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.

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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

- Brain
- Cerebellum
- Spinal cord
- Peripheral nerve
- Motor neuron (anterior horn cell)
- Neuromuscular junction
- Muscle

Neuromuscular diseases
## Examples of Specific Diagnoses by Anatomic Location

<table>
<thead>
<tr>
<th>Anatomic location</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor neuron</td>
<td>Spinal Muscular Atrophy (SMA)</td>
</tr>
<tr>
<td>Peripheral nerve</td>
<td>Hereditary peripheral neuropathy (CMT)</td>
</tr>
<tr>
<td>Neuromuscular junction</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td></td>
<td>Congenital myasthenic syndromes</td>
</tr>
<tr>
<td>Muscle</td>
<td>Myopathies</td>
</tr>
<tr>
<td></td>
<td>Muscular dystrophies</td>
</tr>
</tbody>
</table>
Neuromuscular Diseases

Brain/spinal cord

Muscle

Anterior horn cell

Peripheral nerve

Neuromuscular junction
Neuromuscular Diseases (Reality)
## Prevalence of Early Childhood Disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learning disabilities</td>
<td>65 per 1000 (1 in 15)</td>
</tr>
<tr>
<td>Autism spectrum disorders</td>
<td>11.3 per 1000 (1 in 88)</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>3.3 per 1000 (1 in 303)</td>
</tr>
<tr>
<td>NM diseases</td>
<td>0.3 per 1000 (1 in 3000)</td>
</tr>
</tbody>
</table>

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

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

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

CK, creatine kinase.
Diagnostic Delay in Spinal Muscular Atrophy ~1 Year in Later Onset Types

Age of Onset and Diagnoses by Type of SMA

Type I
- Age of Onset: 2.5 months
- Weighted Mean Age: 6.3 months

Type II
- Age of Onset: 8.3 months
- Weighted Mean Age: 20.7 months

Type III
- Age of Onset: 39 months
- Weighted Mean Age: 50.3 months

SMA, spinal muscular atrophy.
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
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

Early diagnosis makes a difference.

Listen, Observe, Evaluate, Test, Refer
## Developmental Screening Tools

- childmuscleweakness.org

### Milestone: Gait (12+ Months)

<table>
<thead>
<tr>
<th>Developmental Norms</th>
<th>Walking Alone</th>
<th>Running</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% by 12 months</td>
<td>50% by 16 months</td>
<td></td>
</tr>
<tr>
<td>75% by 13.1 months</td>
<td>75% by 18.5 months</td>
<td></td>
</tr>
<tr>
<td>90% by 14.4 months</td>
<td>90% by 21 months</td>
<td></td>
</tr>
</tbody>
</table>

**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.
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
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

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

Making A Difference in Duchenne Muscular Dystrophy & Spinal Muscular Atrophy: PEDIATRICIANS AT THE FRONT LINE OF EARLY DIAGNOSIS & IMPROVED SURVIVAL
• 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.
• 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
Making A Difference in **Duchenne Muscular Dystrophy & Spinal Muscular Atrophy:**

**PEdiATRICIANS AT THE FRONT LINE OF EARLY DIAGNOSIS & IMPROVED SURVIVAL**

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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
Due to a genetic mutation, the dystrophin protein is missing or not functional in Duchenne.
What Does Dystrophin Do?

Shock absorption preventing contraction-induced injury to muscle fibers
What Happens When Dystrophin is Missing?

- Calcium
- Free radicals
- Inflammation
- Oxygen deprivation
- Fibrosis (scarring)
- Muscle cell death

no linkage
DMD Pathomechanism

Gene abnormality at Xp21 loci
↓
Absence of dystrophin

Structural defect

Membrane instability

Apoptosis/Necrosis

Activation of NF-κB

Inflammation

Fibrosis

Satellite Cell Activation
Muscle Fiber Regeneration

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

Making A Difference in Duchenne Muscular Dystrophy & Spinal Muscular Atrophy: PEDIATRICIANS AT THE FRONT LINE OF EARLY DIAGNOSIS & IMPROVED SURVIVAL
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)
Occasionally, an increased ALT, AST, or LDH concentration prompts an inappropriate focus on hepatic dysfunction, delaying the diagnosis of DMD.
• 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
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

Mitochondrial dysfunction

Correcting perturbations in calcium handling

Correcting blood flow regulation

Increasing muscle mass and regeneration

Decreasing inflammation and fibrosis

DMD Therapeutic Development

Replacement of dystrophin/utrophin
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)


Making A Difference in Duchenne Muscular Dystrophy & Spinal Muscular Atrophy: PEDIATRICIANS AT THE FRONT LINE OF EARLY DIAGNOSIS & IMPROVED SURVIVAL
Declining FVC%p Linked to Clinically Meaningful Thresholds and Risk of Death (Based on CINRG Data)

10% reduction in FVC%p impacts risk of hypoventilation

Increased risk of death

Nocturnal hypoventilation

Continuous ventilation

Night bi-level ventilation

Intervention

Clinical Progression

Mean (SEM) PFT Value

FVC%p

Age (Years)

0 20 40 60 80 100

0 6 8 10 12 14 16 18 20 22 24 26 28 30

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

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)

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)

Bayley-III Gross Motor Scaled Scores versus Age
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)
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

Mitochondrial dysfunction
Replacement of dystrophin/utrophin
Increasing muscle mass and regeneration
Decreasing inflammation and fibrosis
Correcting perturbations in calcium handling
Correcting blood flow regulation

DMD Therapeutic Development

Making A Difference in Duchenne Muscular Dystrophy & Spinal Muscular Atrophy: PEDIATRICIANS AT THE FRONT LINE OF EARLY DIAGNOSIS & IMPROVED SURVIVAL
Potential for Combination Treatments in DMD

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

- Mitochondrial dysfunction
- Correcting perturbations in calcium handling
- Correcting blood flow regulation
- Increasing muscle mass and regeneration
- Decreasing inflammation and fibrosis

DMD Therapeutic Development
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


Making A Difference in Duchenne Muscular Dystrophy & Spinal Muscular Atrophy: PEDIATRICIANS AT THE FRONT LINE OF EARLY DIAGNOSIS & IMPROVED SURVIVAL
• 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

Making A Difference in Duchenne Muscular Dystrophy & Spinal Muscular Atrophy: PEDIATRICIANS AT THE FRONT LINE OF EARLY DIAGNOSIS & IMPROVED SURVIVAL
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\(^4\)

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

Normal Dystrophin mRNA

Exon 48-50 Disrupts Reading Frame

Skipping Exon 51 Restores Reading Frame

Target Outcome: Shortened Dystrophin Protein

Normal Dystrophin Protein

Unstable/No Dystrophin Protein: DMD
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

Mutations not amenable to exon skipping, 20%
Other mutations amenable to exon skipping, 30%


Making A Difference in *Duchenne Muscular Dystrophy & Spinal Muscular Atrophy: PEDIATRICIANS AT THE FRONT LINE OF EARLY DIAGNOSIS & IMPROVED SURVIVAL*
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)

<table>
<thead>
<tr>
<th>Eteplirsen-Treated Week 180</th>
<th>Untreated Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>01002</td>
<td>DMD #1</td>
</tr>
<tr>
<td>01003</td>
<td>DMD #2</td>
</tr>
<tr>
<td>01004</td>
<td>DMD #3</td>
</tr>
<tr>
<td>01006</td>
<td>DMD #4</td>
</tr>
<tr>
<td>01007</td>
<td>DMD #5</td>
</tr>
<tr>
<td>01008</td>
<td>DMD #6</td>
</tr>
<tr>
<td>01012</td>
<td>01008</td>
</tr>
<tr>
<td>01013</td>
<td>01013</td>
</tr>
<tr>
<td>01015</td>
<td>01015</td>
</tr>
</tbody>
</table>

Patient 01005 declined the optional 4th surgical biopsy
**Study 201/202**  
Increased Dystrophin Detected by All 3 Methods at Week 180 With Eteplirsen

<table>
<thead>
<tr>
<th>Method</th>
<th>Absolute Differences of Means (Treated vs Untreated Exon 51–Amenable Patient*) (% of Normal)</th>
<th>Fold Increase</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDPF</td>
<td>+16.27%</td>
<td>15.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intensity</td>
<td>+13.20%</td>
<td>2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Western blot</td>
<td>+0.85%</td>
<td>11.6</td>
<td>0.007</td>
</tr>
</tbody>
</table>

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

Making A Difference in Duchenne Muscular Dystrophy & Spinal Muscular Atrophy: PEDIATRICIANS AT THE FRONT LINE OF EARLY DIAGNOSIS & IMPROVED SURVIVAL
Less than 3% of Dystrophin Is Clinically Relevant

Western Blot

**Dystrophin Protein (% normal control)**

- **DMD Untreated (Exon 51)**
  - n=18*
  - 48 weeks

- **Study 301**
  - n=12
  - 48 weeks

- **Study 201/202**
  - n=11
  - 180 weeks

- **Exon 44 Skip—Amenable Untreated**
  - LOA: >19 years

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

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

*Making A Difference in Duchenne Muscular Dystrophy & Spinal Muscular Atrophy: PEDIATRICIANS AT THE FRONT LINE OF EARLY DIAGNOSIS & IMPROVED SURVIVAL*
Clinically Meaningful Benefit Greater After 1 Year

**DYSTROPHIN**

- % Normal Dystrophin

**FVC %p**

- Mean (SE)

**6MWT (m)**

- Probability of Remaining Ambulatory (%)

**6MWT**

- 400
- 300
- 200
- 100
- 0

**LOA**

- 100
- 90
- 80
- 70
- 60
- 50
- 40
- 30
- 20
- 10
- 0

*Making A Difference in Duchenne Muscular Dystrophy & Spinal Muscular Atrophy: PEDIATRICIANS AT THE FRONT LINE OF EARLY DIAGNOSIS & IMPROVED SURVIVAL*
Golodirsen (Exon 53): Novel Dystrophin Production at Week 48 by Western Blot (n=25)

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

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

<table>
<thead>
<tr>
<th>Method</th>
<th>Dose</th>
<th>Baseline Mean % (SD)</th>
<th>On-treatment Mean % (SD)</th>
<th>Fold Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Exon skipped molality (RT-PCR)</td>
<td>40 mg/kg</td>
<td>0.0 (0.0)</td>
<td>17.4 (7.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>80 mg/kg</td>
<td>0.0 (0.0)</td>
<td>43.9 (16.7)</td>
<td></td>
</tr>
<tr>
<td>% Dystrophin (Western blot)*</td>
<td>40 mg/kg</td>
<td>0.3 (0.1)</td>
<td>5.7 (2.4)</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>80 mg/kg</td>
<td>0.6 (0.8)</td>
<td>5.9 (4.5)</td>
<td>9.8</td>
</tr>
</tbody>
</table>

- **Method**
  - % Exon skipped molality (RT-PCR)
  - % Dystrophin (Western blot)*

- **Dose**
  - 40 mg/kg
  - 80 mg/kg

- **Baseline Mean % (SD)**
  - 0.0 (0.0)
  - 0.0 (0.0)
  - 0.3 (0.1)
  - 0.6 (0.8)

- **On-treatment Mean % (SD)**
  - 17.4 (7.2)
  - 43.9 (16.7)
  - 5.7 (2.4)
  - 5.9 (4.5)

- **Fold Changes**
  - 19
  - 9.8

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Making A Difference in Duchenne Muscular Dystrophy & Spinal Muscular Atrophy: PEDIATRICIANS AT THE FRONT LINE OF EARLY DIAGNOSIS & IMPROVED SURVIVAL
Clinical Changes With Exon 53 Skipping (Viltolarsen)

**Stand from Supine (Velocity)**

- **Baseline:**
  - Viltolarsen: 0
  - DNHS: 0

- **13 weeks:**
  - Viltolarsen: 0.02
  - DNHS: 0.04

- **25 weeks:**
  - Viltolarsen: 0.06
  - DNHS: 0.12

**Climb 4-Stairs (Velocity)**

- **Baseline:**
  - Viltolarsen: 0
  - DNHS: 0

- **13 weeks:**
  - Viltolarsen: 0.04
  - DNHS: 0.06

- **25 weeks:**
  - Viltolarsen: 0.08
  - DNHS: 0.16
Clinical Changes With Exon 53 Skipping (Viltolarsen)

Run/walk 10 meters

<table>
<thead>
<tr>
<th>Time</th>
<th>Viltolarsen</th>
<th>DNHS</th>
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<td>Baseline</td>
<td></td>
<td></td>
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<tr>
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<tr>
<td>25 weeks</td>
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North Star Ambulatory Assessment

<table>
<thead>
<tr>
<th>Time</th>
<th>Viltolarsen</th>
<th>DNHS</th>
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<tbody>
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<td>25 weeks</td>
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Peptide Conjugated PMO (PPMO)\textsuperscript{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 \textit{in vivo} studies have demonstrated targeted delivery to
  - Skeletal muscle
  - Cardiac muscle
  - Smooth muscle

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
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
UC Davis Neuromuscular Medicine & Rehabilitation Research Center and CINRG Network

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

PEDIATRICIANS AT THE FRONT LINE OF EARLY DIAGNOSIS & IMPROVED SURVIVAL

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

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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
• 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

<table>
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<tr>
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<th>TYPE 1</th>
<th>TYPE 2</th>
<th>TYPE 3</th>
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</thead>
<tbody>
<tr>
<td>Age of onset (parental recall)</td>
<td>&lt;6 months</td>
<td>6-18 months</td>
<td>18 months - adult</td>
</tr>
<tr>
<td>Incidence per live birth</td>
<td>~60%</td>
<td>~27%</td>
<td>~13%</td>
</tr>
<tr>
<td>Maximum motor milestones</td>
<td>Never Sits</td>
<td>Never Walks</td>
<td>Walks</td>
</tr>
<tr>
<td>Survival</td>
<td>~30% survival by 2 years of age with supportive care</td>
<td>68% alive at age 25 years</td>
<td>Normal</td>
</tr>
</tbody>
</table>
SMN Genes on 5q

5 base pair differences between SMN1 and SMN2

c.840 C>T
• ~90% of SMN2 undergoes alternative splicing leading to truncated transcript that lacks exon 7 (Δ7SMN)

• Full-length protein is produced from SMN1 and SMN2

2 SMN Genes  ➡️  1 SNN Protein

SMN Protein Deficiency
• 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 Finkel¹ = 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 Kolb² = no death, or no tracheostomy; n = 20


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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”
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

• 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

- 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.

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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)


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HINE Motor Milestone Responses to Nusinersen Rx Over Time Across Studies

Better Response Among Those Treated Early After Diagnosis

Scheduled Visit Day

Max score

Mean (SE) Total Motor Milestones Score

NURTURE (presymptomatic infantile-onset SMA; 2 SMN2 copies; 6/2017 data cut)
NURTURE (presymptomatic infantile-onset SMA; 2 SMN2 copies; 5/2018 data cut)
CS3A (infantile-onset SMA; 2 SMN2 copies; final analysis)\textsuperscript{b}
ENDEAR sham control/SHINE nusinersen (infantile-onset SMA; 2 SMN2 copies; 6/2017 data cut)
ENDEAR sham control (infantile-onset SMA; 2 SMN2 copies; final analysis)

Courtesy of Biogen.

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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


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Newborn Screening for SMA

- Newborn screening for SMA is feasible\textsuperscript{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

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

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