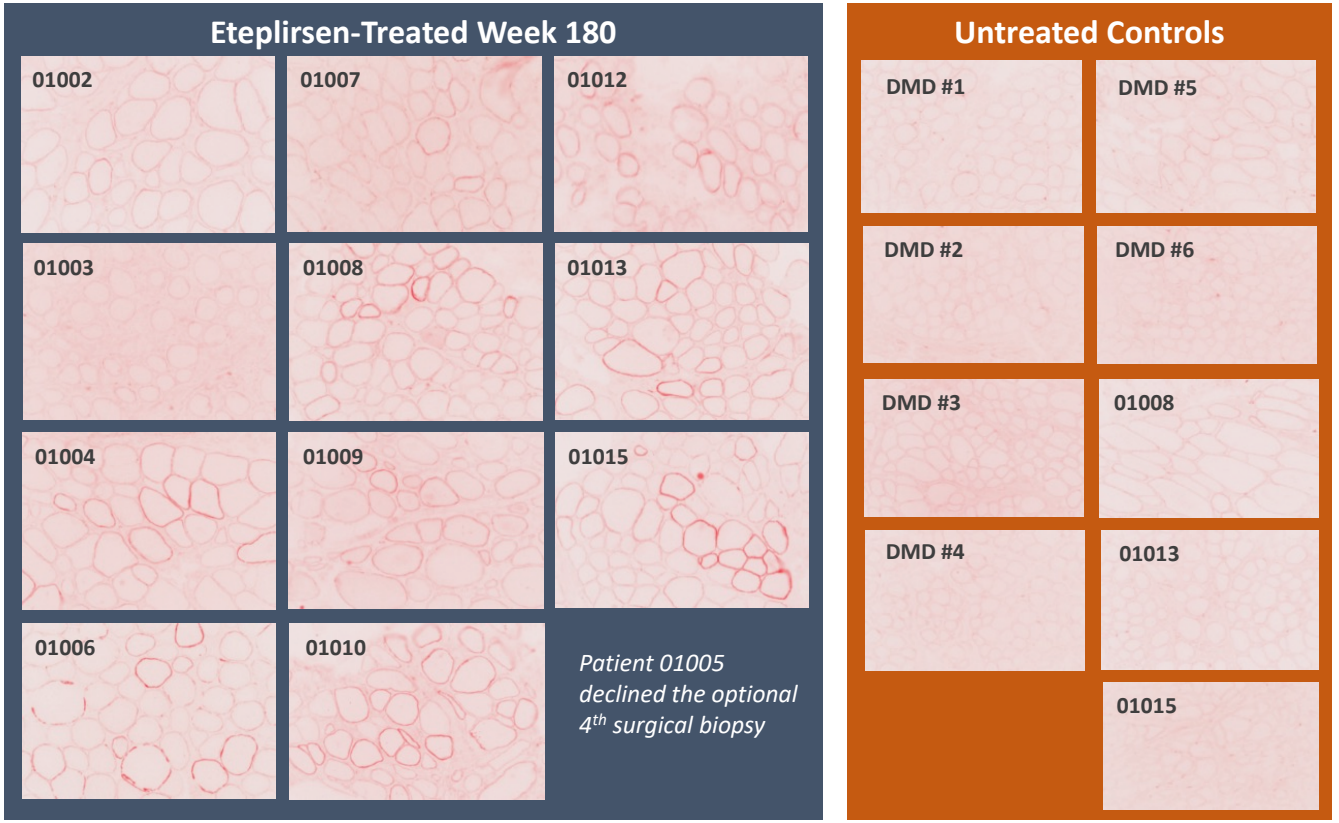
1. Annemieke Aartsma-Rus, et al. Hum Mutat. 2009;30(3):293-299.
2. Flanigan MC, et al. Hum Mutat. 2009;30(12):1657–1666.

Eteplirsen Is a Phosphorodiamidate Morpholino Oligomer (PMO)



- Sequence length: 30 nucleotide bases
- Administered through weekly IV infusions of 30 mg/kg
- Doses studied (IV) 0.5 – 50 mg/kg
- Safety database of >150 patients
- >260 patients post-marketing

Dystrophin Increases and Correct Localization after Eteplirsen Treatment (Study 202 Week 180)



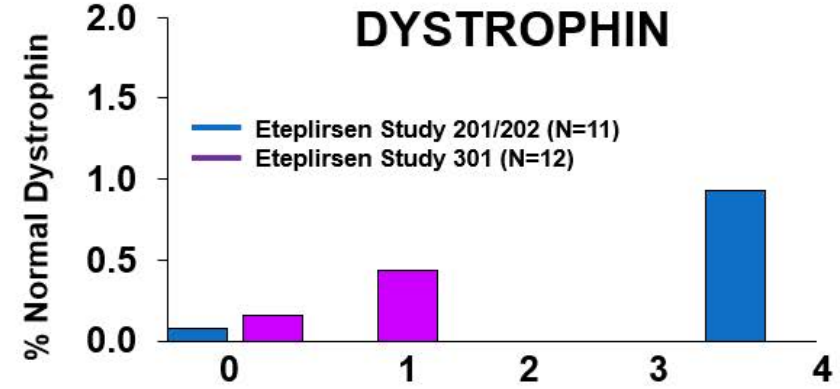
Inverted Images for Display Purposes Only

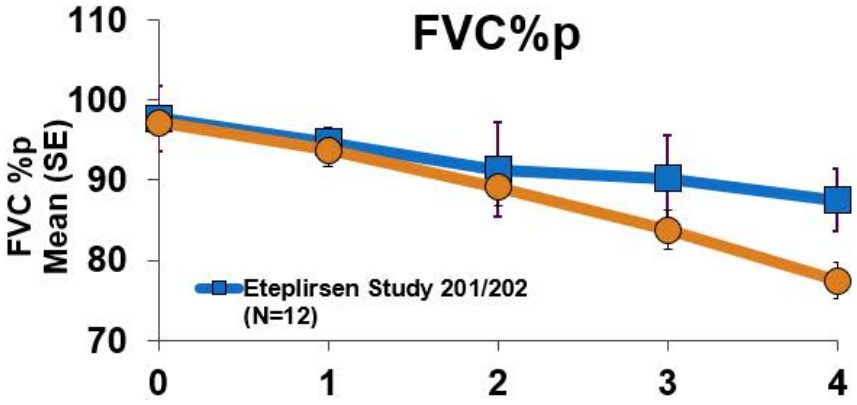
Increased Dystrophin Detected by All 3 Methods at Week 180 with Eteplirsen

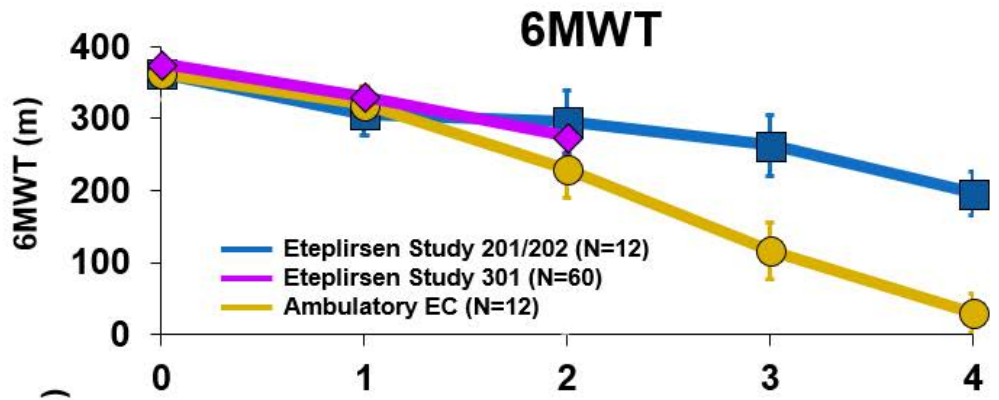
Method	Absolute Differences of Means (Treated vs Untreated Exon 51–Amenable Patient*) (% of Normal)	Fold Increase	P-value
PDPF	+16.27%	15.5	<0.001
Intensity	+13.20%	2.4	<0.001
Western blot	+0.85%	11.6	0.007

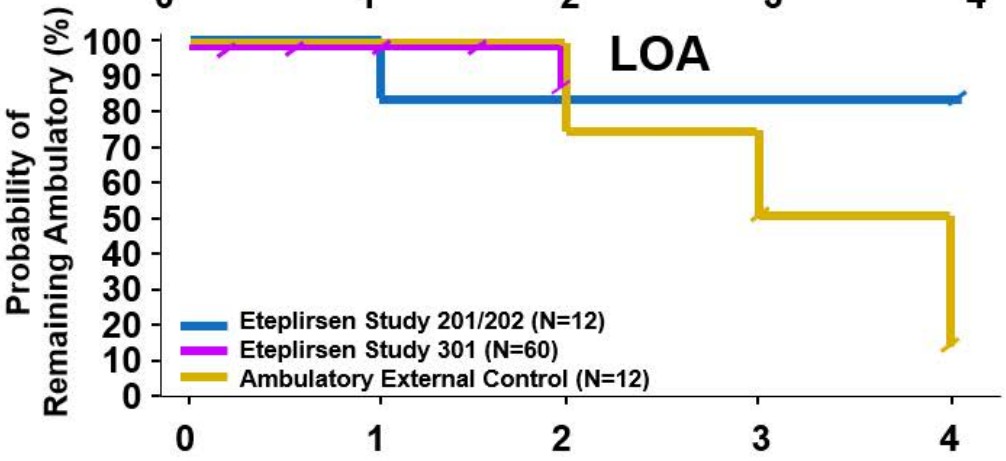
*Untreated Control Group n=3 201/201 baseline + n=6 study 301 baseline

Clinically Meaningful Benefit Greater After 1 Year

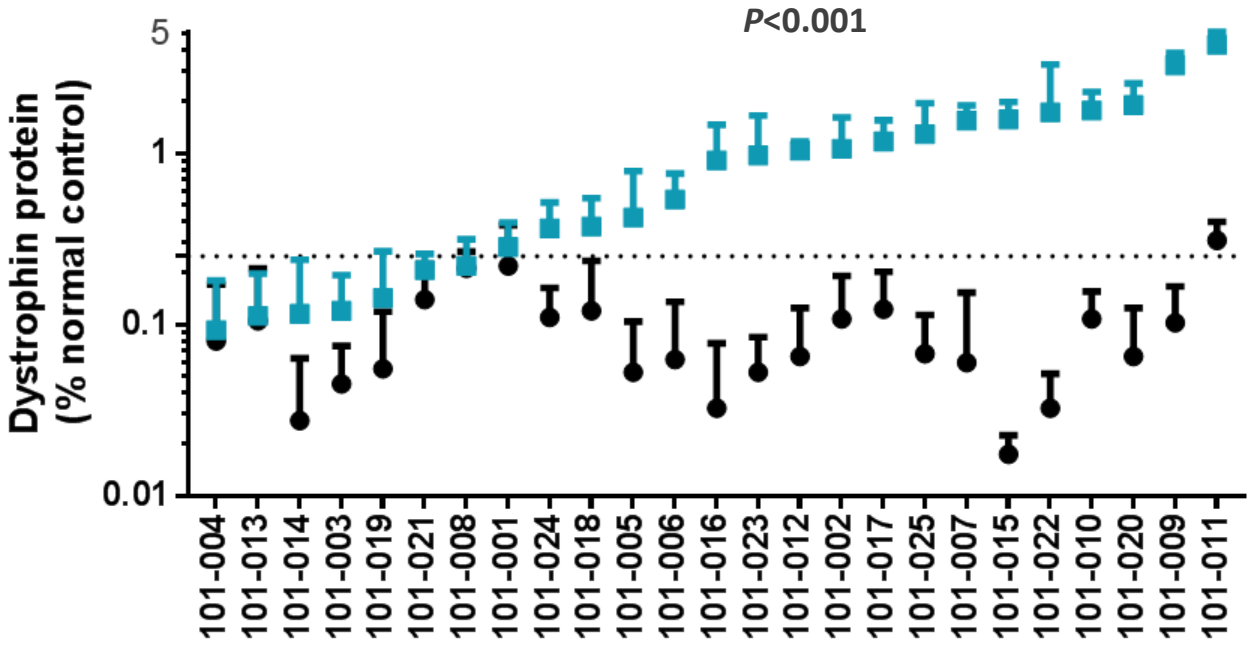








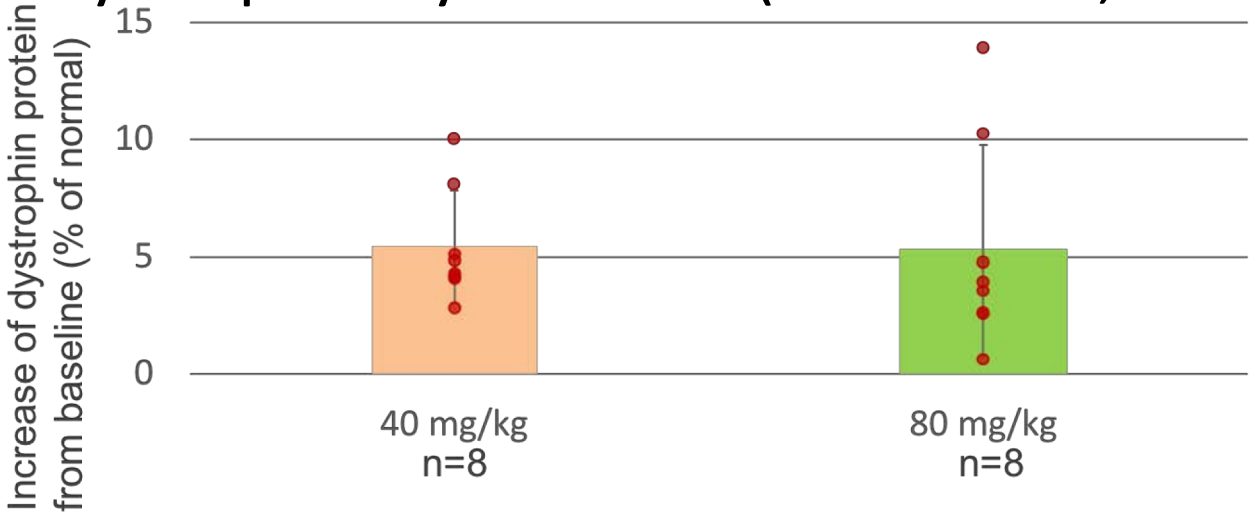
Golodirsen (Exon 53): Novel Dystrophin Production at Week 48 by Western blot (n=25)



10.7-Fold Increase in Mean Dystrophin by Western Blot (Week 48)

Mean Baseline = 0.095% normal (SD 0.0680)
Mean On-treatment = 1.019% normal (SD 1.0328)

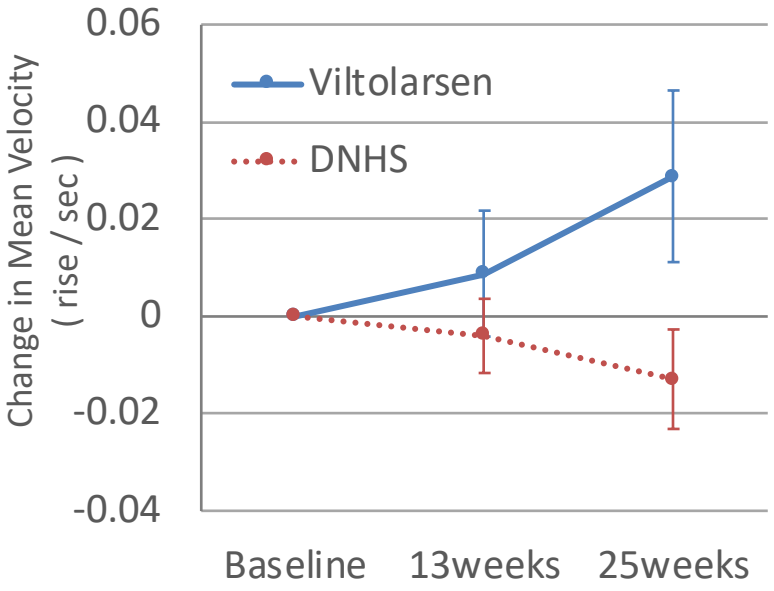
% Dystrophin by Western (Viltolarsen, NS Pharma)



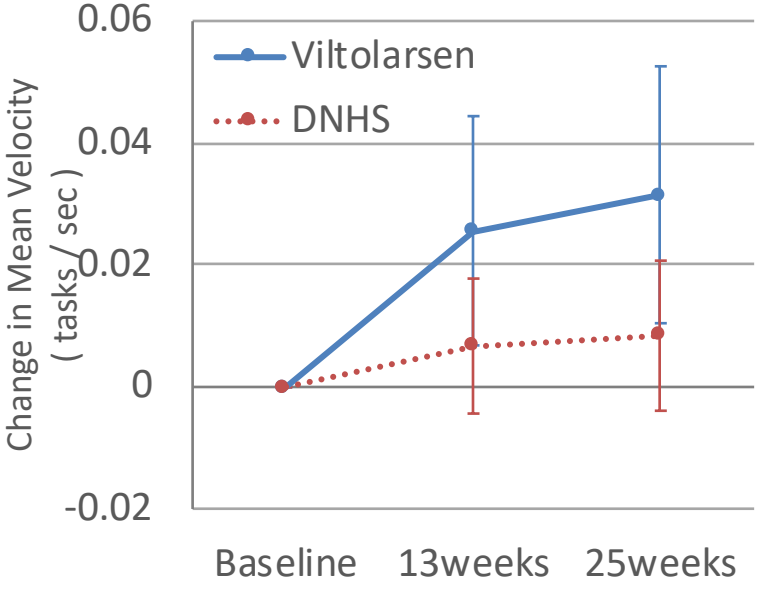
Method	Dose	Baseline Mean % (SD)	On-treatment Mean % (SD)	Fold Changes
% exon skipped molality (RT-PCR)	40 mg/kg	0.0 (0.0)	17.4 (7.2)	
	80 mg/kg	0.0 (0.0)	43.9 (16.7)	
% dystrophin (Western blot)*	40 mg/kg	0.3 (0.1)	5.7 (2.4)	19
	80 mg/kg	0.6 (0.8)	5.9 (4.5)	9.8

Clinical changes with Exon 53 skipping (Viltolarsen)

Stand from Supine (Velocity)

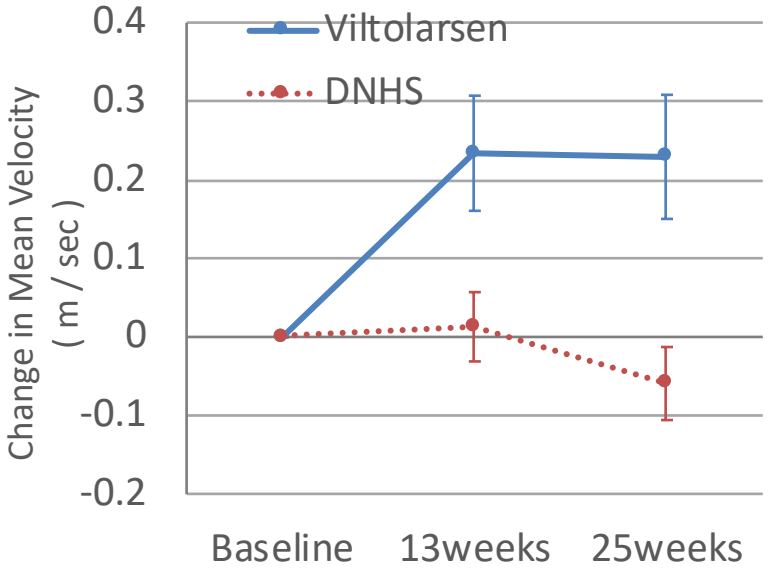


Climb 4-stairs (Velocity)

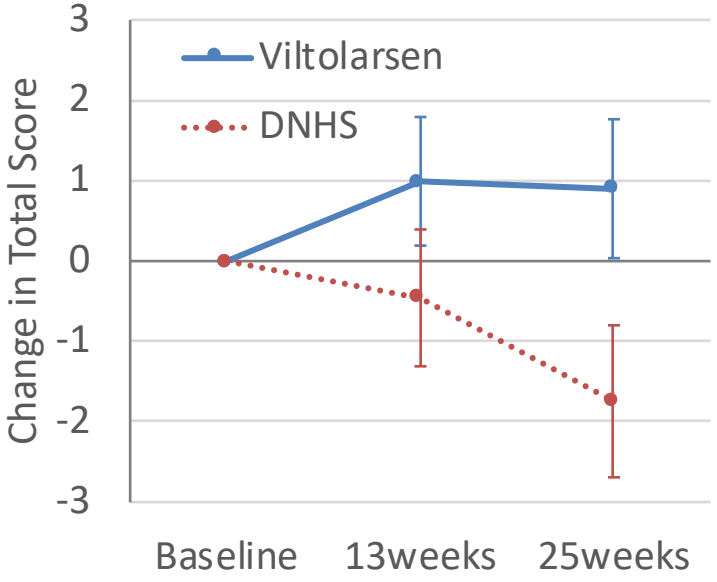


Clinical changes with Exon 53 skipping (Viltolarsen)

Run/walk 10 meters



North Star Ambulatory Assessment



Clinical Outcome Measures in DMD

- Function tests:
  - Northstar Ambulatory Assessment (NSAA)
  - 6 minute walk test
  - Manual and quantitative strength assessments
  - Pulmonary function testing (PFTs)
  - Performance of upper limb score (PUL)
  - Patient reported outcomes

- Currently, there are no reliable clinical ambulation endpoint outcome measurement tools ***for children ages 2 to 5 years old.***

- What are some limitations of prior studies (ie 6mw)?
  - Interpretation of velocity based data as a measure of functional ability requires adjustment for age and stature.
  - Why?
    - Velocity is a product of stride length and cadence
    - Stride length has not previously been normalized for height and age in many of our routine clinical outcome measures for community ambulation.

- Problems with interpreting data from community based step monitoring:
  - Stride length is the variable most altered in DMD
    - Higher predictor of clinical outcomes (especially in early disease)
  - Step Cadence varies only slightly in DMD (until later stages of disease)

- How do we normalize stride length using anthropometric data?:
    - divide stride length by height to create a standardized stride to height ratio (SHR).

Stride:Height Ratio - A developmentally adjusted anthropometric standard

Stride length = Height(X) **at different gaits / velocities in humans**

SHR	0.8	1.2	1.5-1.9	>=2

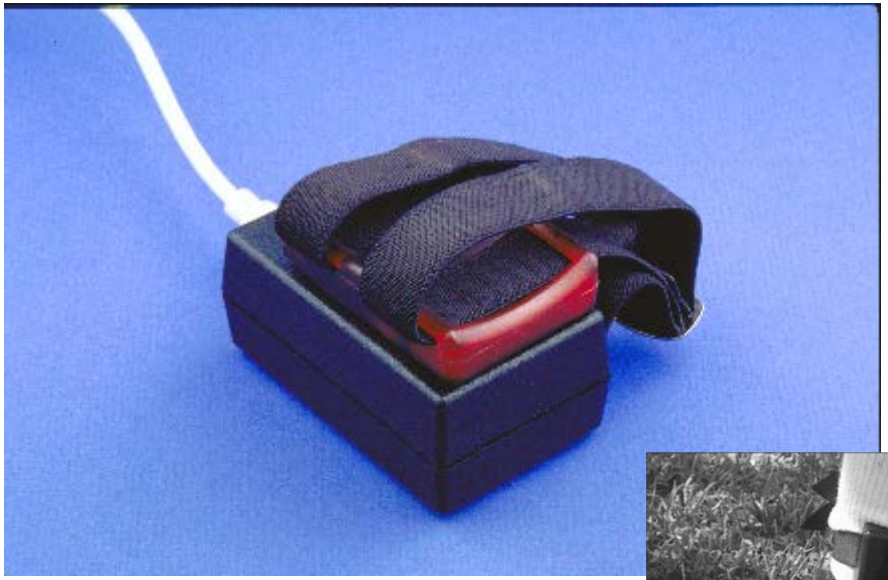
Stride:Height Ratio (SHR) in DMD

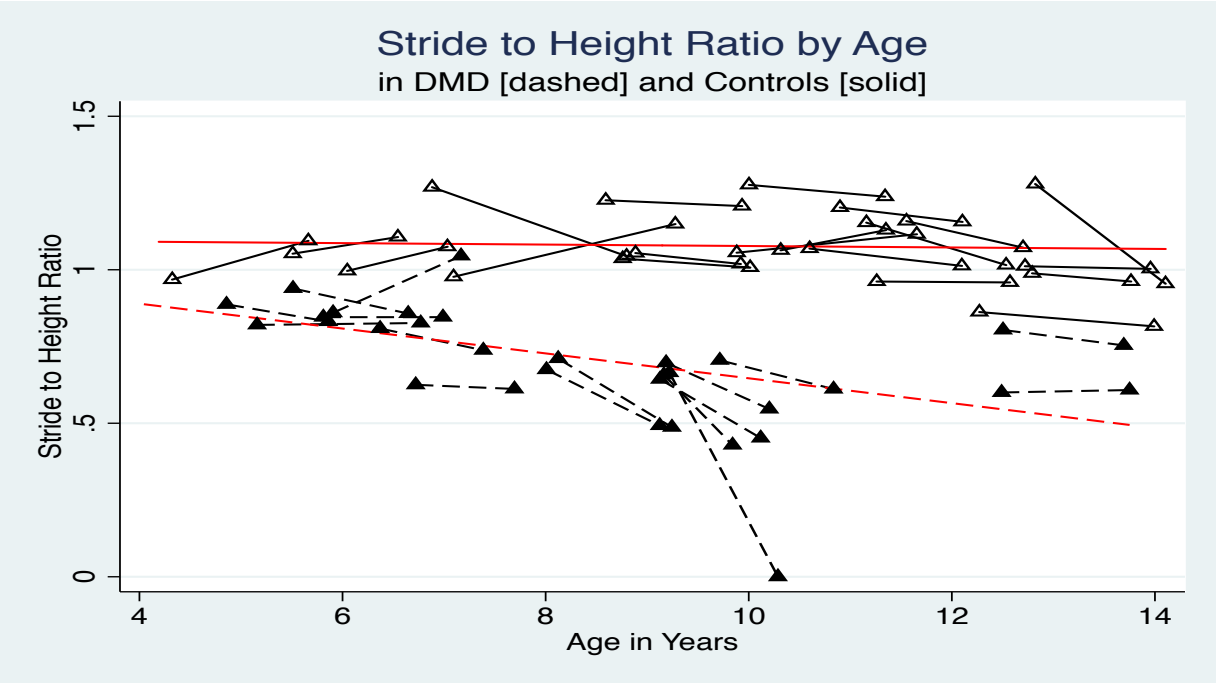
- Methods:
  - 24 boys with DMD (Dx Confirmed) and 36 typically-developing control boys
  - Ages of 4 to 12 Y.O
  - Participants assessed at baseline and at 1 year

Stride:Height Ratio (SHR) in DMD

- Methods Cont':
  - Clinical assessments used:
    - Anthropometric measures
    - Six-minute walk test (6MWT)
    - Timed 10 and 25 meter walk/run tests
    - ***Stride length (m) =total distance (m) /#strides registered on calibrated StepWatch™ activity monitor.***
    - ***Patient reported outcomes: PODC1***

StepWatch®
Activity Monitor
In DMD shows
decreased function





SHR Trajectory declines with age in DMD relative to peers.

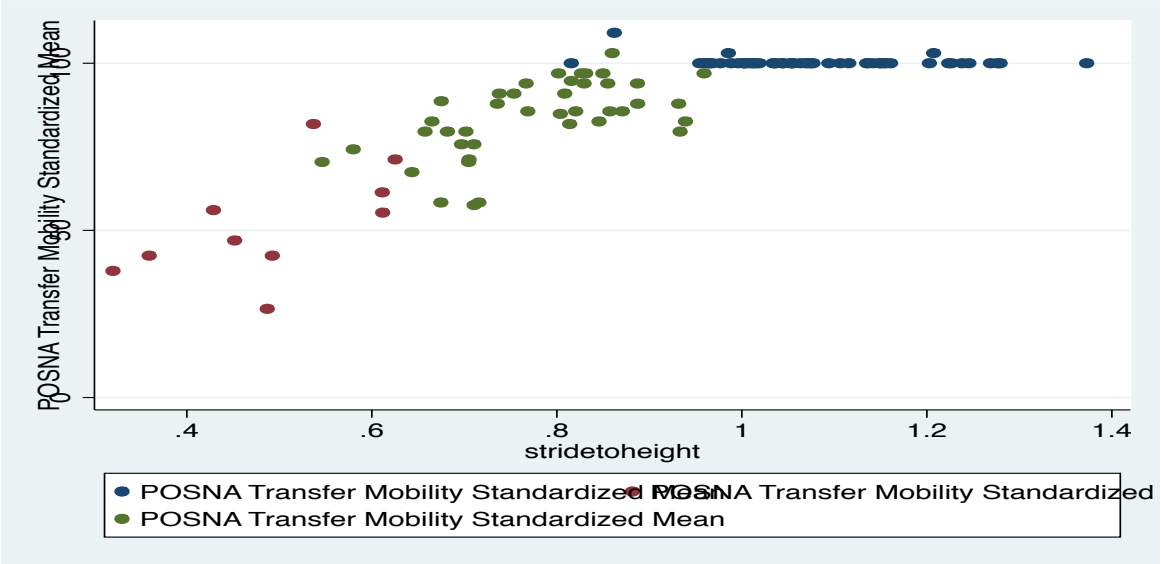
SHR at fastest pace:

-Controls: 1.08 +/- 0.12 with no change at one year

-DMD: 0.74 +/- 0.14, $p<0.0001$

*shortening of SHR with disease progression over one year: 0.08 +/1 0.11 ($p<0.0081$

Transfers and Basic Mobility Subscale Score vs. Stride:Height



POSNA pediatric musculoskeletal functional health questionnaire

Clinical important because it trends with the patient's report using a mobility based self report assessments

Use of Stride:Height as a clinical outcome tool

- Stride: height ratio (SHR) using step activity monitors can serve as a simple clinic or community-based to standardize ambulatory measures across ages in DMD for use in clinical trials.
- SHR is a gait parameter indicative of disease status and to determine responsiveness to newer therapies and record a longitudinal record as they age and progress through the disease course
- Normalization of SHR in DMD may indicate benefits from treatments
- May be a useful tool in all children with mobility impairments

Acknowledgments

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