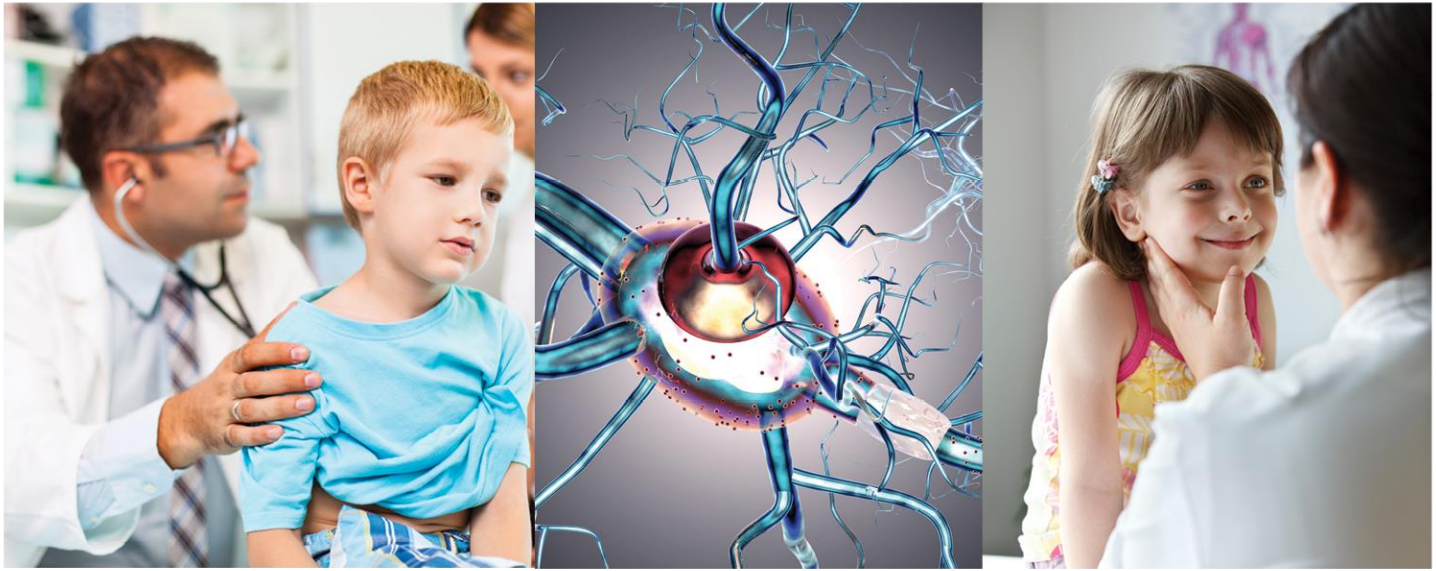
Making A Difference in Duchenne Muscular Dystrophy & Spinal Muscular Atrophy:

PEDIATRICIANS AT THE FRONT LINE OF EARLY DIAGNOSIS & IMPROVED SURVIVAL



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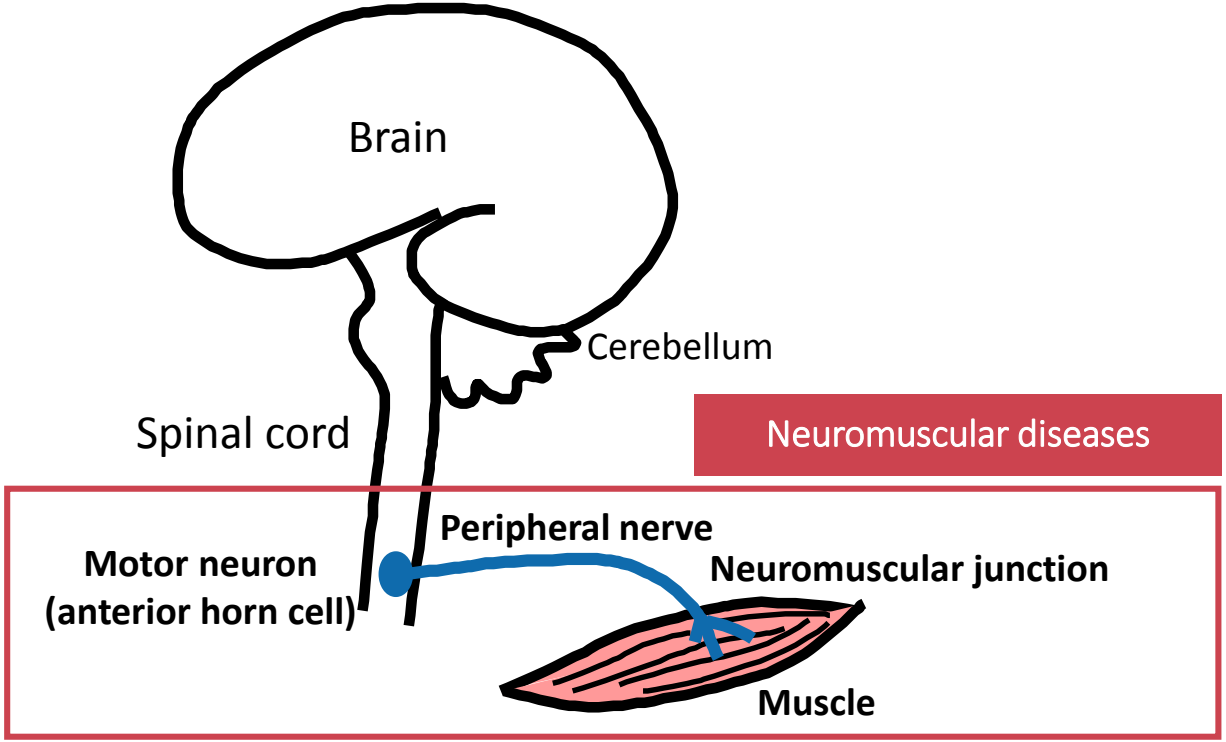
This activity is supported by an independent educational grant from **Sarepta Therapeutics.**

Outline

- Introduction to neuromuscular diseases
- Importance of early recognition and diagnosis
- Hints for evaluating motor function
- Resources for evaluating a child with motor delay or weakness
  - childmuscleweakness.org
  - American Academy of Pediatrics (AAP) algorithm

Motor System



Examples of Specific Diagnoses by Anatomic Location

Anatomic location	Disease
Motor neuron	Spinal Muscular Atrophy (SMA)
Peripheral nerve	Hereditary peripheral neuropathy (CMT)
Neuromuscular junction	Myasthenia gravis Congenital myasthenic syndromes
Muscle	Myopathies Muscular dystrophies

Neuromuscular Diseases

Brain/ spinal cord

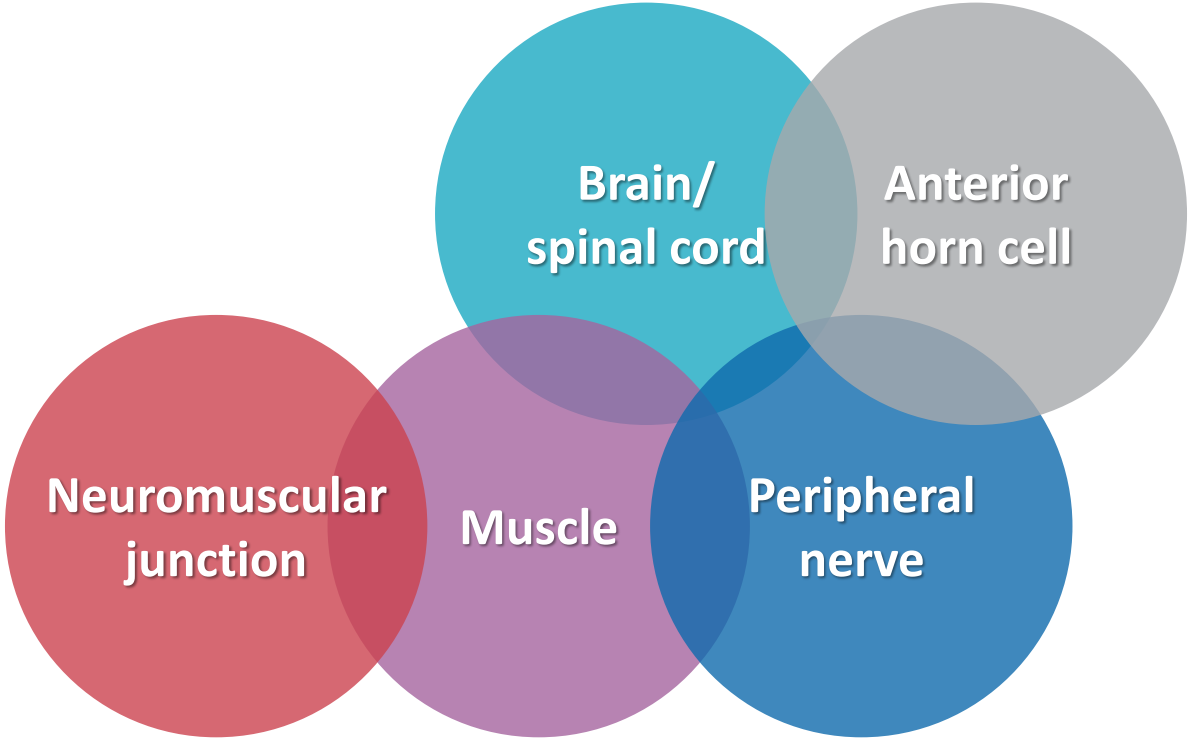
Muscle

Anterior horn cell

Peripheral nerve

Neuromuscular junction

Neuromuscular Diseases (Reality)



Prevalence of Early Childhood Disorders

Condition	Prevalence
Learning disabilities	65 per 1000 (1 in 15)
Autism spectrum disorders	11.3 per 1000 (1 in 88)
Cerebral palsy	3.3 per 1000 (1 in 303)
NM diseases	0.3 per 1000 (1 in 3000)

Adapted from :
Boyle, Decoufle, Yeargin-Allsopp, 1994; Autism and Developmental Disabilities, 2012; Center for Disease Control and Prevention, 2012; Emery, 1991.

There is Often a Delay in the Diagnosis of Neuromuscular Disease in Childhood

- First concerns noticed by parents before they discuss with medical professional (Ciafaloni, 2009)
- Clinical judgment alone = missed motor delay in up to 2/3 patients (Smith, 1978)
- Surveillance, screening and recognition are critical to make an early diagnosis

Diagnostic Delay in Duchenne/Becker Muscular Dystrophy

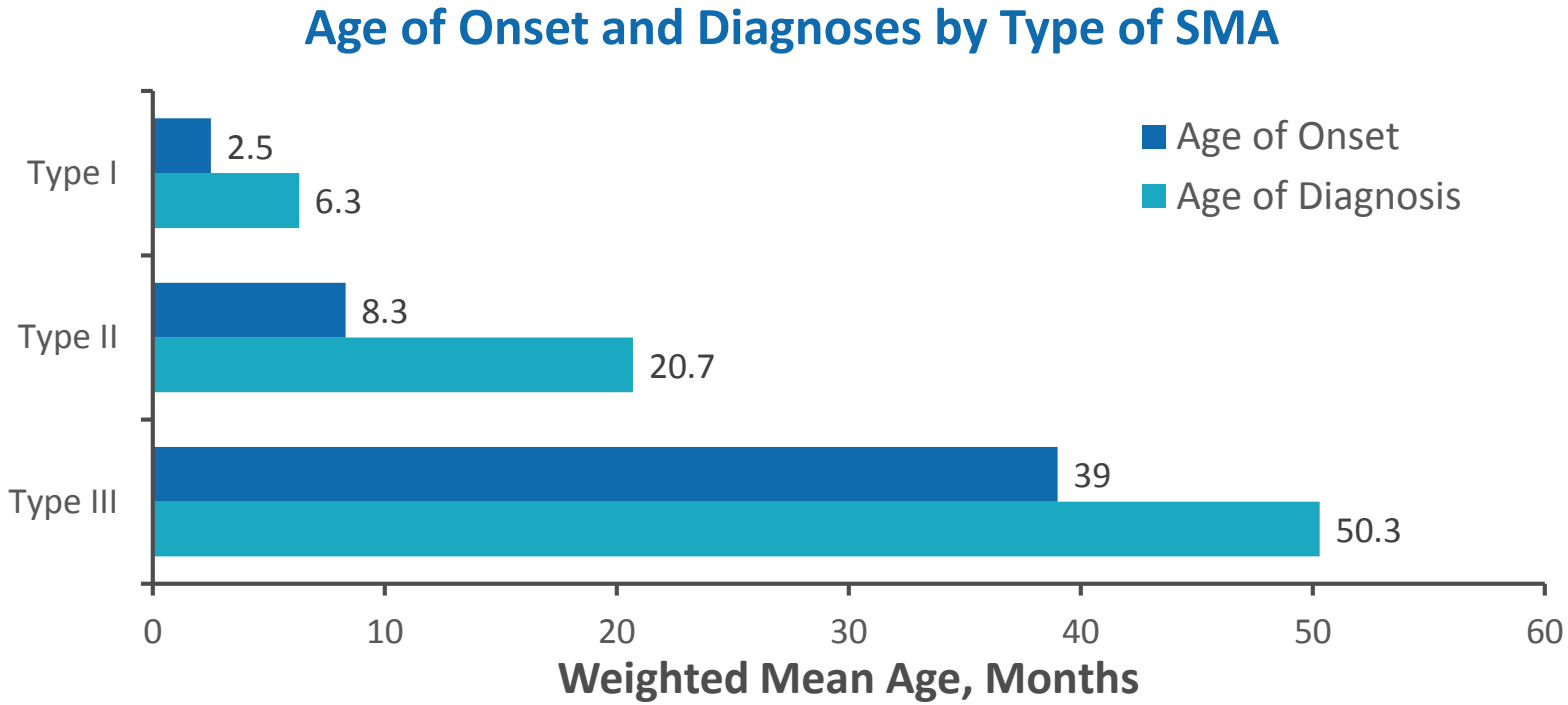
Parameter	Mean Age (y)	Age Range (y)
Earliest s/sx	2.5 ± 1.4	0.2-6.1
1st health care eval	3.6 ± 1.7	0.2-8.0
1st neuro visit	4.6 ± 1.7	0.3-8.6
1st CK	4.7 ± 1.7	0.3-8.6
Dx made	4.9 ± 1.7	0.3-8.8

- Average delay in diagnosis ~2.5 years
- Diagnosis made shortly after seeing neurologist

CK, creatine kinase.

Ciafaloni E, et al. *JPeds* .2009; 155:380-385.

Diagnostic Delay in Spinal Muscular Atrophy ~1 Year in Later Onset Types



SMA, spinal muscular atrophy.

Lin CW, et al. *Pediatr Neurol* .2015; 53: 293-300.

Why Early Identification?

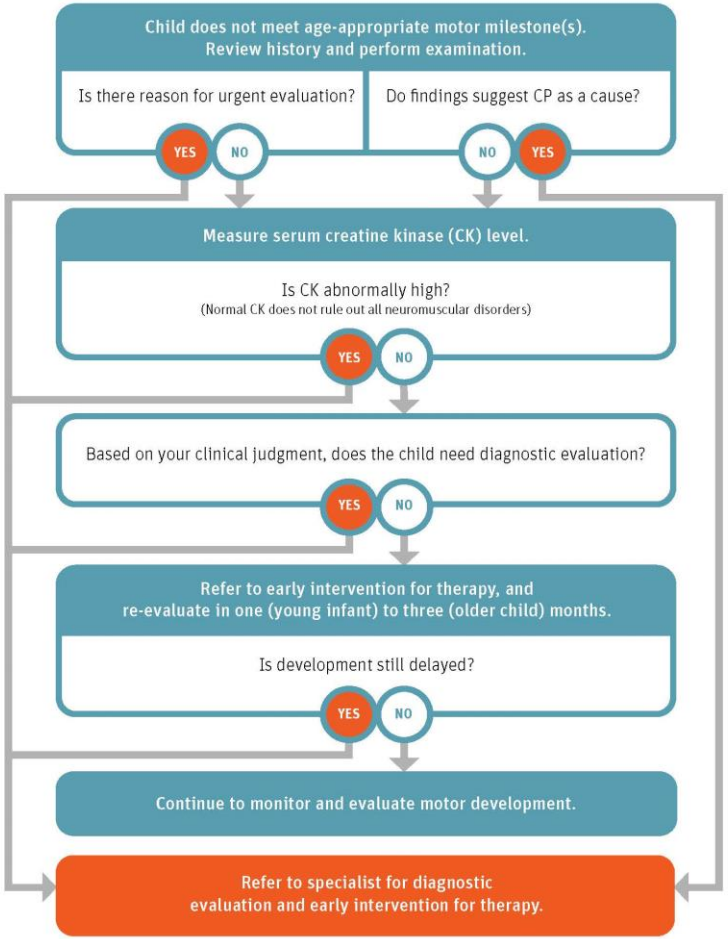
- Reduce diagnostic odyssey and relieve associated caregiver stress (Developmental Surveillance, 2001)
- Initiation of treatment to slow/reverse disease progression (Lurio, Peay & Mathews, 2015)
  - Recent FDA approved therapies
- Genetic counseling (Lurio, Peay & Mathews, 2015)
- Participation in treatment trials (Lurio, Peay & Mathews, 2015)

childmuscleweakness.org Launched 2012

- Real time quick reference
- Educational tool

- Motor development assessment
- Motor delay algorithm
- Videos
- Interpretation of CK

- Steady increase in use views annually based on Google analytic analysis

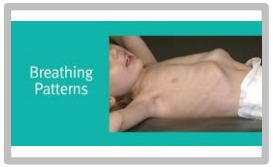


childmuscleweakness.org

Video Library

Pull to Sit-Head Lag

Breathing Patterns

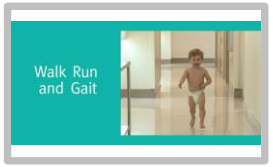


Slipping Through When Lifted

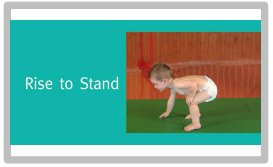
Tongue Fasiculations

Acquiring Sitting Balance

Walk Run and Gait



Rise to Stand



Jump and Hop

Tone and Reflexes

Downloadable PDF Designed for Primary Care

Guide for primary care providers includes:

- Surveillance Aid: Assessing Weakness by Age
- Clinical Evaluation for Muscle Weakness
- Developmental Delay, Do a CK
- Motor Delay Algorithm

Developmental Screening Tools

- childmuscleweakness.org

Milestone: Gait (12+ Months)

Description

Watch child walk after parents report s/he can walk independently. Watch or ask about ability to run at 18-month and 24-month visits or until running is achieved. Ask about any concerns with walking, running, or frequent falls at all visits after milestone is achieved.

Surveillance & Next Steps

Walking

If a child does not walk at 15 months, consider referral for early intervention and physical therapy for developmental stimulation, taking into account overall motor development, and re-evaluate within 2–3 months. A child who does not walk well at 18 months, or shows regression in ability to walk, needs further evaluation and should receive a CK test and referral. See the *Motor Delay Algorithm* on page 10.

Running

If a child does not run at 20 months, consider referral for early intervention and physical therapy for developmental stimulation, taking into account overall motor development, and re-evaluate within 2–3 months. Particularly note the quality of running, especially if there are other motor concerns. A child who does not run at 24 months, or shows regression in ability to run, needs further evaluation and should receive a CK test and referral. See the *Motor Delay Algorithm* on page 10.

Developmental Norms

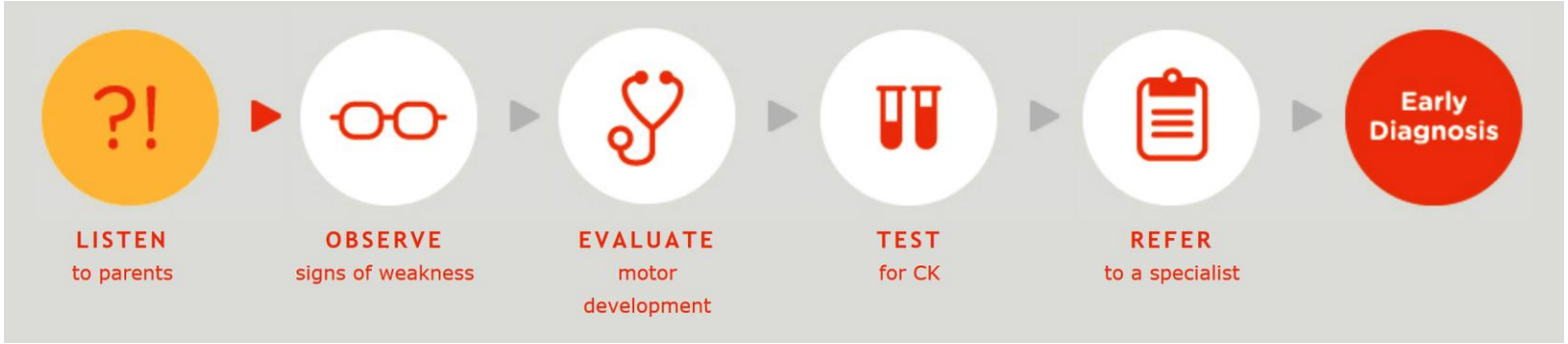
Walking Alone	*Running*
50% by 12 months	50% by 16 months
75% by 13.1 months	75% by 18.5 months
90% by 14.4 months	90% by 21 months
Source: WHO Motor Development Study	*Source: Denver II*

AAP Guidance

- Developmental surveillance at every visit
  - Tables of motor milestones
- Formal screening at 9, 18, 30 and 48 months
  - Typically parent-report
- Differential diagnosis table
  - Nortitz GH, et al. Motor Delays: Early Identification and Evaluation. *Pediatrics*, 2013.

Steps to Early Diagnosis

1. Listen to parents' concerns
2. Observe for signs of weakness
3. Evaluate motor development
4. Check CK ("Developmental delay, do a CK")
5. Refer to specialist



Listen to Parents' Concerns (Surveillance)

- Take developmental history
  - When were milestones achieved?
  - Keeping up with peers?
  - Falls?
  - Course and progression?
  - Loss of skills?
  - Family history?
- 80% of parents' concerns are correct and accurate
- Ask questions, especially if parents present vague concerns

National Center for Medical Home Implementation, AAP.

Localize the Problem: Peripheral versus Central Cause of Weakness

Sign	Peripheral Cause	Central Cause
Chest size	May be small with bell shape	Usually normal
Facial movement	Often weak “myopathic” with high arched palate	Usually normal
Tongue fasciculation	May be present, particularly in SMA	Absent
Tone	Reduced tone	Reduced tone or increased tone with scissoring
Deep tendon reflexes	Decreased or absent	Increased, possible clonus
Gait	Toe walking Waddling Hyperlordotic	Toe walking Hemiparetic Spastic

Observe Signs of Weakness

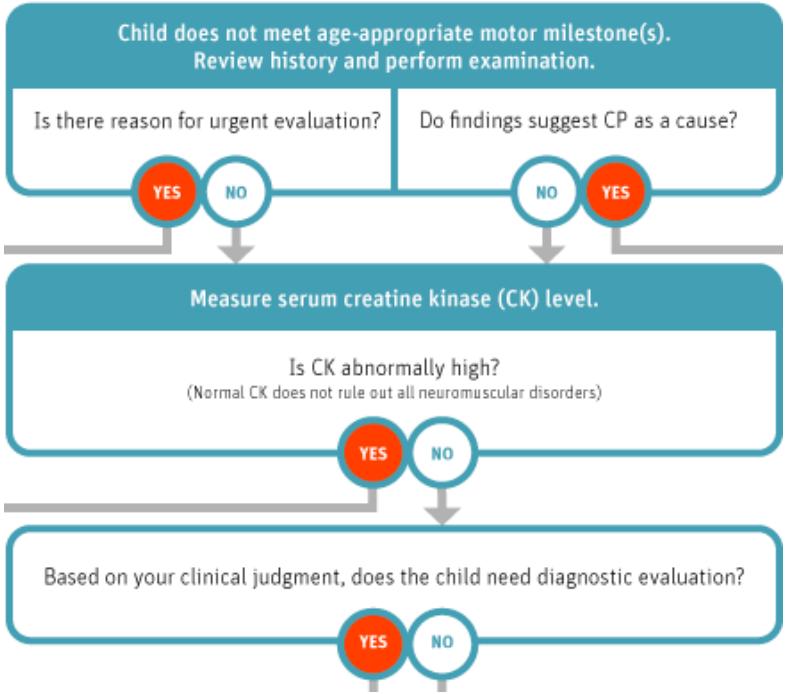
- Muscle bulk
  - Muscle hypertrophy or atrophy, particularly calves
- Posture
  - Resting position in infants
  - Hyperlordosis
  - Scapular winging
- Movement (“Watch them walk”)
  - Gowers maneuver with rise from floor
  - Waddling gait, hyperlordosis, toe walking

Rise to Stand: Gowers Maneuver

https://vimeo.com/47831448

Motor Delay Algorithm

- Determine if there is a central cause, such as CP
- If not, measure CK
- Based on CK, clinical evaluation, is urgent referral needed?
- If not, Early Access referral and close follow-up (1 month for infant, up to 3 months)



Red Flags: Any Age

- Regression in developmental milestones
- Tongue fasciculations
- Delayed motor milestones
  - Head lag at 5 months
  - Sitting by 7 months
  - Walking and rising to stand by 1.5 years
  - Jumping by 2.5 years
  - Stairs with alternating feet by 3.5 years

Communicating one or more red flags to the specialist/neurologist will often expedite referral.

Clinical Pearls

- Developmental progress does not exclude an underlying neuromuscular condition
- Neuromuscular diseases can involve the brain and cognition
- Normal CK does not eliminate a neuromuscular condition
- AST and ALT also come from muscle and can imply elevated CK
- Negative family history does not rule out NM conditions
- All weak children are hypotonic, but not all hypotonic children are weak

Case: Three-year-old Boy Seen for Well-child Check

- Mother reports that he is making steady developmental progress, but he is slower than peers on the playground
- You review his developmental records and see that he walked at 16 months and didn't start talking until around 18 months
- Prenatal and perinatal history were unremarkable
- He has been healthy and isn't on any medications
- There is no family history of neurologic disease
- Exam:
  - Growth including OFC has followed the 50th percentile
  - General exam is normal
  - He is not able to run but walking appears normal
  - He puts his hand on his knee when he arises from sitting on the floor
  - He has firm calf muscles
  - Reflexes are 2+ and symmetric

Summary

- Developmental surveillance and screening can result in early diagnosis of rare neuromuscular diseases
- Physical exam findings help to localize the cause of weakness
- Elevated CK can be a clue to some neuromuscular diseases
- Early recognition matters!
  - Management and treatments result in better outcomes

Acknowledgements

- Holly Peay, Ann Martin, PPMD and colleagues who contributed to childmuscleweakness.org
- CDC for supporting this work
- NIH for support of ongoing support

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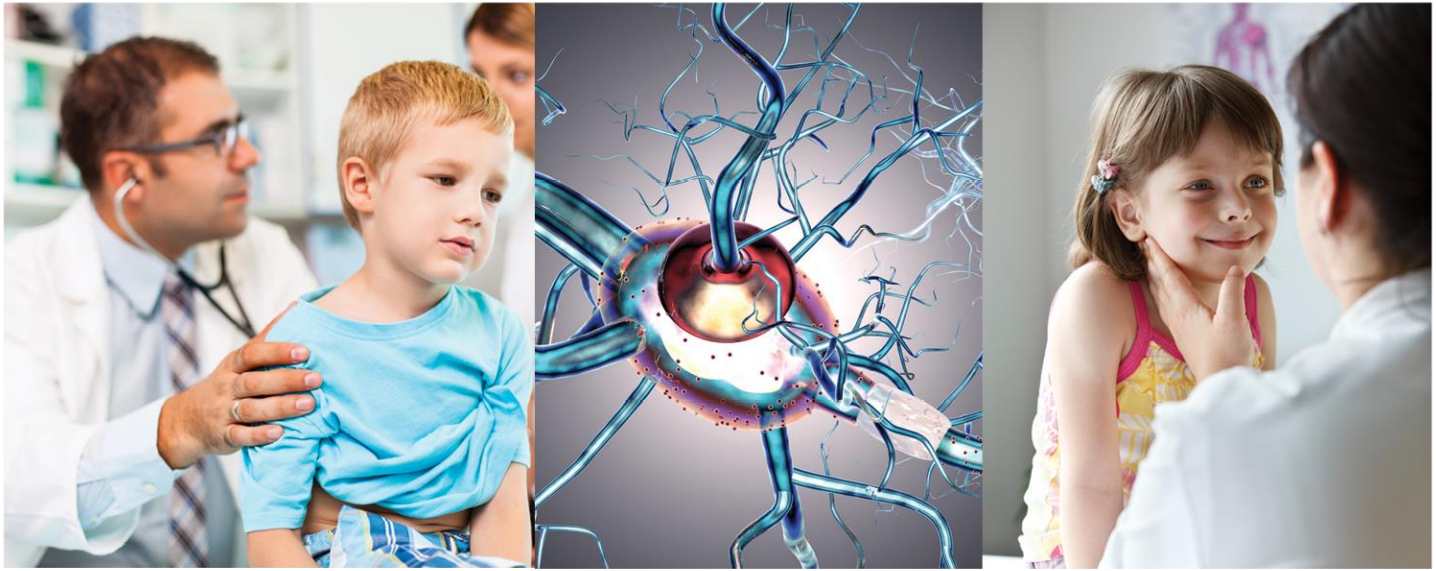

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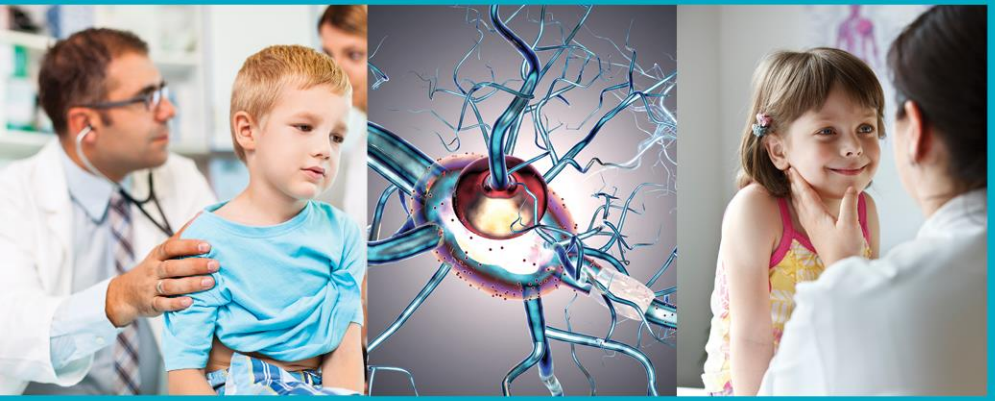


Classification, Tests, Guidelines, Early Diagnosis and Treatment for DMD

Craig M. McDonald, MD

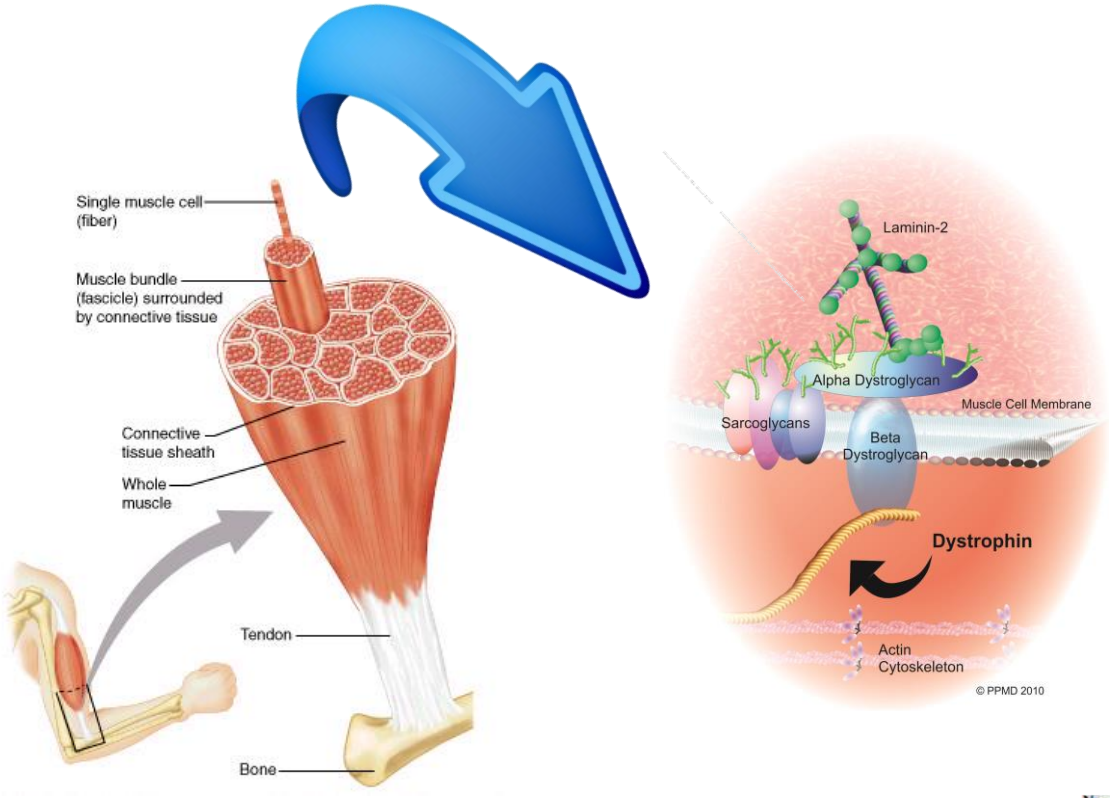
Professor and Chair of Physical Medicine and Rehabilitation
Professor of Pediatrics
Study Chair CINRG Duchenne Natural History Study
University of California Davis Health
Sacramento, CA

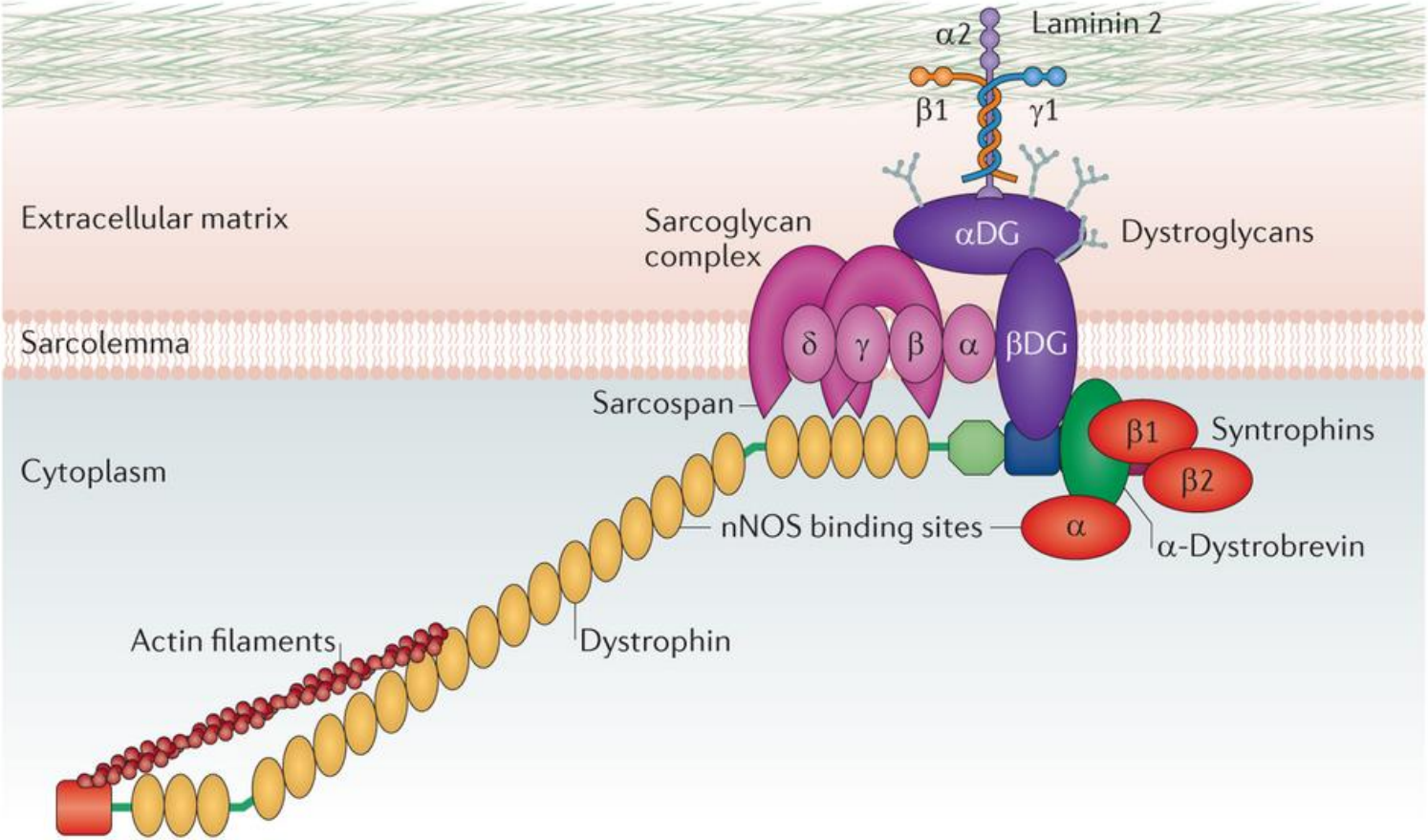
2 Year 10 Month Old With Early Motor Delay

- Early motor delay
- Slight language delay
- Ambulated at 17 months
- Labs: CK = 28,000
- AST and AST 8X elevated
- LDH elevated 6X normal
- Complete gene sequencing of Dystrophin gene with deletion testing with multiplex ligation-dependent probe amplification (MLPA) shows deletion of exon 48-50 c/w diagnosis of Duchenne muscular dystrophy

Starting at the Beginning

Due to a genetic mutation, the dystrophin protein is missing or not functional in Duchenne.

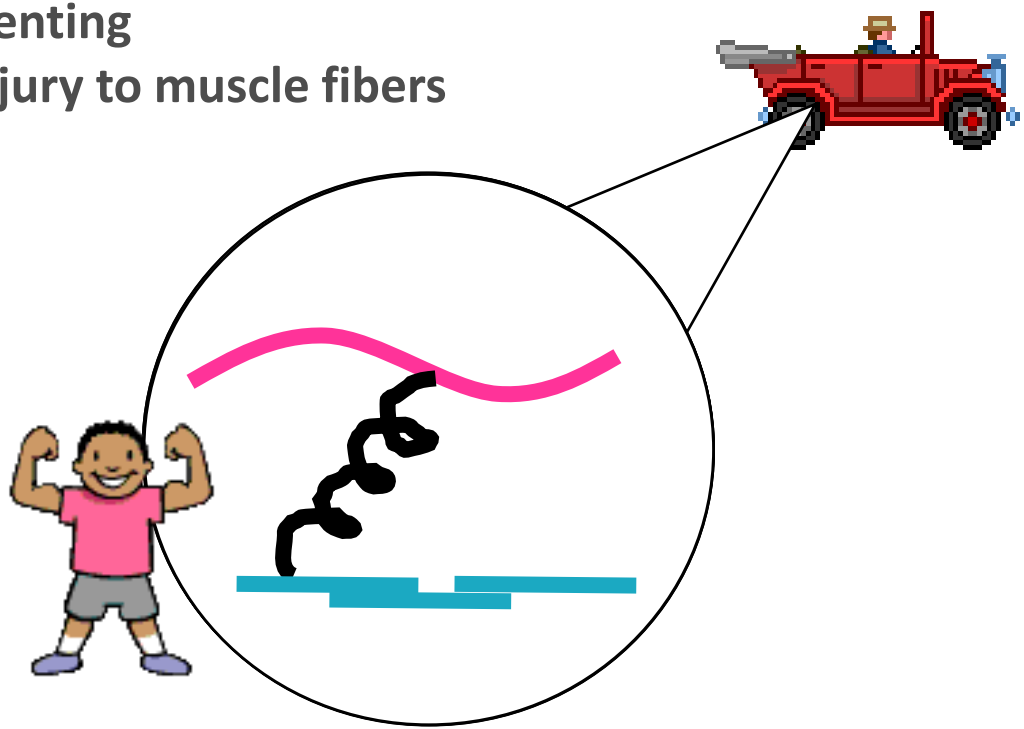




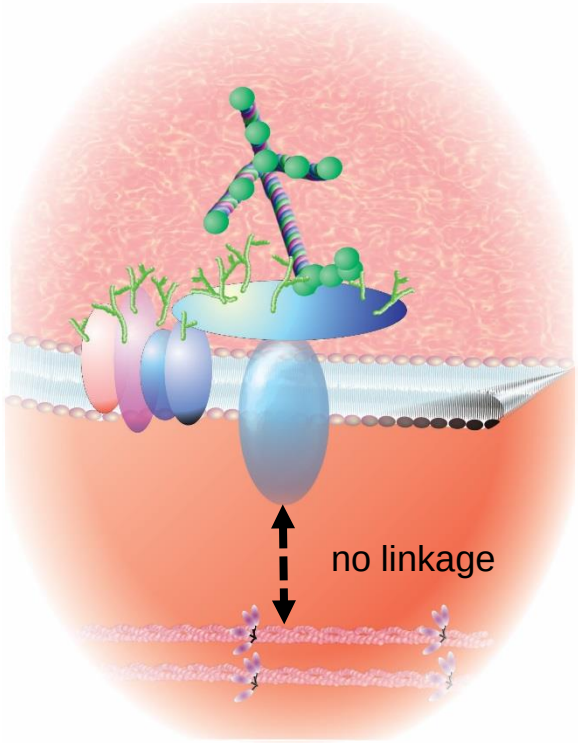
Nature Reviews | Genetics

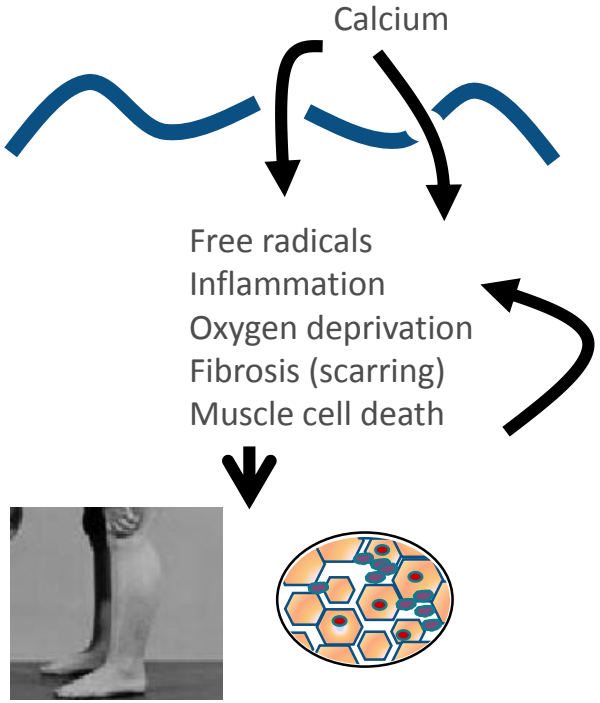
What Does Dystrophin *Do*?

Shock absorption preventing contraction-induced injury to muscle fibers



What Happens When Dystrophin is Missing?





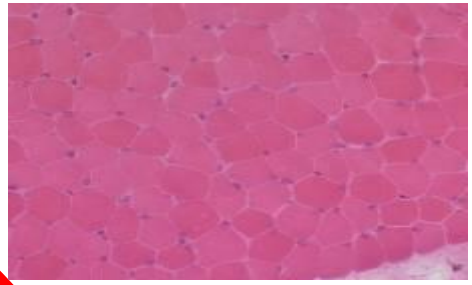
DMD Pathomechanism

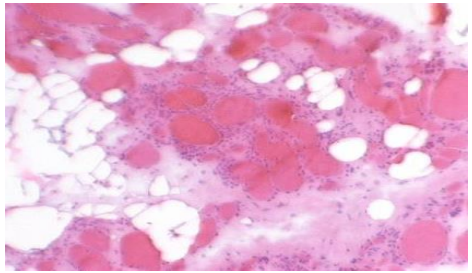
Gene abnormality at Xp21 loci

↓

Absence of dystrophin

Structural defect





Membrane instability

Apoptosis/Necrosis

Satellite Cell Activation
Muscle Fiber Regeneration

Activation of NF-kB

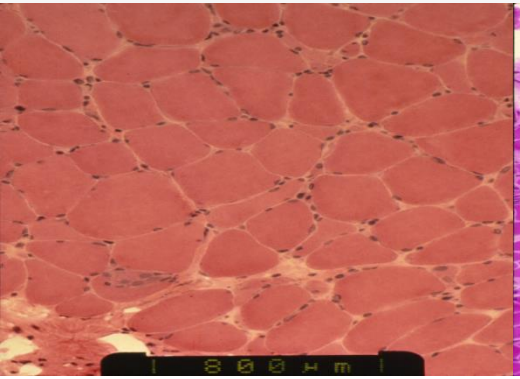
Inflammation

Fibrosis

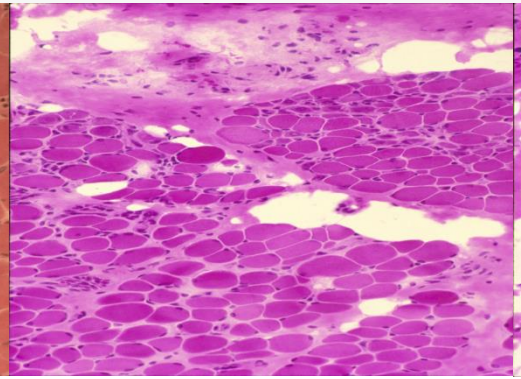
Fiber Death

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

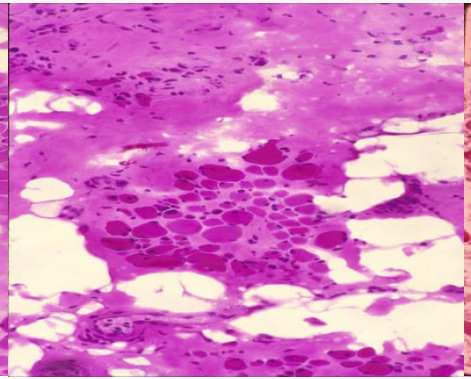
Loss of Muscle Fiber in DMD



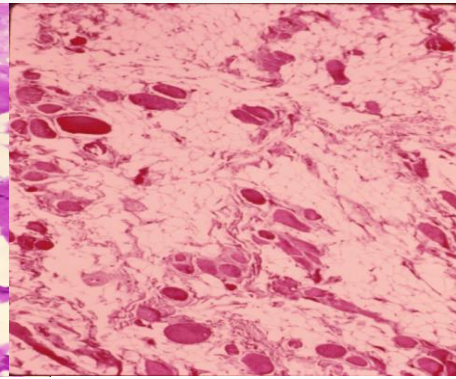
Normal



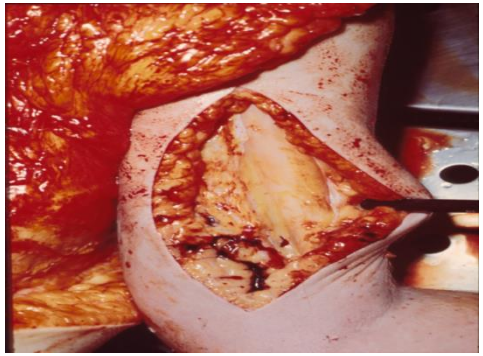
3-year-old

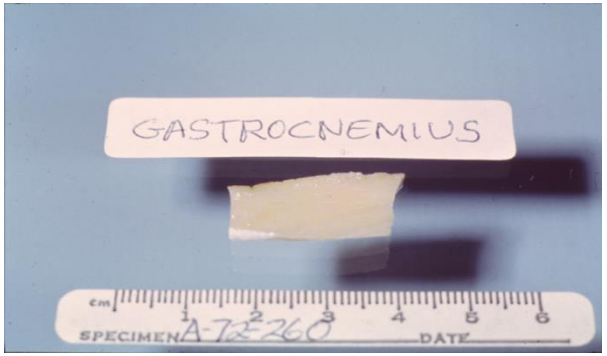


9-year-old



Post-Mortem



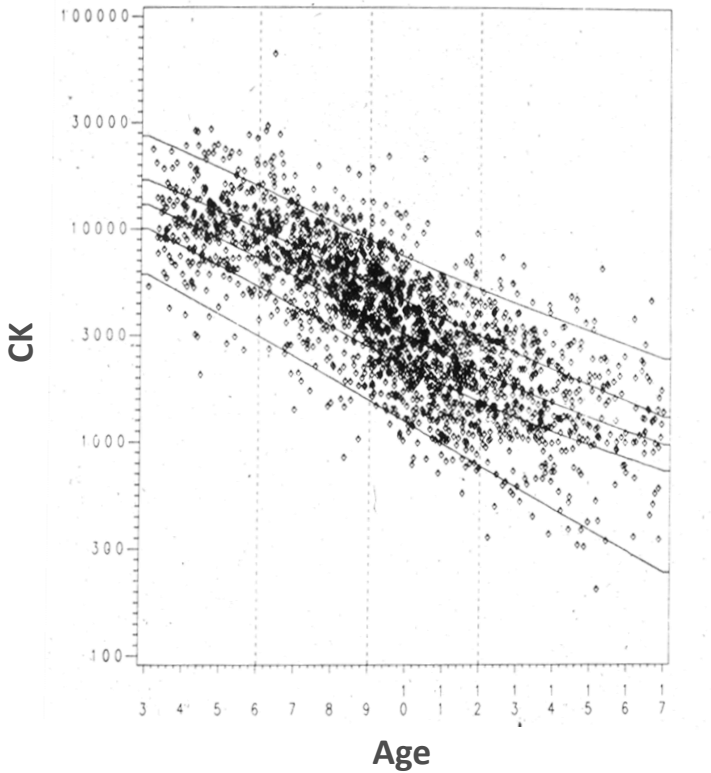


19-year-old (Post-Mortem in Year 1990)

Serum CK

Creatine Kinase (CK) vs. Age (3 to 17 years)

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

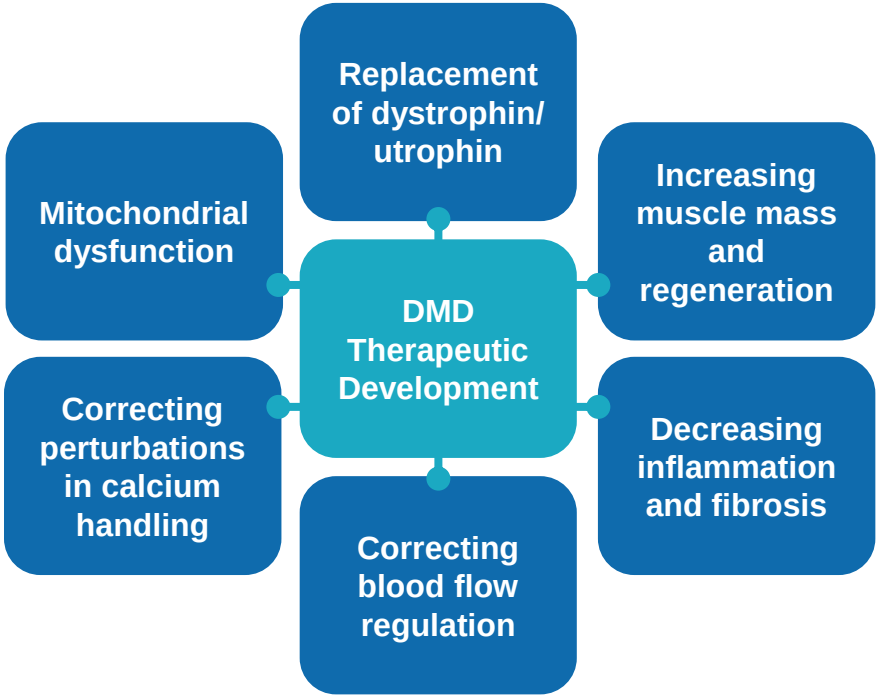


Scatter plot of CK values against the patients' age expressed on a logarithmic scale. The lines represent the 5th, 25th, 50th, 75th, and 95th percentiles.

Liver Function Tests Elevated in Muscular Dystrophy

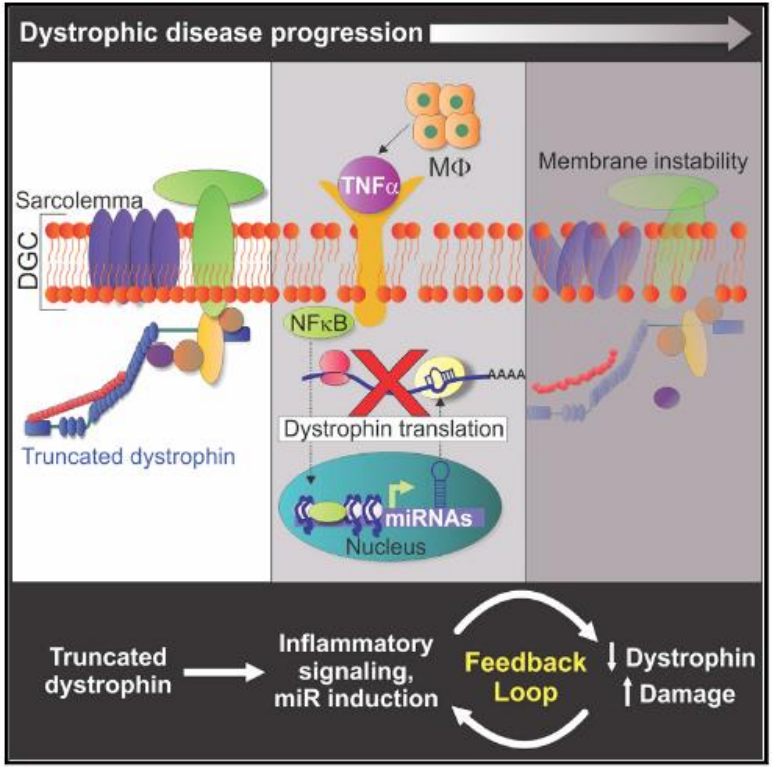
Occasionally, an increased ALT, AST, or LDH concentration prompts an inappropriate focus on hepatic dysfunction, delaying the diagnosis of DMD.

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

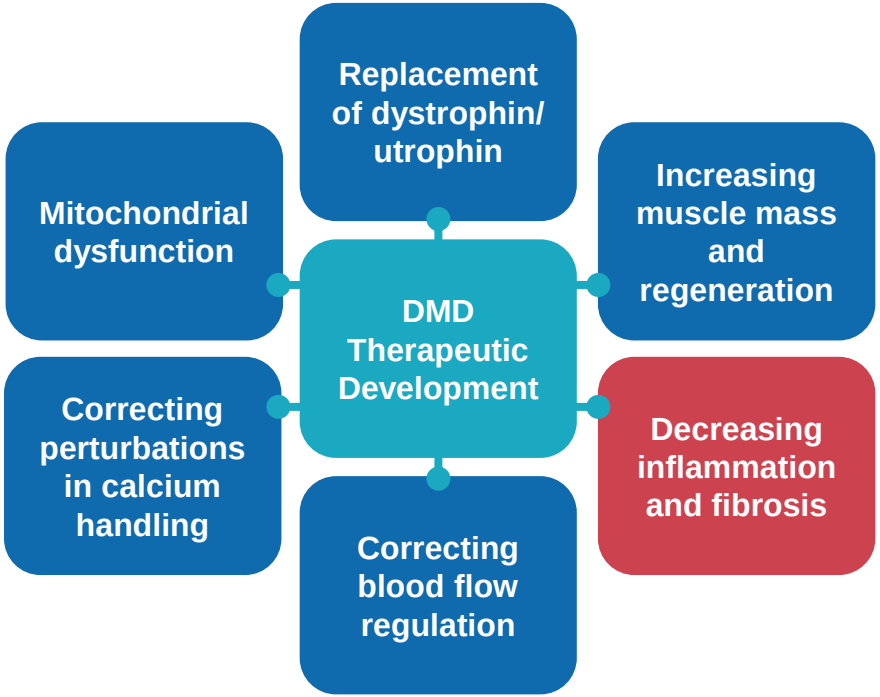


- Six main categories for therapeutic targets for DMD
- One addresses primary genetic defect; rest address downstream aspects of the pathogenesis
- Targeting any single pathway may be an approvable monotherapy
- Future treatment paradigm may involve targeting multiple pathways to have greater patient 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 disease severity
- Inflammatory cytokines induce miRNAs, and antiinflammatories block their expression
- miRNAs provide a precision medicine target in dystrophy



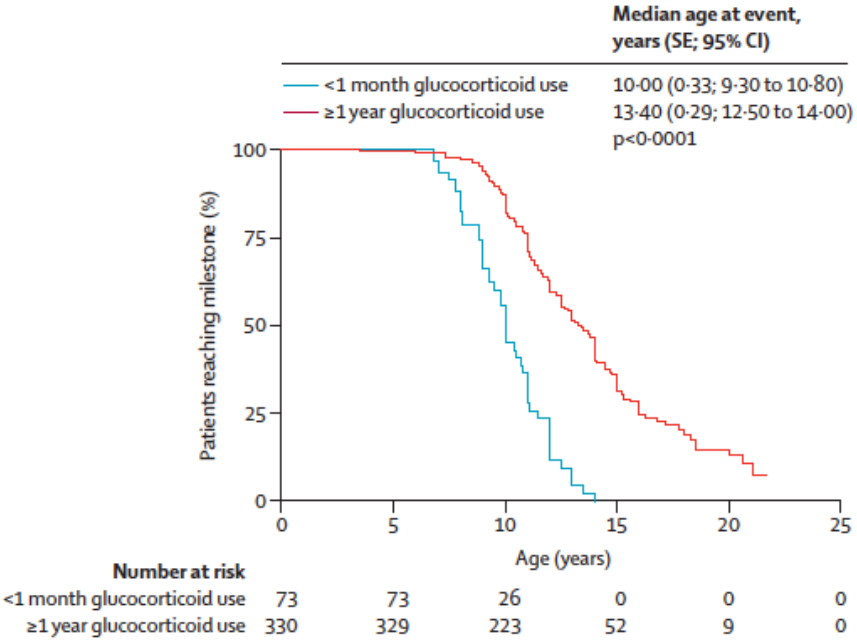
- **NF-κB Is Chronically Activated in DMD**
- Prednisone/Prednisolone
- Deflazacort

Contemporary Treatments That Have Affected the Natural History of Disease Progression and Survival in DMD

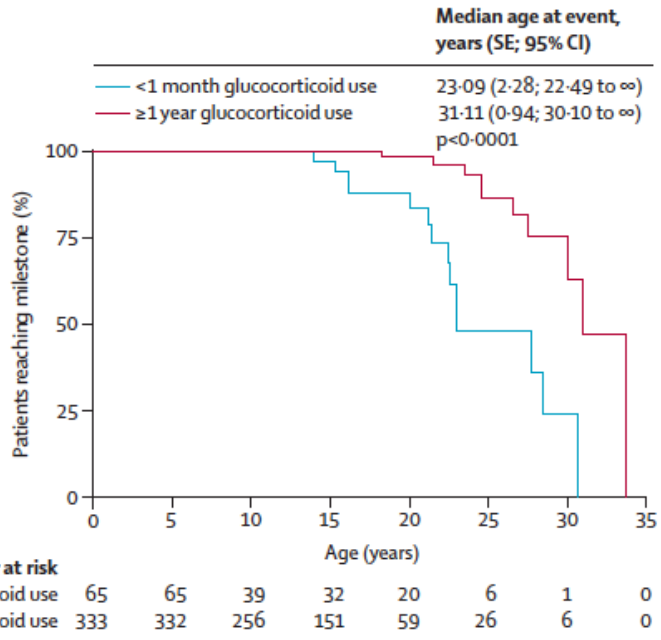
1. **Glucocorticoids**
2. **Management of spine deformity**
   - Glucocorticoids
   - Timely spine surgery for curves >30 to 40 degrees
3. **Pulmonary management**
   - Airway clearance strategies/mechanical cough assistance
   - Noninvasive ventilation
4. **Cardiac management**
   - Early afterload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

THE LANCET:
Long-term Effects of Glucocorticoids on Function, Quality of Lie, and Survival in Patients With Duchenne Muscular Dystrophy: A Prospective Cohort Study

Age at Loss of Ambulation

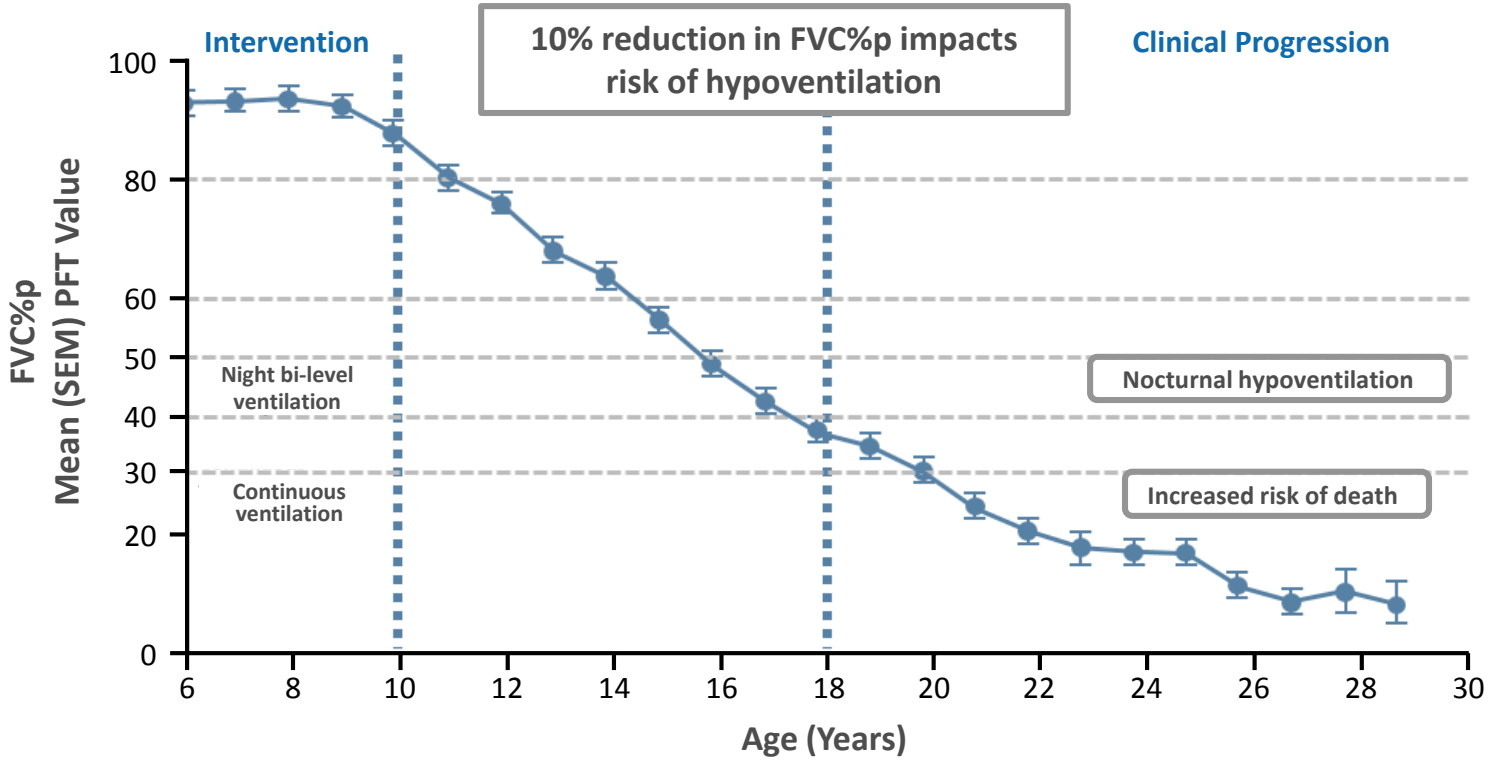


Age at Loss Hand Function (picking up small objects)



McDonald C, et al. *Lancet*. 2018; 391(10119): 451-461.

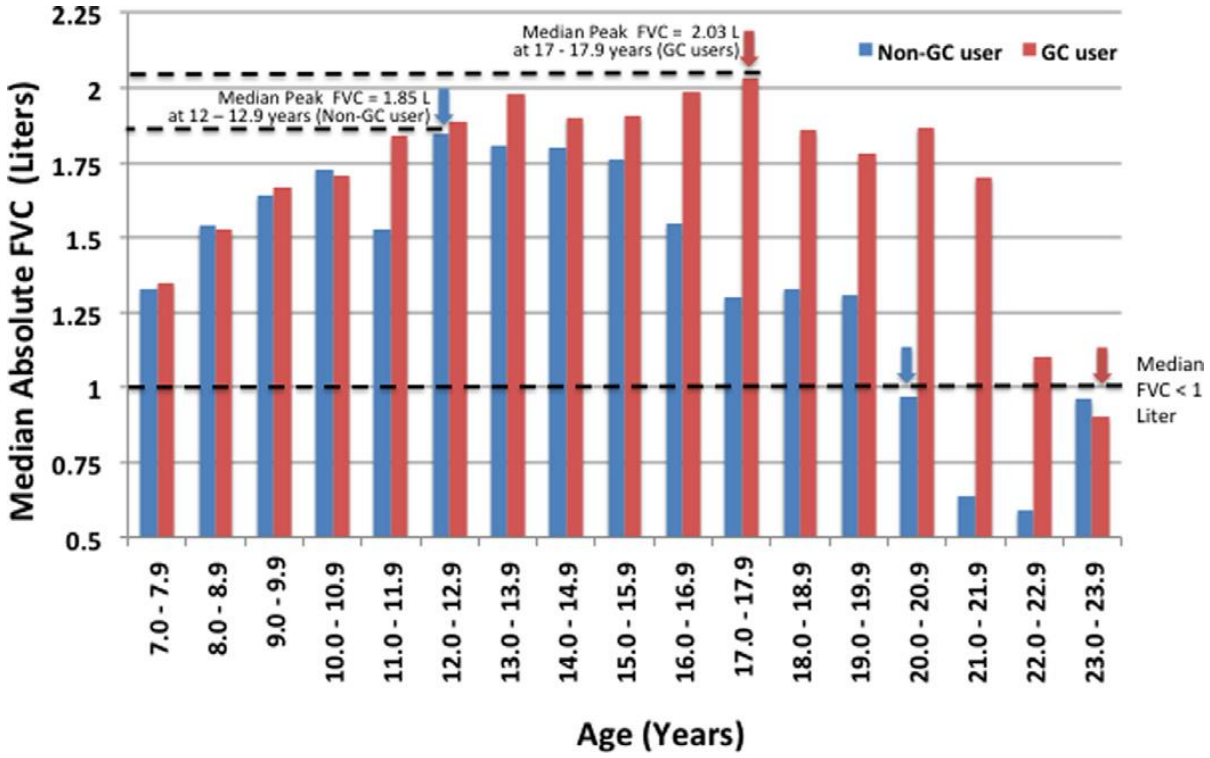
Declining FVC%p Linked to Clinically Meaningful Thresholds and Risk of Death (Based on CINRG Data)



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

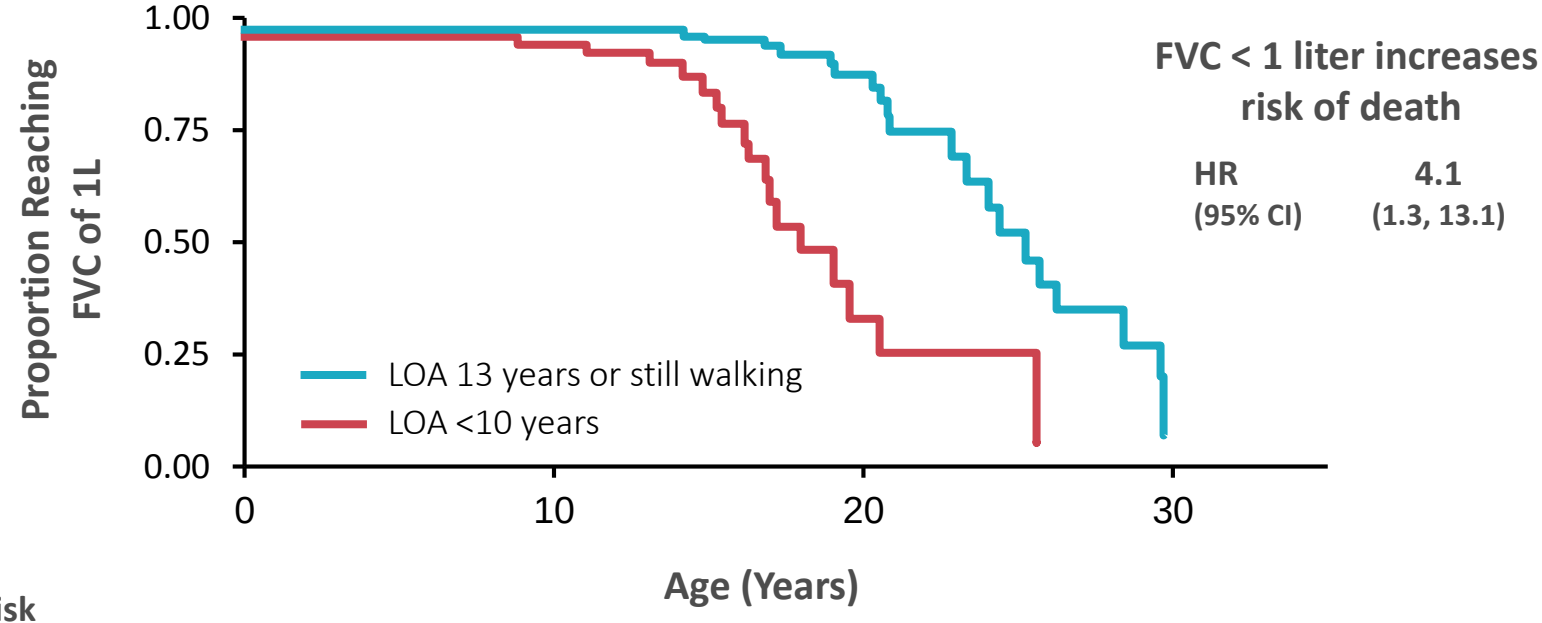
Median Absolute FVC (Liters) by Age and GC Use in DMD

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



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

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



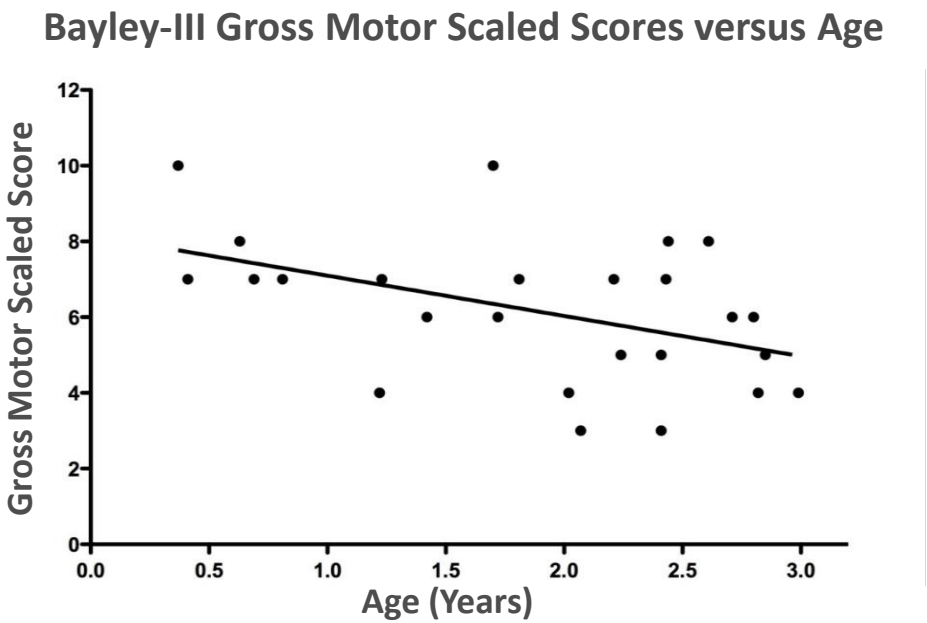
Number at Risk

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 entr. McDonald et al. *Lancet*. 2018;391(10119):451-461.

Motor and Cognitive Assessment of Infants and Young Boys With Duchenne Muscular Dystrophy

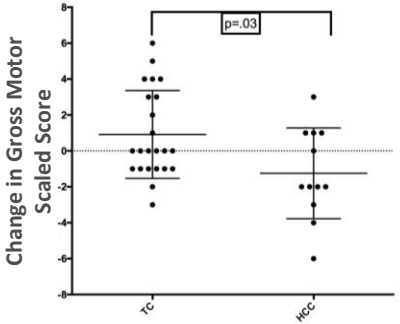
Results from the Muscular Dystrophy Association DMD Clinical Research Network. Connolly et al. (n=25; 1.8±0.8 years)



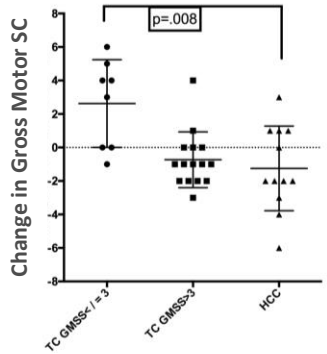
Steroids in Infants With DMD

- Twenty-five steroid-naïve boys 4 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)

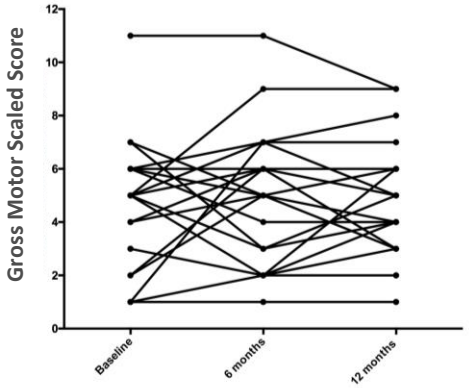
Figure 4. GMSS Changes in TC vs HCC



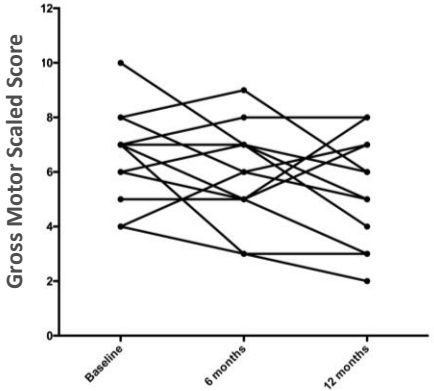
One year change in GMSS Historical control (HCC) boys with DMD (=12) versus treated cohort (TC) boys with DMD (n=23).



One year change in GMSS in HCC DMD (=12) versus TC with DMD with GMSS < or = to 3 (n=8) or >3 at baseline (n=12).



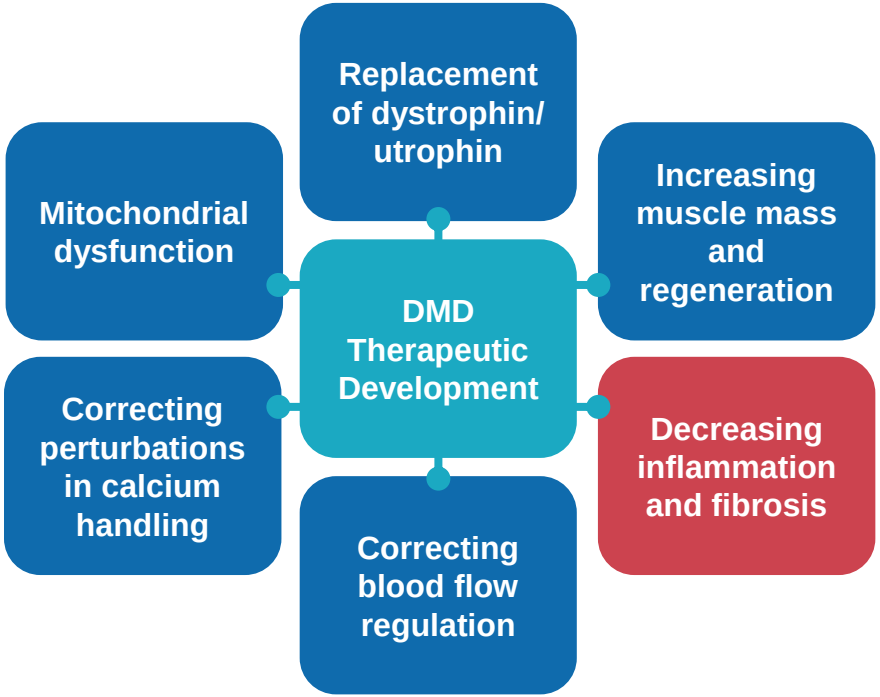
Treated for 1 year (n=23)



Untreated Historical control DMD boys (n=12)

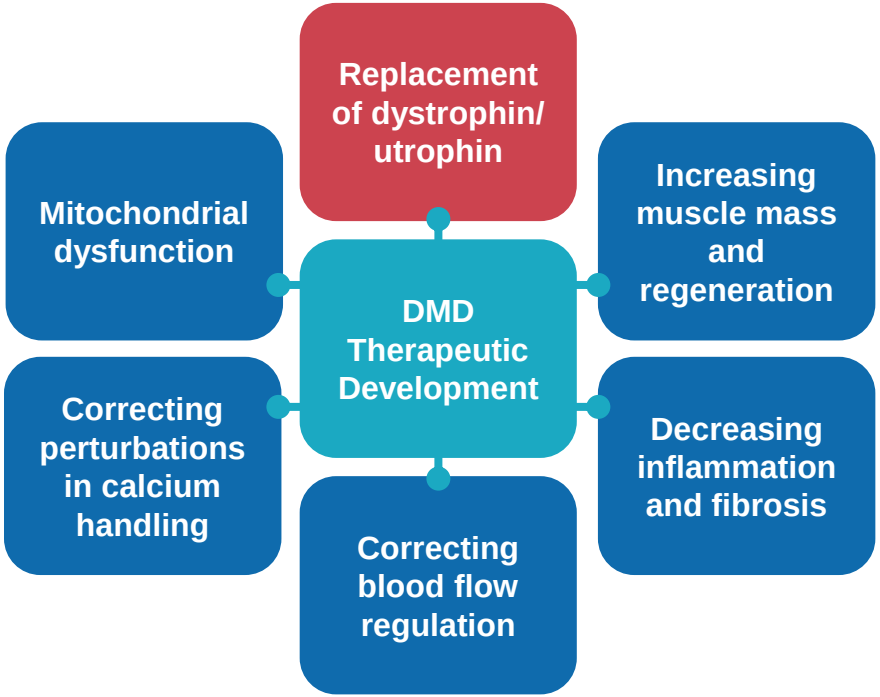
Connolly et al. Submitted 2018.

Potential for Combination Treatments in DMD

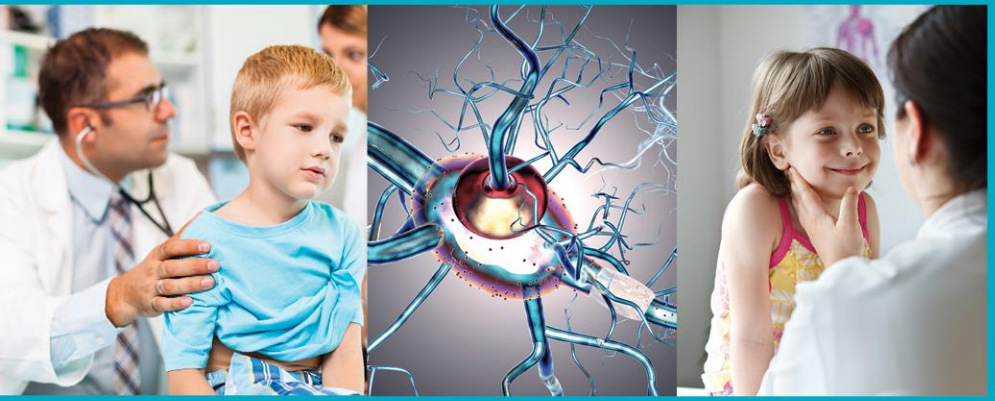


- **NF-κB Is Chronically Activated in DMD**
- Prednisone/Prednisolone
- Deflazacort
- Current Trials:
- Vamorolone
  - Dissociative steroids (decreased AEs)
- Edasalonexent
  - Covalently linked salicylic acid (ASA) and docosahexaenoic acid (DHA),
  - Synergistically leverages the ability of both compounds to intracellularly inhibit activated NF-κB

Potential for Combination Treatments in DMD

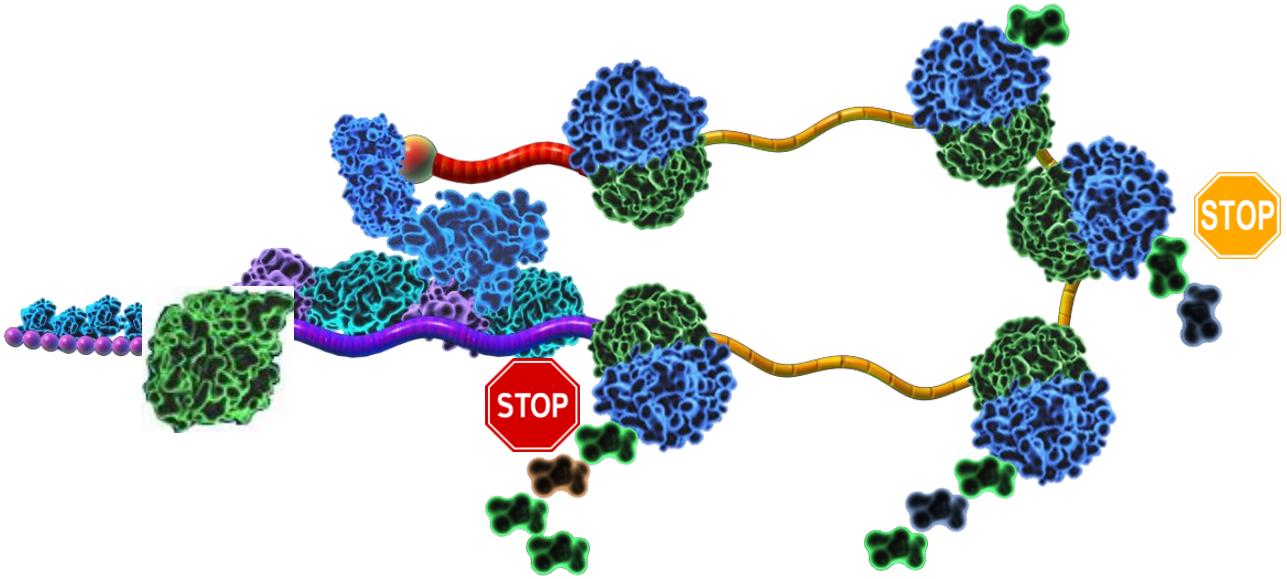


- Therapeutics targeting dystrophin restoration
- Antisense oligonucleotides
- PMOs
- PPMOs
- AAV microdystrophin gene therapy



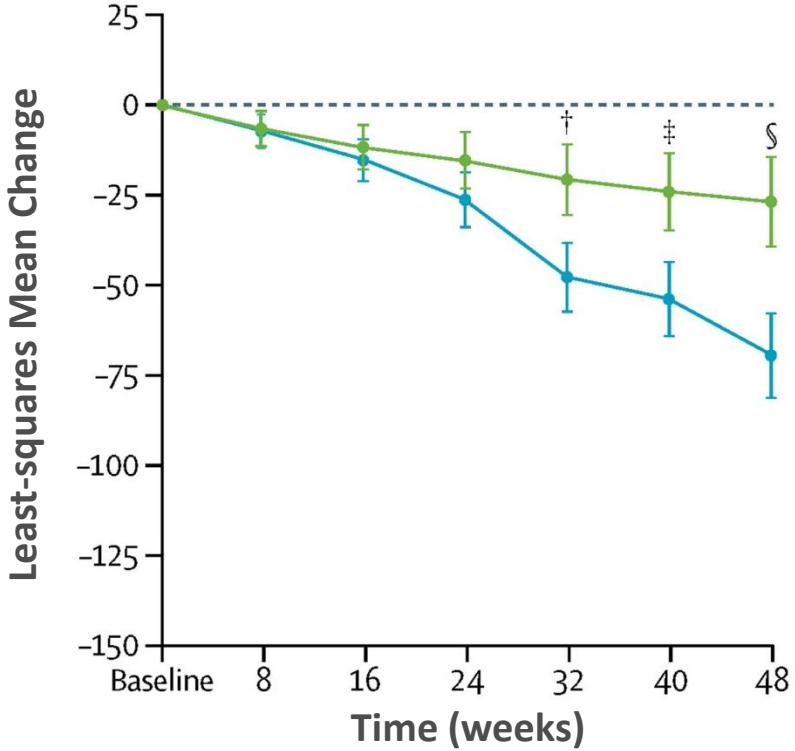
Advancements in RNA Therapy & Exon Skipping in DMD

Ataluren Enables the Ribosome to Bypass a Nonsense Mutation and Produces 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



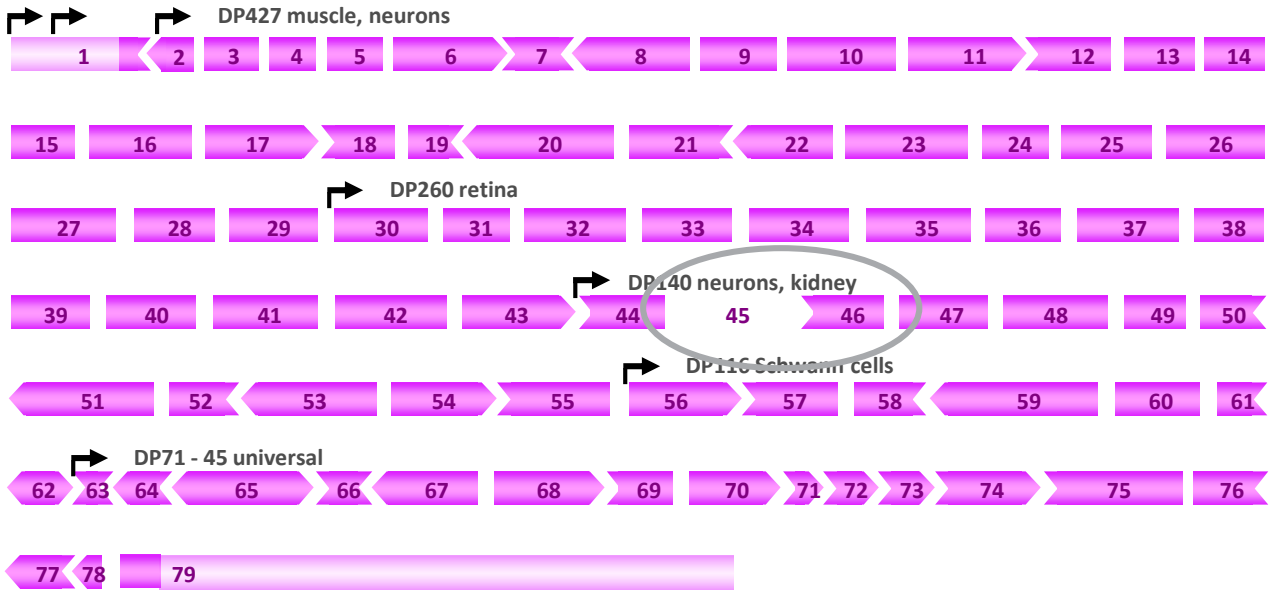
6MWD
difference = 42·9 m
95% CI 11·8–74·0;
P=0·007

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

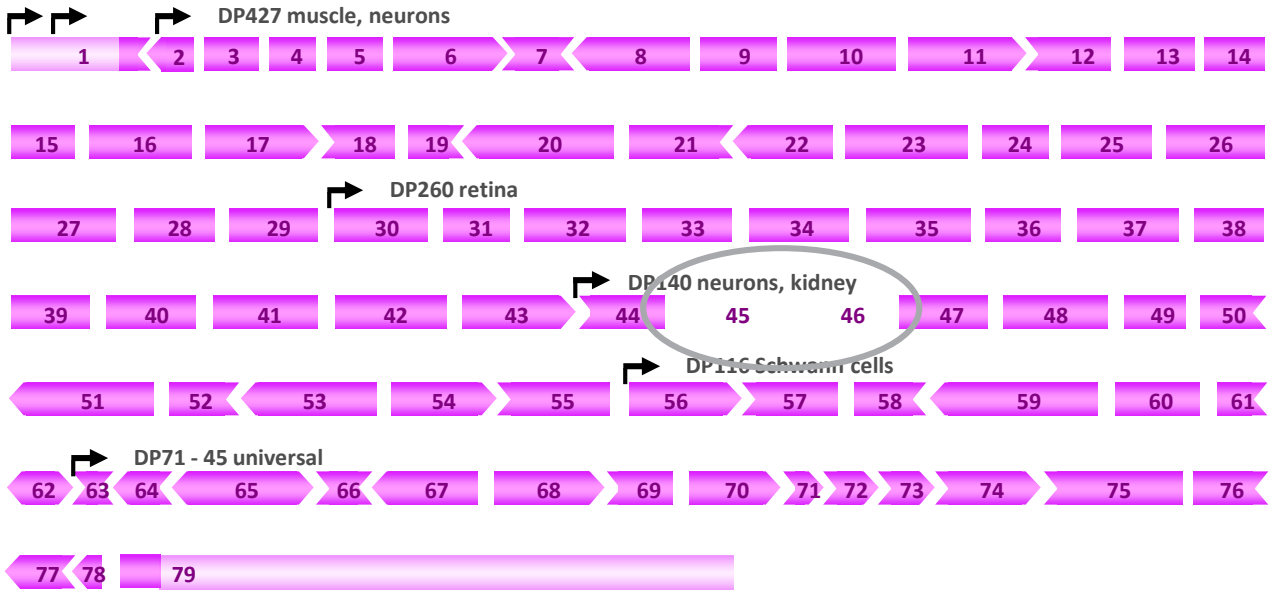
Reading Frame Rule

- Out-of-frame mutations result in disruption of ORF
  - → premature stop codon
  - → truncated dystrophin/non-functional protein
  - → **DMD**
- In-frame mutations that preserve the ORF
  - → replacements of amino acids in dystrophin
  - → partially functional protein
  - → **BMD**
- Majority of DMD and BMD follow this rule

Deletions that Disrupt the Codon Reading Frame Produce Severe Duchenne Dystrophy



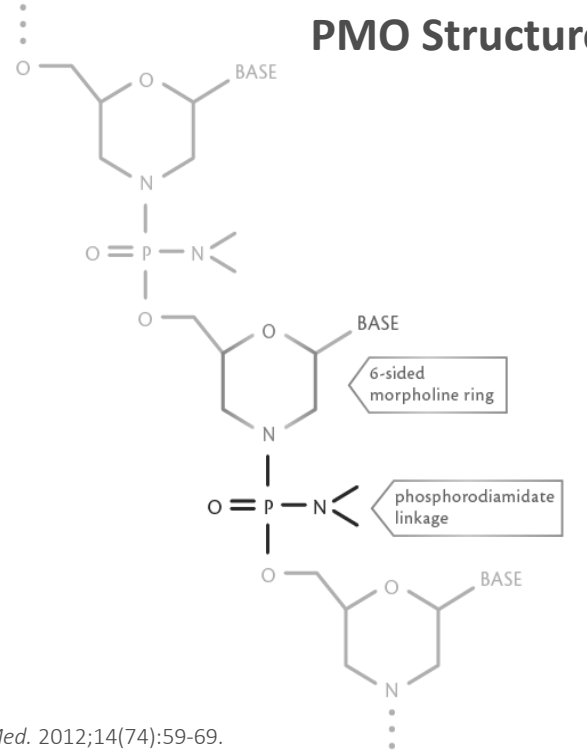
Deletions That Do Not Disrupt the Codon Reading Frame Produce Mild Becker Dystrophy



Phosphorodiamidate Morpholino Oligomer (PMO)

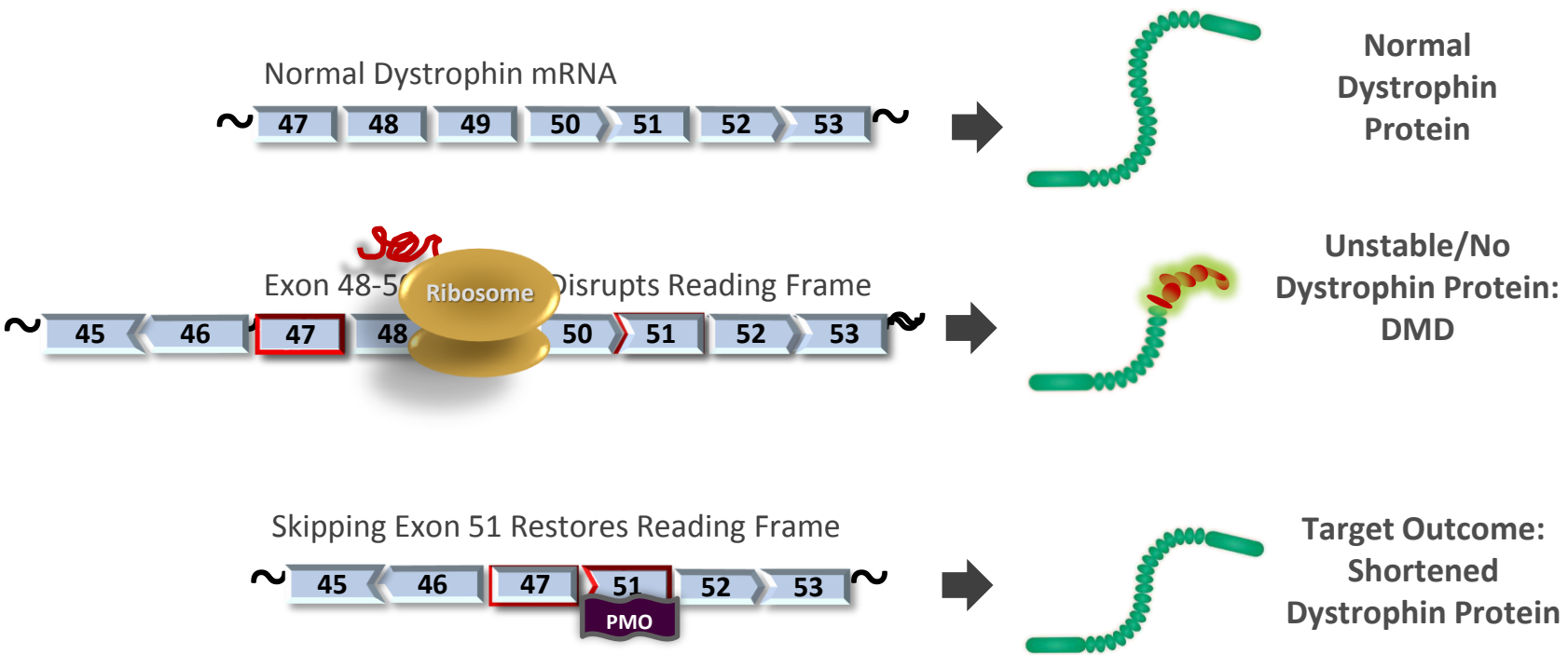
- Bind sequence-specifically to RNA targets[1]
- Chemically modified nucleic acid analog[2]
- Stable in serum and intracellularly[3]
- Uncharged backbone[4]

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.

Exon Skipping Proposed Mechanism of Action eg Exon-51–Amenable DMD Patients

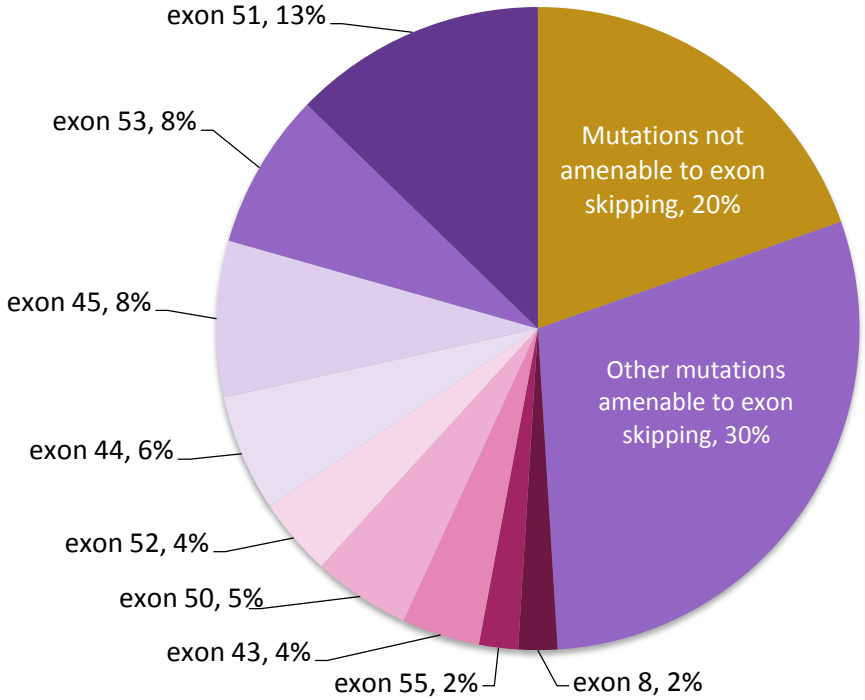


Exon Skipping PMOs in Late Stage Clinical Development Programs to Address up to ~30% of All DMD Patients

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

Golodirsen; Viltolarsen:
PMO for skipping of Exon 53

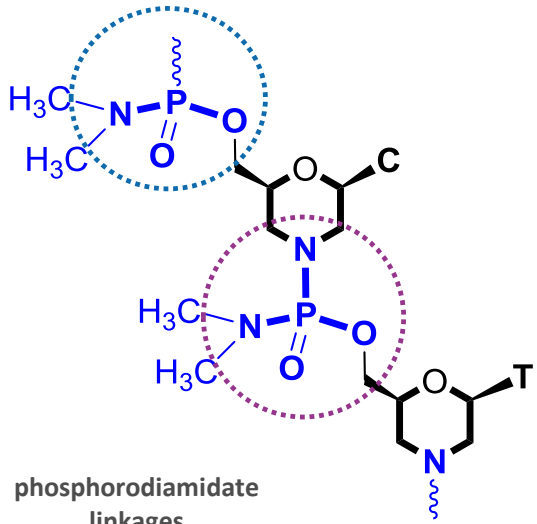
Casimersen:
PMO for skipping of Exon 45



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

Eteplirsen Is a Phosphorodiamidate Morpholino Oligomer (PMO)

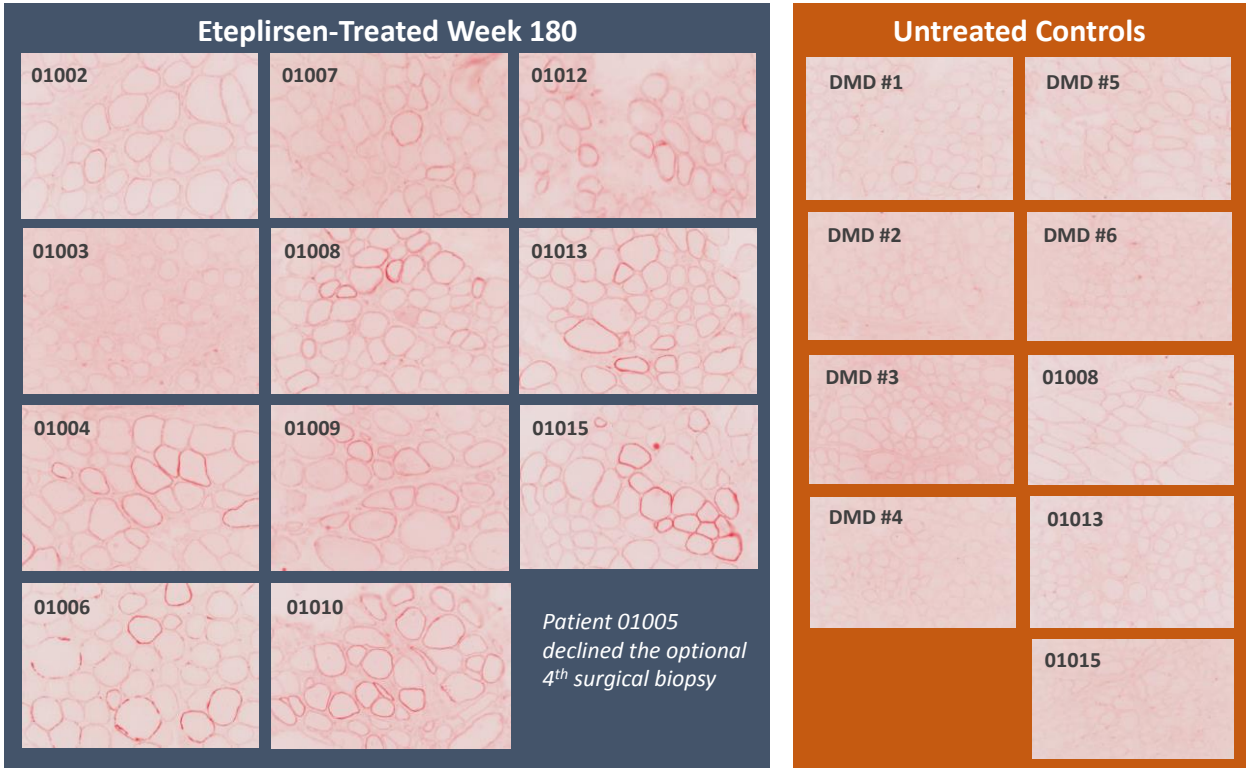
Eteplirsen (PMO)



phosphorodiamidate linkages (uncharged)

- 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

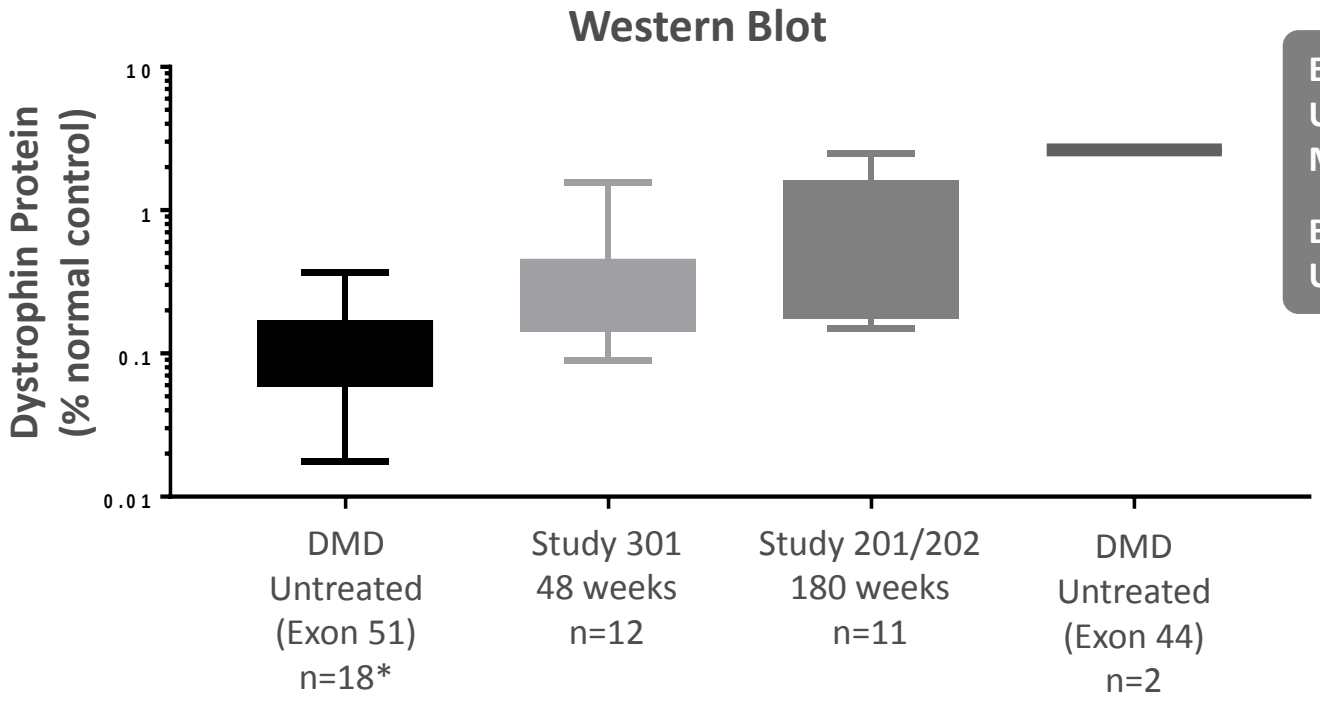
Study 201/202

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

Less than 3% of Dystrophin Is Clinically Relevant

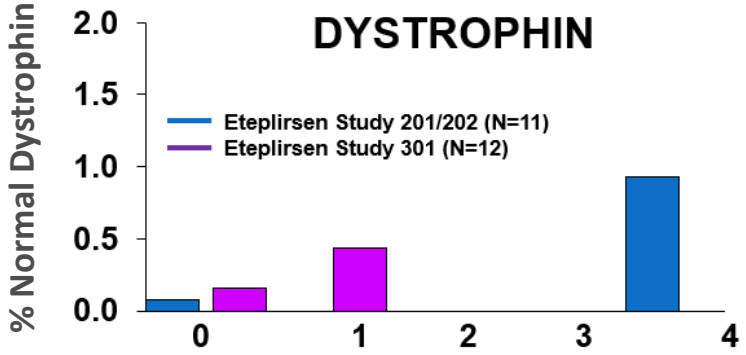


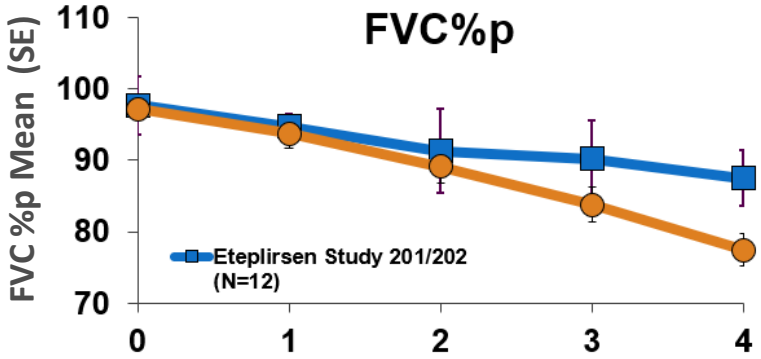
Exon 51 Skip–Amenable
Untreated
Mean Age LOA: 11-13 years

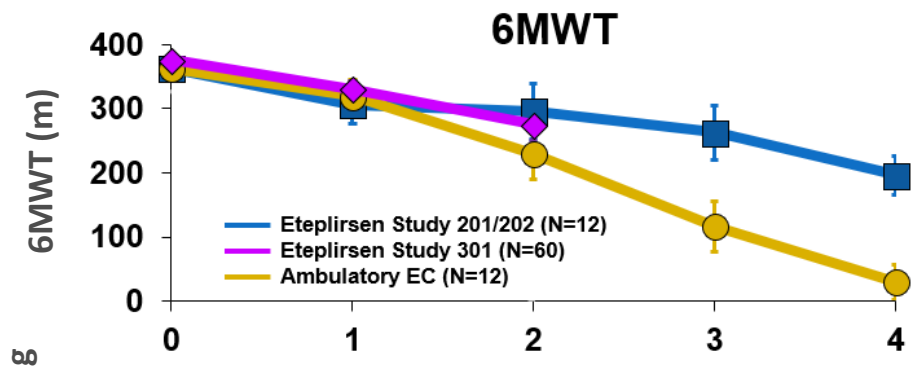
Exon 44 Skip–Amenable
Untreated LOA: >19 years

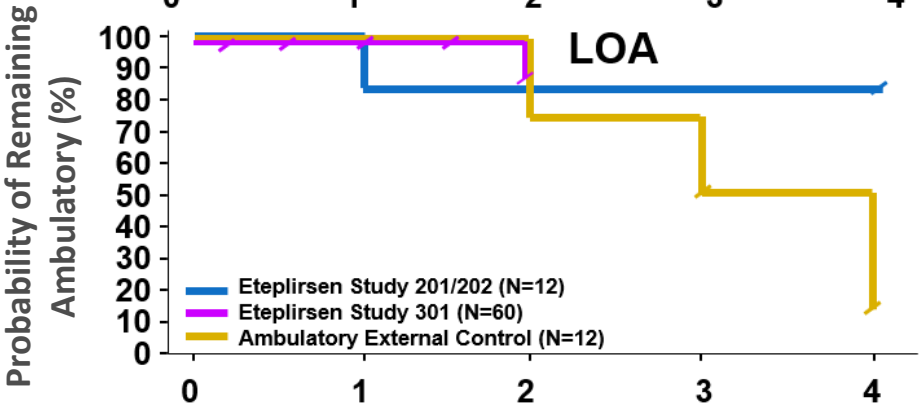
*Study 301 (n=12) + Study 201/202 (n=6).

Clinically Meaningful Benefit Greater After 1 Year

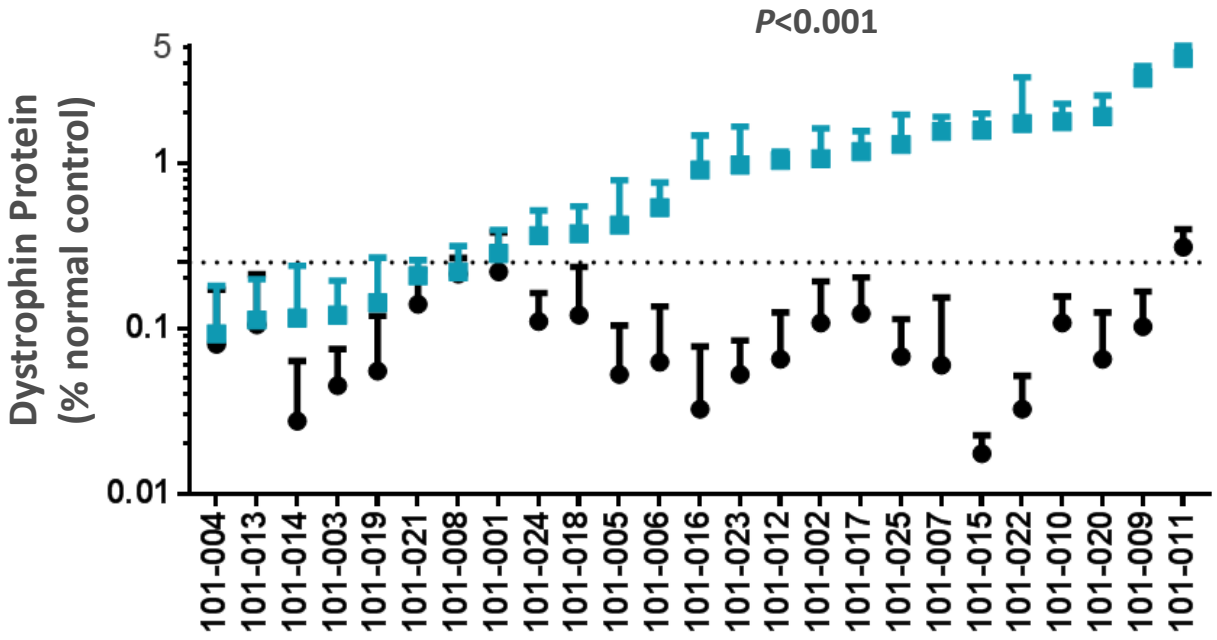








Golodirsen (Exon 53): Novel Dystrophin Production at Week 48 by Western Blot (n=25)



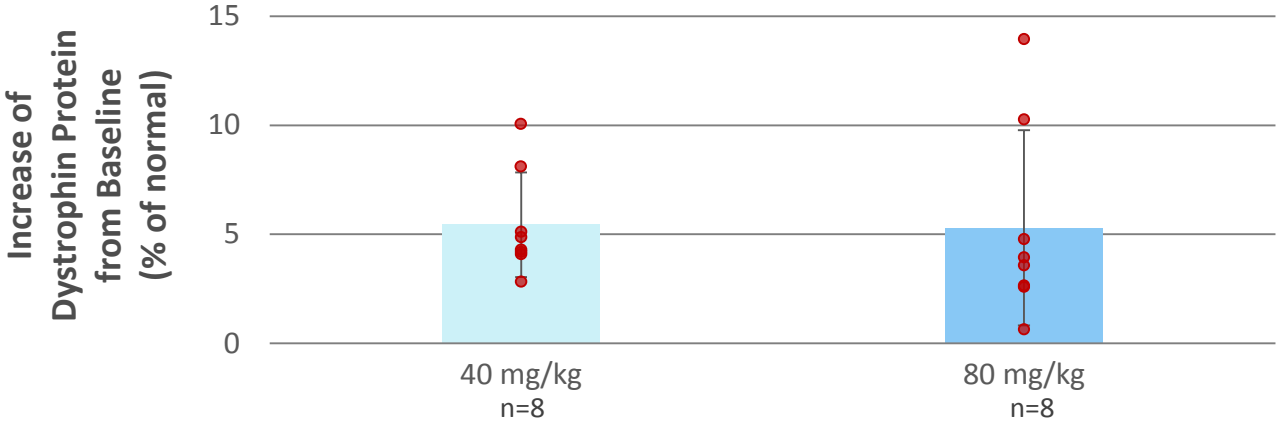
Baseline

On-Treatment

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

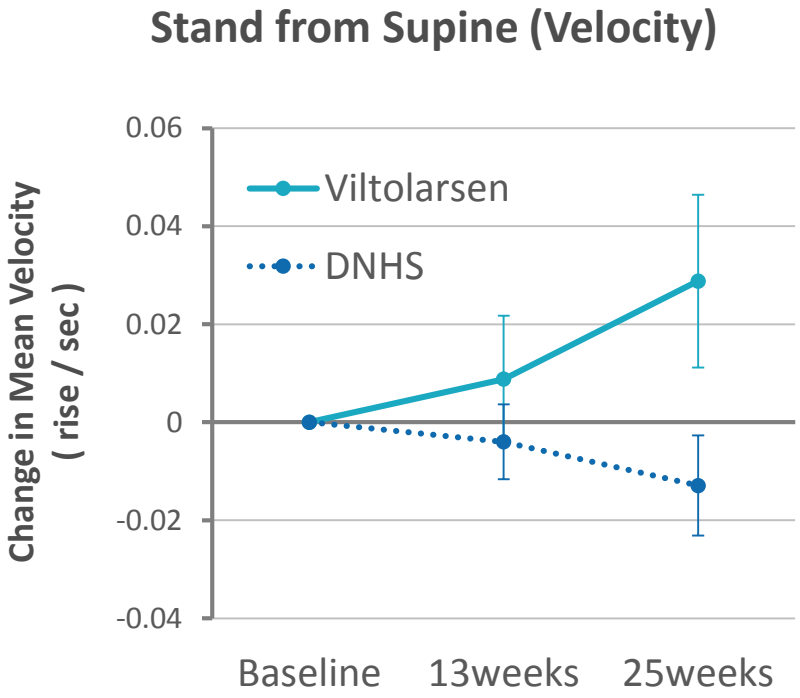
Mean Baseline = 0.095% normal (SD 0.0680)
Mean On-treatment = 1.019% normal (SD 1.0328)

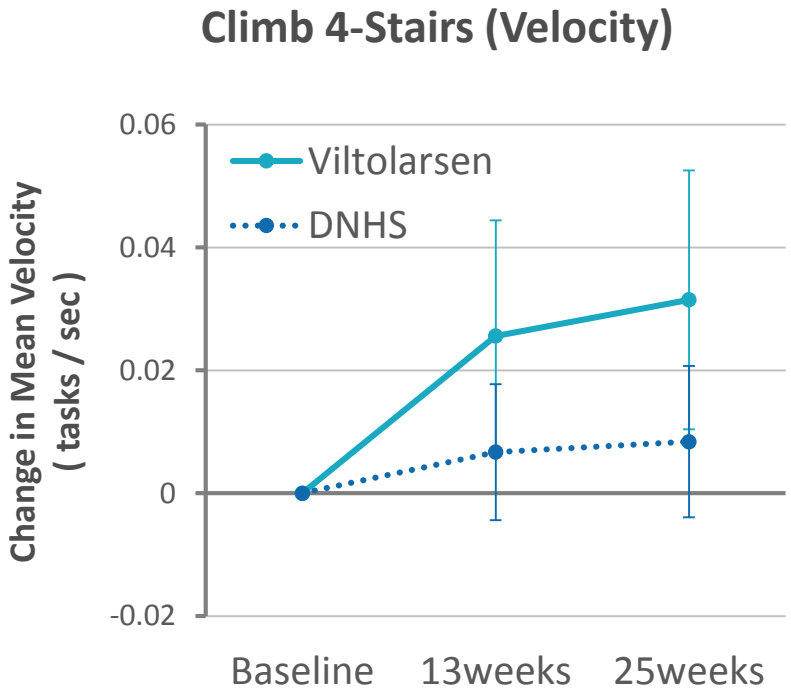
% Dystrophin by Western (Viltolarsen)



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

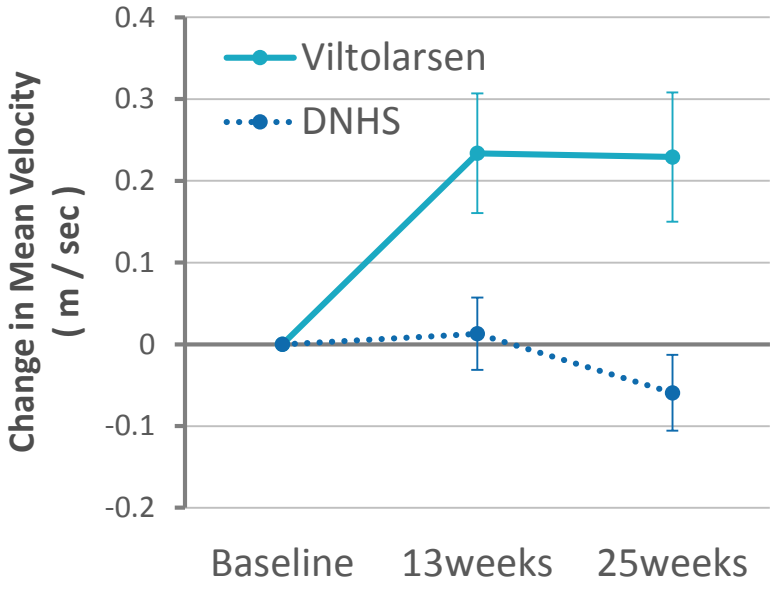
Clinical Changes With Exon 53 Skipping (Viltolarsen)



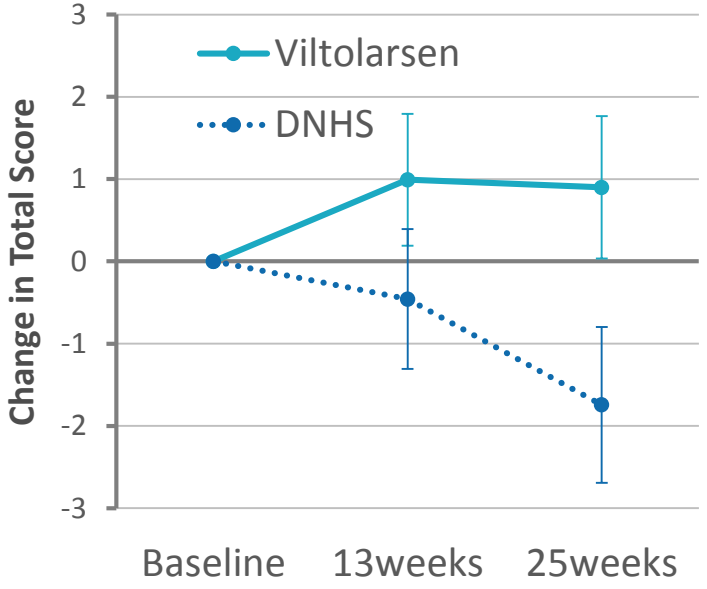


Clinical Changes With Exon 53 Skipping (Viltolarsen)

Run/walk 10 meters

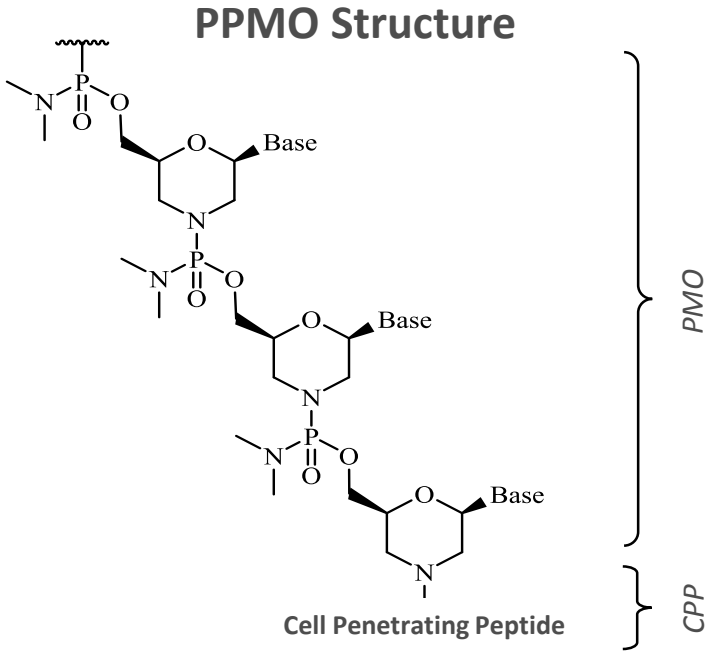


North Star Ambulatory Assessment

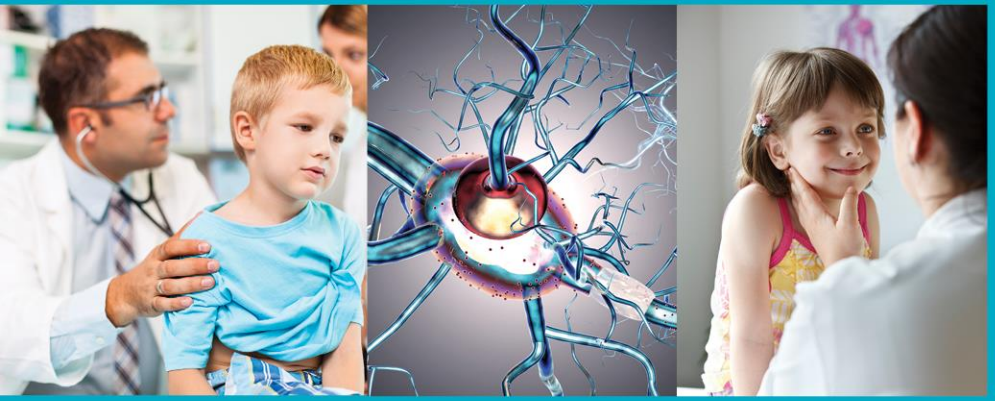


Peptide Conjugated PMO (PPMO)[1,2]

- PPMOs have a positively charged cell-penetrating peptide (CPP) attached to an uncharged PMO backbone
- Mechanism of action:
  - Sequence-specific binding to RNA targets
- Pre-clinical *in vivo* studies have demonstrated targeted delivery to
  - Skeletal muscle
  - Cardiac muscle
  - Smooth muscle



1. Passini M, et al. Presented at: 13th Annual Meeting of the Oligonucleotide Therapeutics Society (OTS); 24-27 September 2017; Bordeaux, France.
2. Jarver P, et al. *Nucleic Acid Ther*. 2014;24(1):37-47.



Microdystrophin Gene Therapy

The Promise of Microdystrophin Gene Therapy in DMD

DATA PUBLISHED IN *NATURE COMMUNICATIONS*

- Study conducted in 12 dogs naturally affected by DMD and treated with Genethon's micro-dystrophin gene therapy
- At two-year follow-up, muscle function was significantly restored and clinical symptoms had stabilized
- Dystrophin expression had returned to a high level in the high-dose group
- No immunosuppressive treatment was administered beforehand, and no side-effects were observed

Video courtesy of Genethon

Microdystrophin Gene Therapy (60+ yo ambulatory patient deleted exons 17-58)

- AAVrh74.MHCK7.Micro-dystrophin
  - (Nationwide: Jerry Mendell, MD)
- SGT-001: AAV9 vector containing muscle-specific promoter and microdystrophin construct
  - (Florida Gainesville: Barry Byrne, MD, PhD)
- Micro-Dystrophin Gene Therapy
- PF-06939926: adeno-associated virus serotype 9 (AAV9) capsid/mini-dystrophin gene
  - (Duke: Edward Smith)

Key Issues With Microdystrophin

- Safety unknown
- Durability of effect at 2 yrs; 5 yrs unknown (decrease expression with somatic growth)
- Antibody titers affect eligibility
- Age and steroid pulse X 4-6 wks impacts initial efficacy
- Doses may be 10-fold different between constructs
- Does gene AAV gene therapy transduce the satellite cells?
- Redosing may be possible with plasmaphoresis

Summary

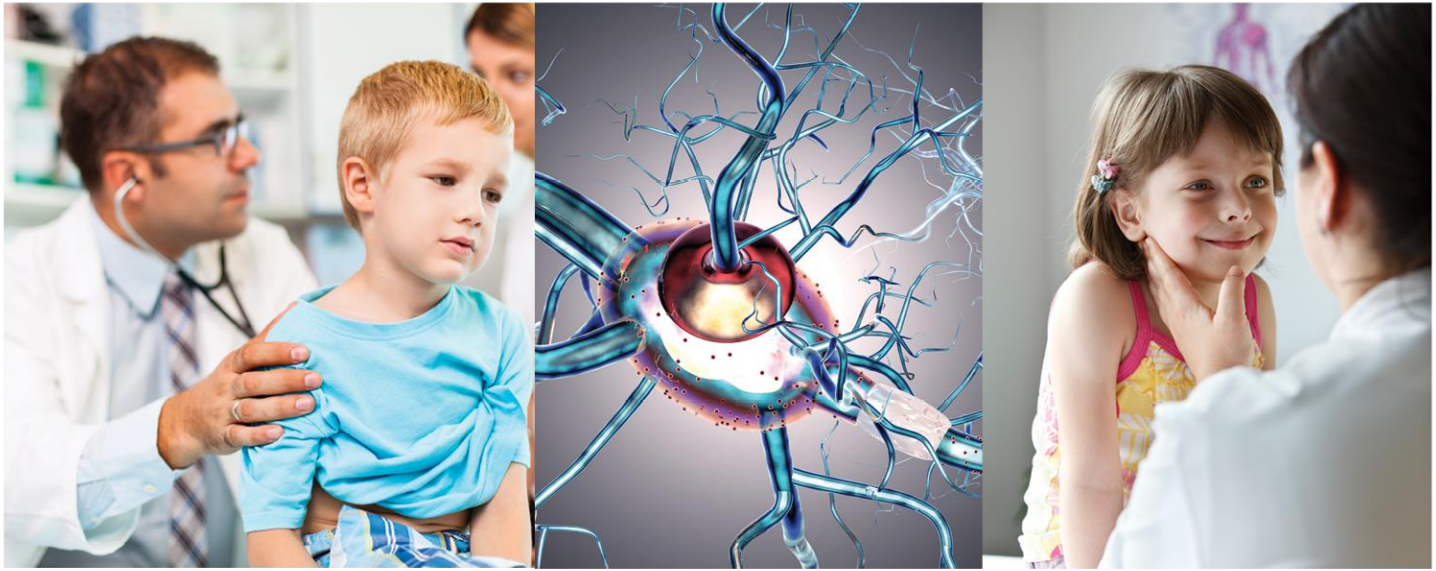
- Check CK (“Developmental delay, do a CK”)
- Check for neck flexor weakness; Gowers sign
- Steroids increasingly prescribed by neurologists at the time of diagnosis
- Precision medicine therapeutics offer great hope for meaningful disease modifying management, greater function, and longer lifespan in DMD

Acknowledgments

UC Davis Neuromuscular Medicine & Rehabilitation Research Center and CINRG Network

Making A Difference in Duchenne Muscular Dystrophy & Spinal Muscular Atrophy:

PEDIATRICIANS AT THE FRONT LINE OF EARLY DIAGNOSIS & IMPROVED SURVIVAL

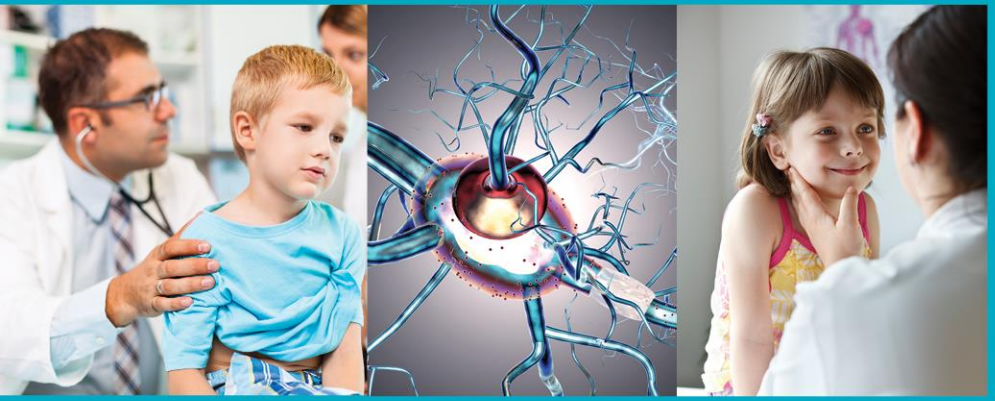


This activity is jointly provided by Global Education Group and HealthmattersCME.

This symposium is neither sponsored nor endorsed by the American Academy of Pediatrics.

Photo credits: istock.com/fotostorm; istock.com/Ralwel; istock.com/damircudic. People shown are professional models and are not patients.

This activity is supported by an independent educational grant from **Sarepta Therapeutics.**



Classification, Tests, Guidelines, Early Diagnosis and Treatment for SMA

Richard S. Finkel, MD

Professor, Department of Neurology
University of Central Florida College of Medicine
Division Chief, Division of Neurology
Department of Pediatrics
Nemours Children's Health System
Orlando, FL

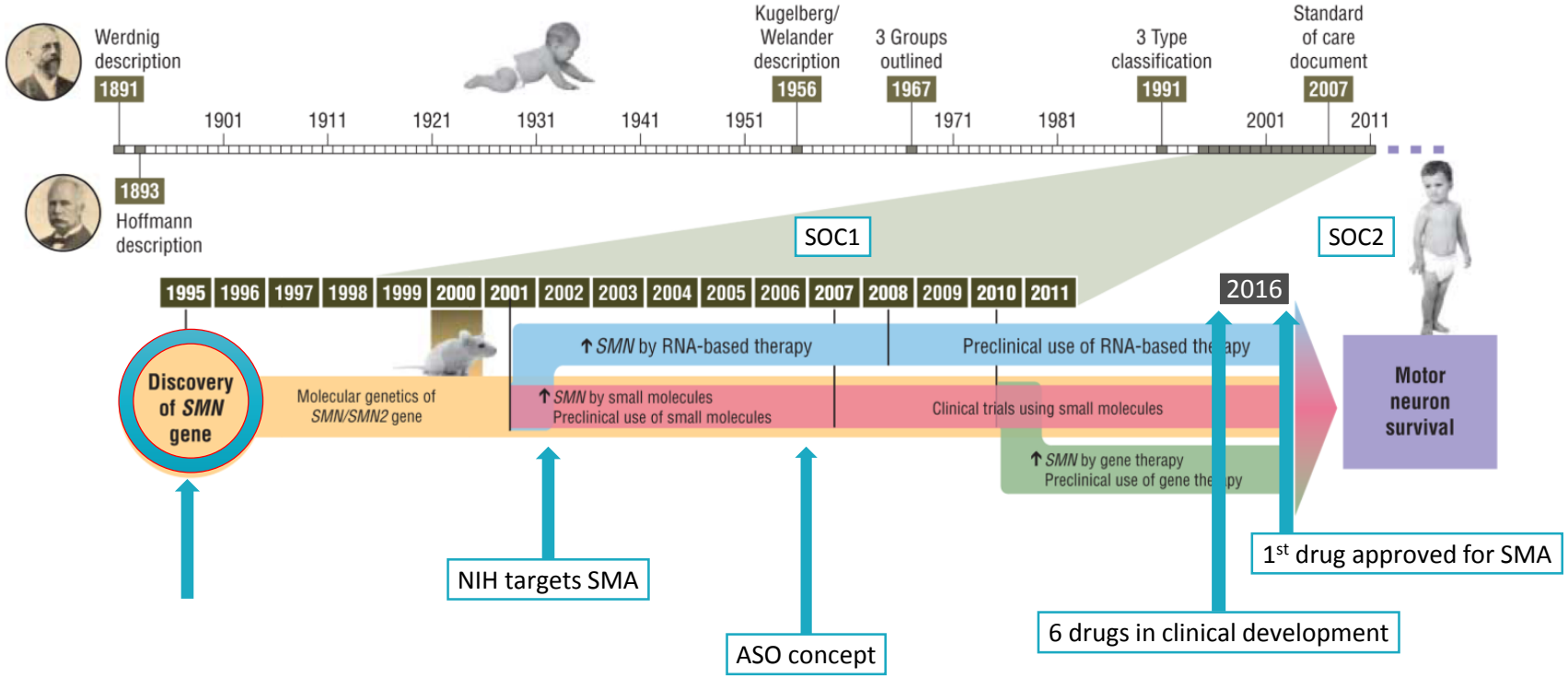
Outline

- Classification of spinal muscular atrophy (SMA)
- Diagnostic testing
- Treatment guidelines
- Early diagnosis
- Treatment
- Newborn screening

SMA

- Incidence — 1:11,000 live births
- Prevalence — ~25,000 in US
- Cause — Deficiency of SMN protein
- Basis — Monogenic, autosomal recessive
Deletions/mutation in *SMN1* gene
- Pathology — Motor neuron degeneration
Progressive muscle atrophy, weakness
- Phenotype — Typically normal at birth
Spectrum from type 1 to 3

Classic 5q SMA

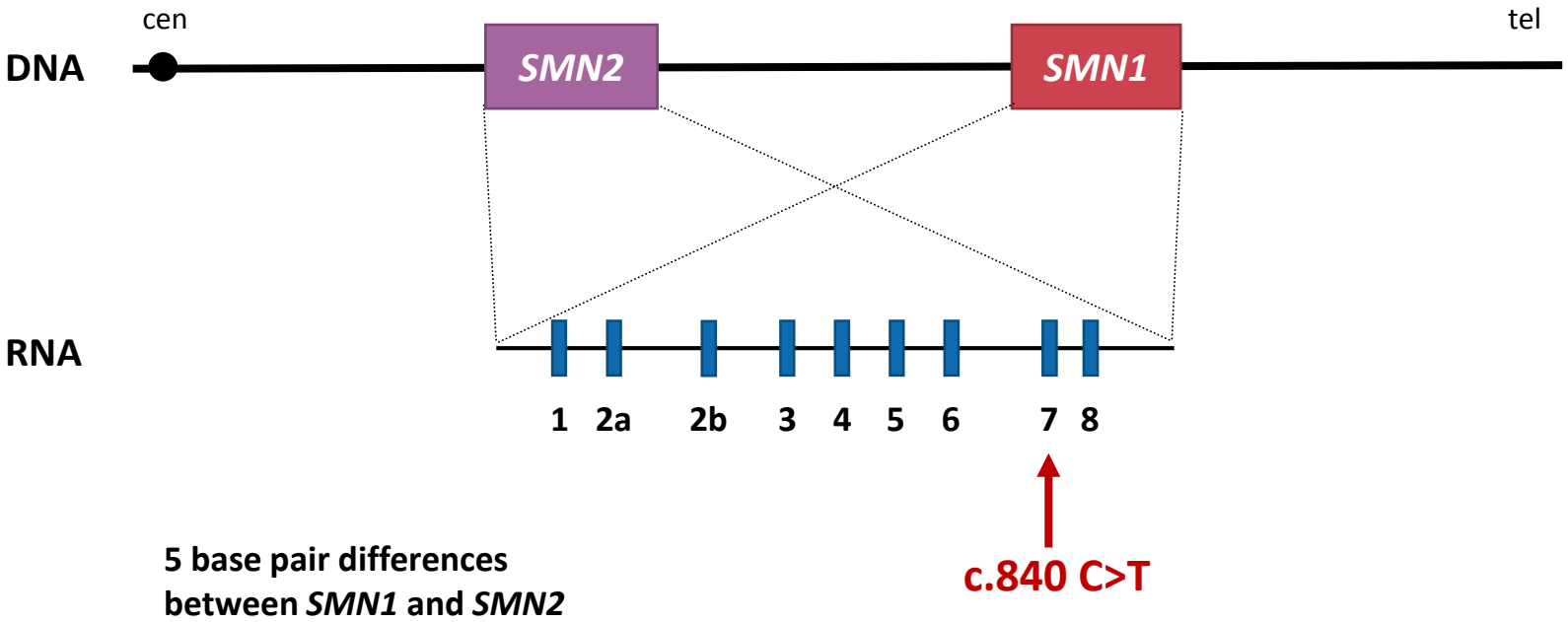


Adapted from Kolb SJ, Kissel JT. *Arch Neurol*. 2011;68:979-984.

Spectrum of SMA

	TYPE 1	TYPE 2	TYPE 3
Age of onset **(parental recall)**	<6 months	6-18 months	18 months - adult
Incidence per live birth	~60%	~27%	~13%
Maximum motor milestones	Never Sits	Never Walks	Walks
Survival	~30% survival by 2 years of age with supportive care	68% alive at age 25 years	Normal

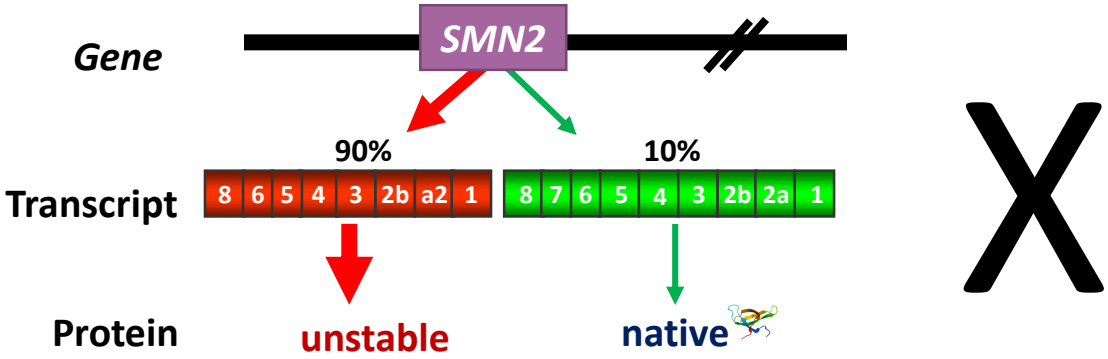
SMN Genes on 5q



5 base pair differences between *SMN1* and *SMN2*

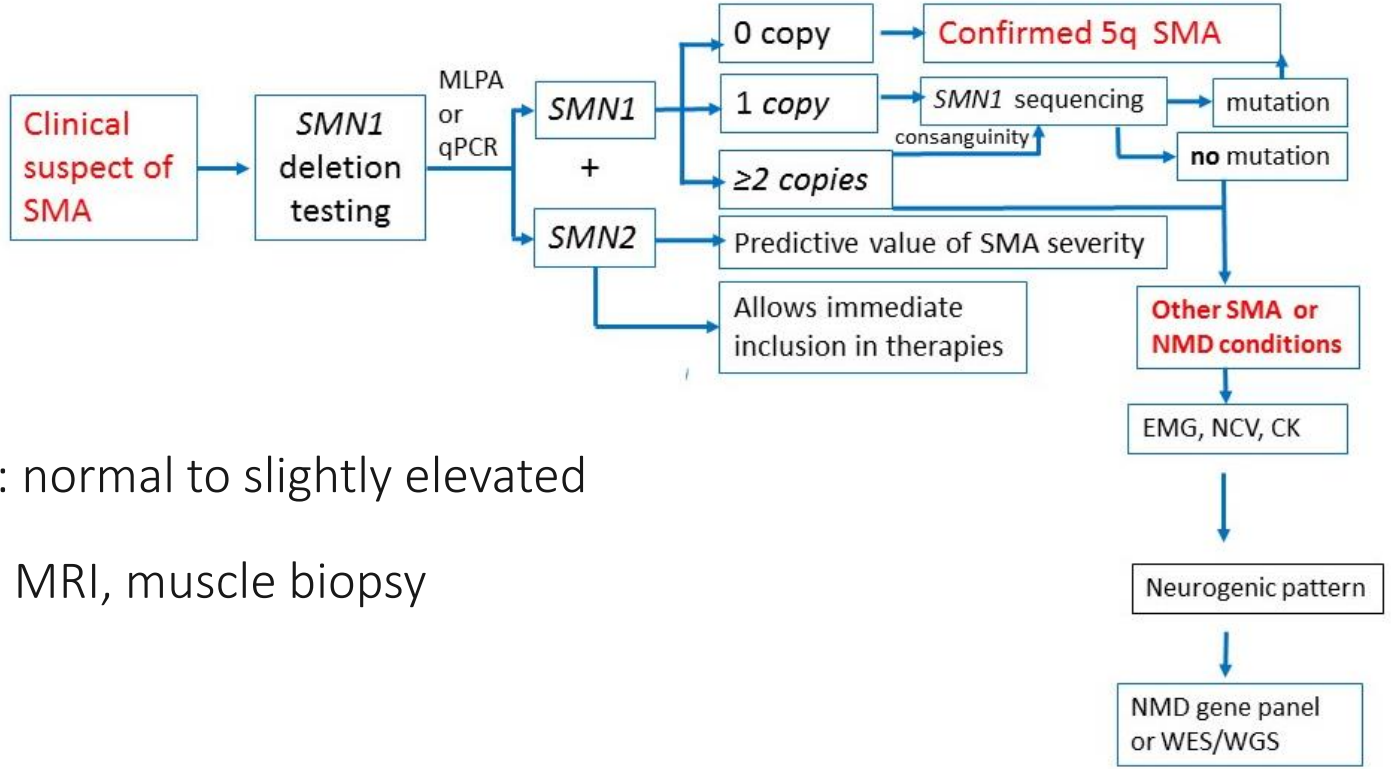
2 SMN Genes ⟶ 1 SNN Protein

- ~90% of *SMN2* undergoes alternative splicing leading to truncated transcript that lacks exon 7 (Δ7SMN)
- Full-length protein is produced from *SMN1* and *SMN2*



SMN Protein Deficiency

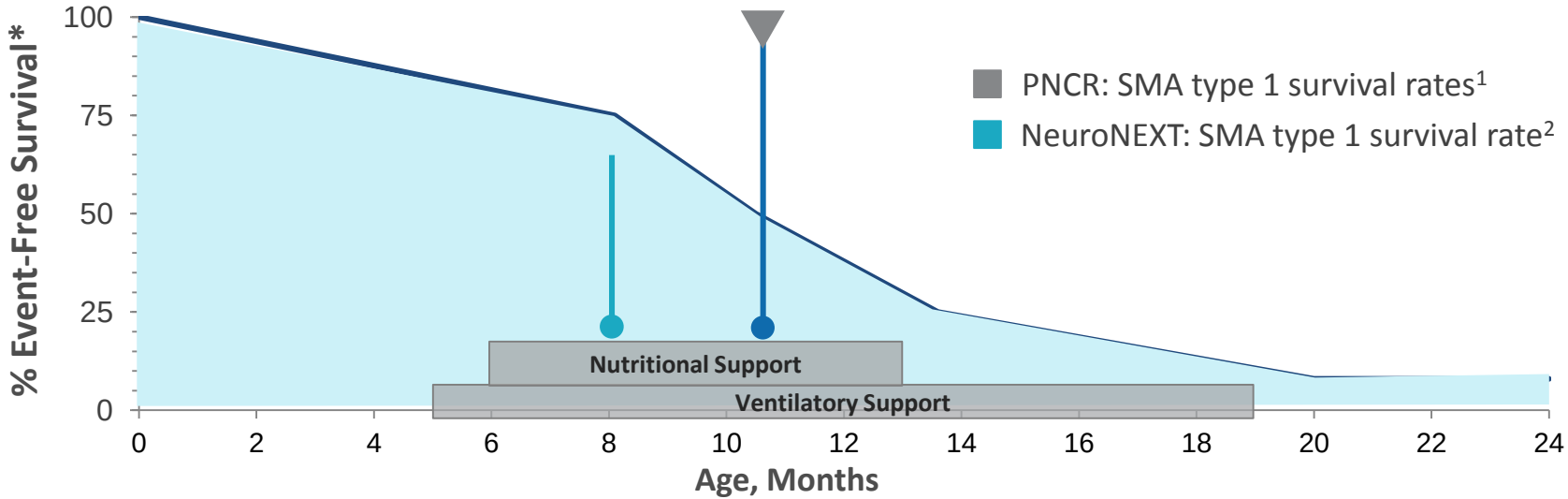
Diagnosis



- CK: normal to slightly elevated
- No MRI, muscle biopsy

SMA Type 1: Natural History

More than 90% of SMA type 1 patients (2 copies of *SMN2*) will not survive or will need permanent ventilatory support by 2 years of age



*Survival per Finkel[1] = no death, or no need for ≥16 hr/day ventilation continuously for ≥2 weeks, in the absence of an acute reversible illness; n = 23 (*2 copies of SMN2*). Survival per Kolb[2] = no death, or no tracheostomy; n = 20

1. Finkel RS, et al. *Neurology*. 2014;83(9):810-817. 2. Kolb SJ, et al. *Ann Clin Trans Neurol*. 2016;3(2):132-145.

When to Suspect SMA

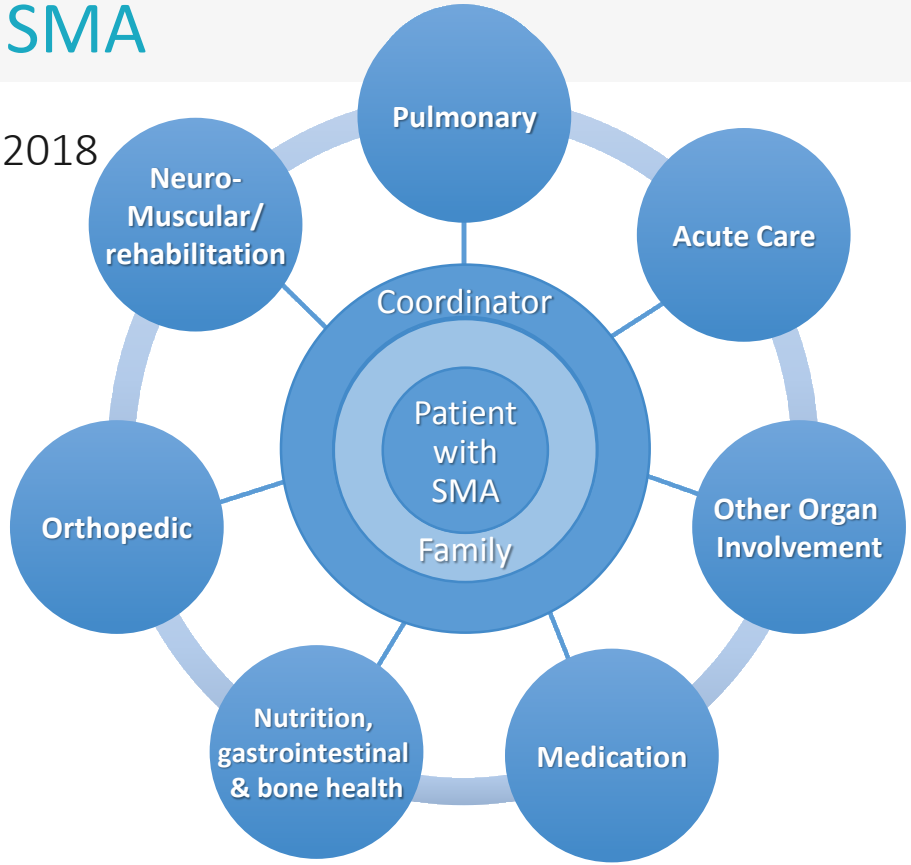
- **Type 1:** Floppy baby, frog-leg posture, poor head control, no weight-bearing, slip-thru, paradoxical breathing pattern, absent reflexes, tongue fasciculation
- **Type 2:** Infant with plateau in motor development, hypotonia, joint laxity, poor weight-bearing, absent reflexes
- **Type 3:** Waddles, Gowers

Parental observations: “floppy, feels like a rag doll”, “lazy”, “walks funny”, “slow, cannot keep up with other kids”, “seems uncoordinated, falls a lot”

See childmuscleweakness.org

Standard of Care Guidelines in SMA

- Standard of care consensus in 2007; update in 2018
- More “expert” opinion than scientific facts
- Supportive care
  - **Proactive:** Initiated presymptomatically
  - **Reactive:** Initiated at symptom onset
  - **Palliative:** Comfort care initiated following diagnosis
- Aims
  - Minimize the “diagnostic odyssey”
  - Promote quality of life



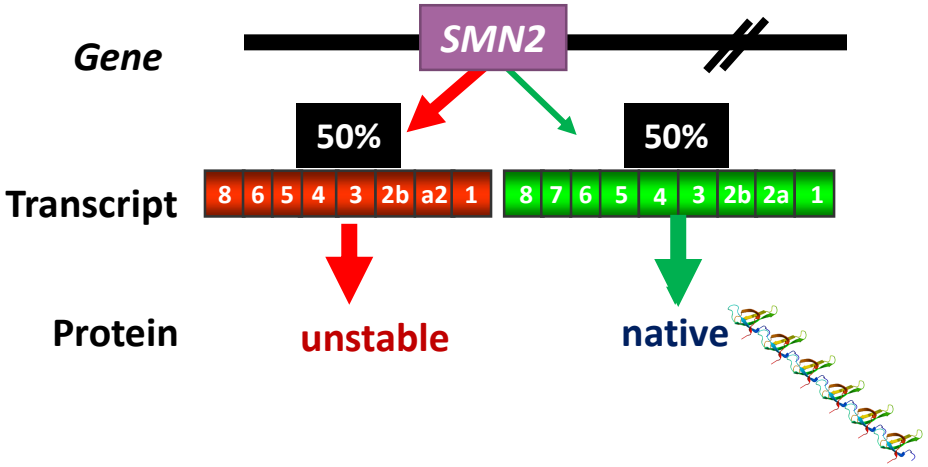
1. Wang CH, et al. *J Child Neurol*. 2007;22(8):1027-1049. 2. Mercuri E and Finkel RS, et al, *Neuromuscular Disorders*. 2018;28:103-115.

Medications

- Immunizations: AAP recommended, pneumococcal, influenza
- RSV prophylaxis (palivizumab for non-sitters, first 2 years of life)
- Respiratory: nebulized bronchodilators, short-term mucolytics
- GI: miralax, senna, zantac
- Bone health: vitamin D, calcium, (bisphosphonates)
- Nusinersen

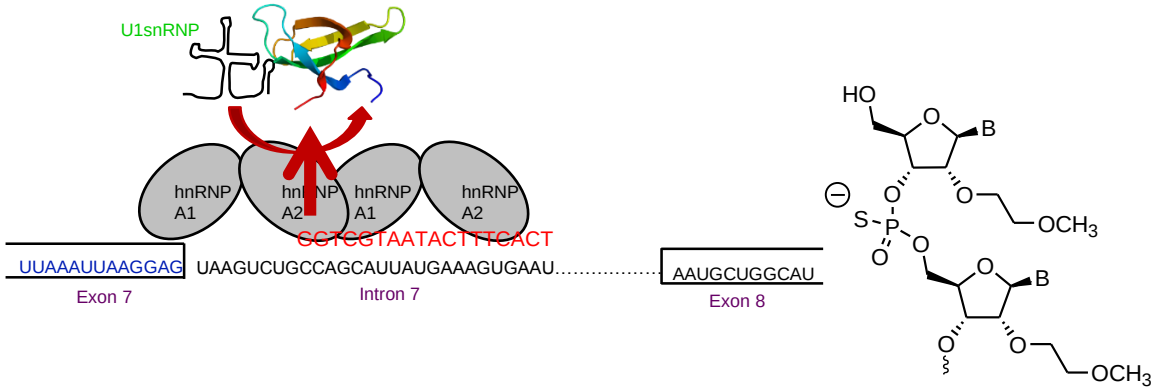
Treatment Strategies

- Replace *SMN1* gene (AVXS-101)
- Modulate splicing of *SMN2* to promote inclusion of exon 7 (nusinersen, branaplam, risdiplam)



Mechanism of Action of Nusinersen

Modulates ISS-N1 Splicing Factors; Promotes Inclusion of Exon 7

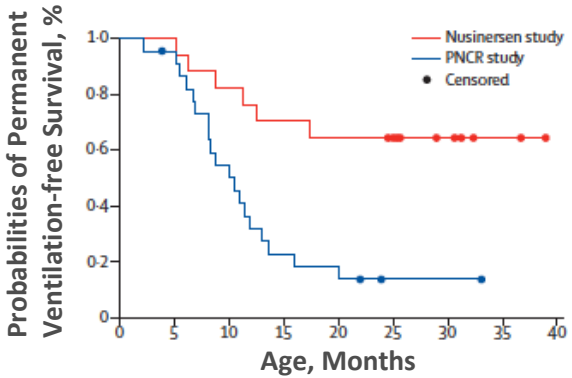


- hnRNP blocks access of U1 snRNP to pre-mRNA
- Nusinersen, a 2'-O-methoxyethyl phosphorothioate-modified ASO (MOE), displaces negative splicing factors on pre-mRNA, promoting inclusion of mis-spliced exon 7
- Promotes synthesis of fully functional SMN protein

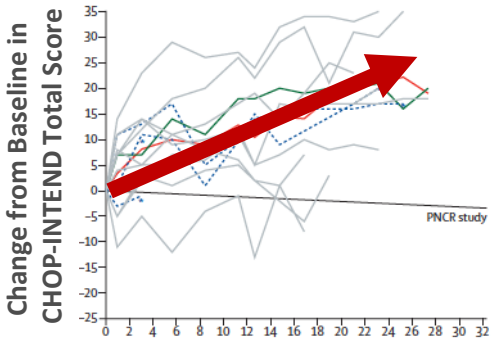
Frank Bennett, Ionis.

Treatment of Infantile-onset Spinal Muscular Atrophy with Nusinersen: A Phase 2, Open-label, Dose-escalation Study

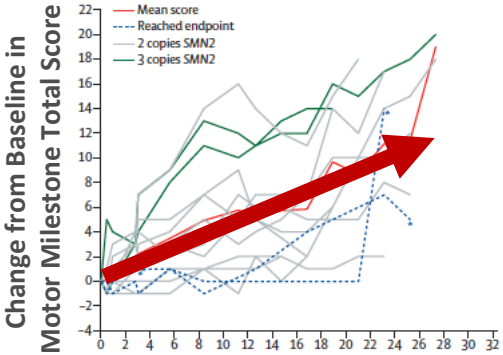
Increased Permanent Ventilation-free Survival



Mean Increase of 11.5 Points in the CHOP-INTEND



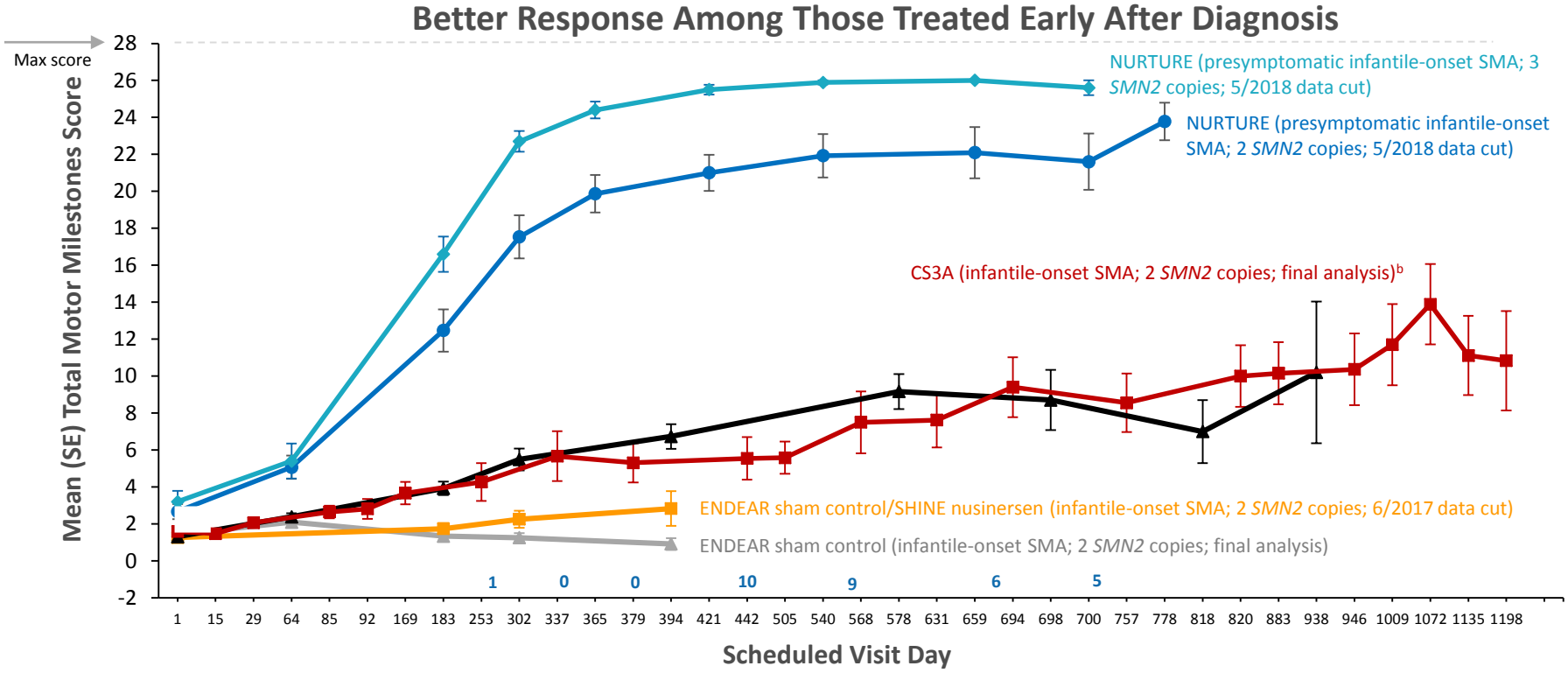
Increases in the HINE-2; 15/15 in High-Dose Cohort



Increased event-free survival & muscle function scores observed in nusinersen-treated infants with SMA (data-cut 1/2016, as compared to Natural History PNCR study)

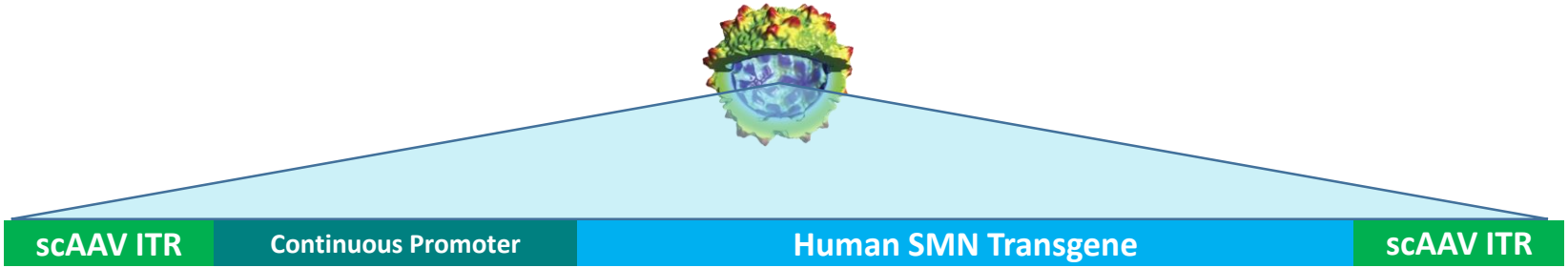
Richard S Finkel, Claudia A Chiriboga, Jiri Vajsar, John W Day, Jacqueline Montes, Darryl C De Vivo, Mason Yamashita, Frank Rigo, Gene Hung, Eugene Schneider, Daniel A Norris, Shuting Xia, C Grank Bennett, Kathie M Bishop. *Lancet*. 2016;388:3017-26.

HINE Motor Milestone Responses to Nusinersen Rx Over Time Across Studies



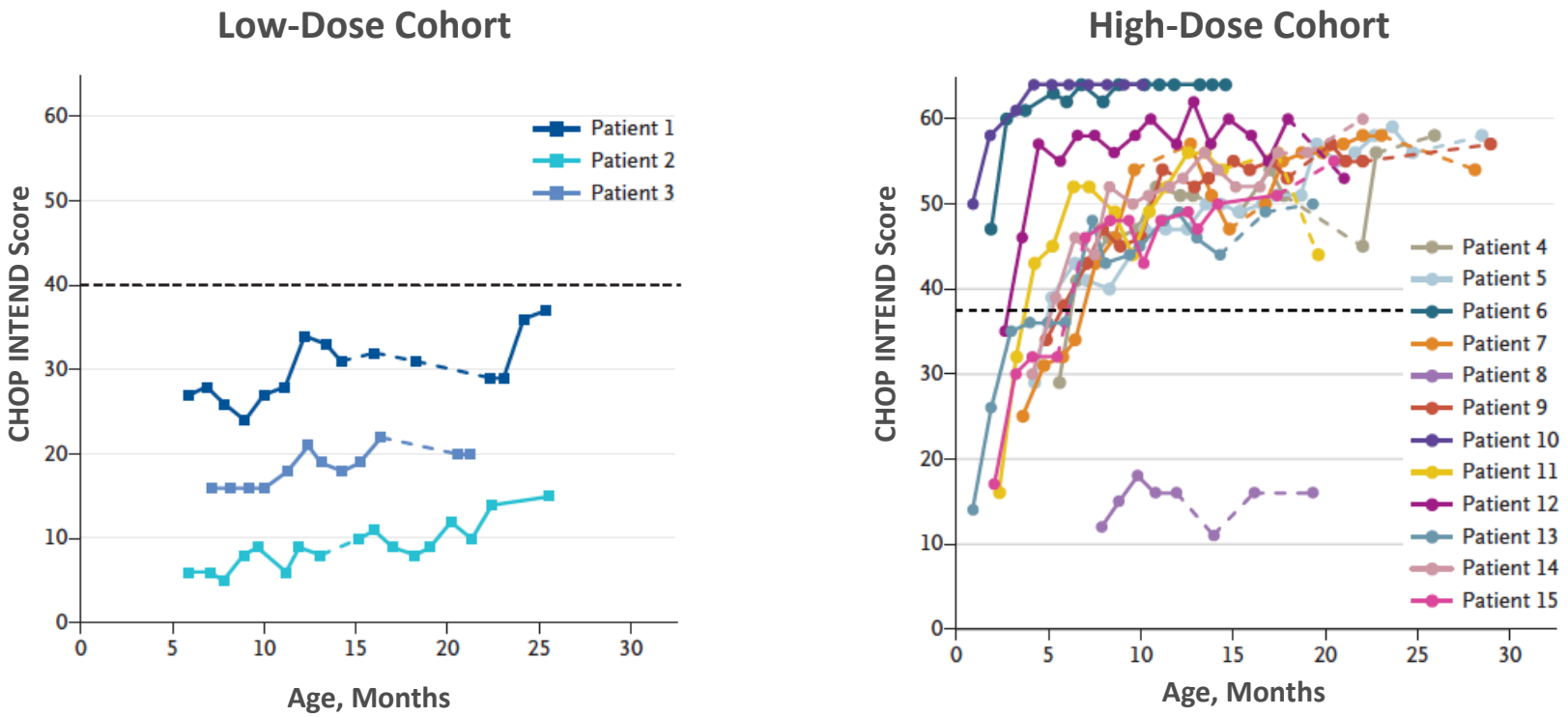
Courtesy of Biogen.

AVXS-101 Gene Transfer of *SMN1* Gene



- Phase 1 study: single dose, IV administration
  - Improved survival
  - Improved motor function
  - Improved pulmonary function
  - Improved feeding
- Better response among those treated early after diagnosis

Motor Function Changes After Gene Transfer: CHOP INTEND motor scale



CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders. Mendell JR, et al. *N Engl J Med*. 2017;377:1713-1722.

Newborn Screening for SMA

- Newborn screening for SMA is feasible[1,2]
- USA: (2/8/18) advisory committee on heritable disorders in newborns and children recommended SMA be included in the uniform newborn screening panel (RUSP); HHS chief Alex Azar approved on 7/3/2018
- 11 states in US now screening
- Europe: early discussions and pilot studies in several countries

1. Phan HC, et al. *Semin Perinatol*. 2015;39(3):217-229.
2. Taylor JT, et al. *Clin Chem*. 2015;61(2):412-419.

Case: A 12-month old girl is seen for a well-child check

- Father shares his concern that she is no longer able to “bounce on her legs”
- She was hospitalized at 9 months of age with RSV, needing CPAP support for 2 days. Since then she seems to have made no gains in motor skills.
- Her chart notes indicate normal prior developmental milestones: sat at 6 months, first word at 10 months.
- Review of family history is positive for cerebral palsy in a cousin.
- VS show a plateau in weight gain since age 9 months, with normal height and OFC

Take-Home Points

- SMA is a treatable disease
- Nusinersen is now a treatment standard
- Gene therapy is likely to be an option soon
- Other drugs in the pipeline
- Changing phenotype in treated patients
- Standard-of-care remains important
- Early ID and treatment makes a difference
- Newborn screening & pre-symptomatic Rx
  - SMA types 1 and 2 may largely disappear

Acknowledgements

- Patients, families and study personnel
- Collaborators
  - Pre-clinical: Adrian Krainer, Cold Spring Harbor; Arthur Burghes, Ohio State; Brunhilda Wirth, Cologne
  - Clinical: G Tennekoon, CHOP; D De Vivo, Columbia; B Darras, Boston Children's; J Day, Stanford; E Mercuri, Rome; F Muntoni, London
- Sponsors: Ionis/Biogen, Roche/PTC, Novartis, AveXis,
- Funding: NIH, Cure SMA, SMA Foundation
- Patient Advocacy Groups: MDA, Cure SMA, SMA Foundation, SMA Europe, TREAT-NMD
- FDA and EMA regulatory authorities