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Duchenne Muscular Dystrophy (DMD)

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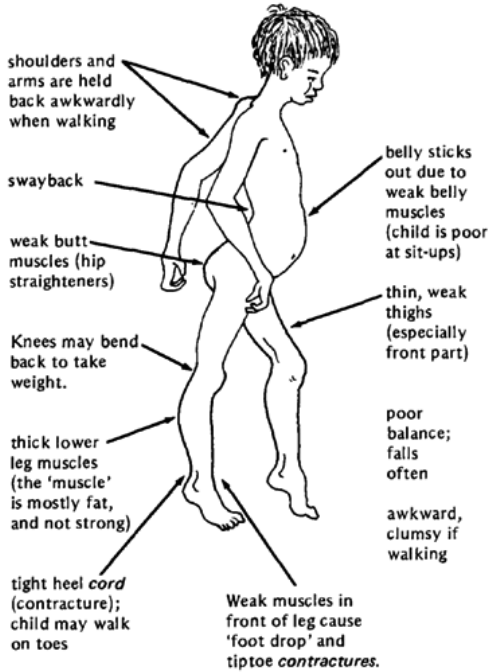
Objectives

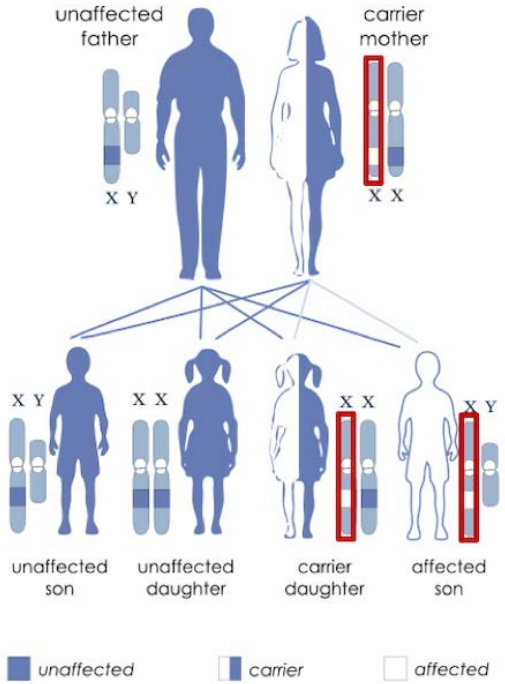
- Overview of Duchenne Muscular Dystrophy (DMD)
- Discuss the complications and impact of DMD
- Review current management strategies
- Review the current drug therapies approved for the treatment of DMD
- Introduce the future of DMD

What is Duchenne Muscular Dystrophy (DMD)?



- Rare, degenerative muscular disease characterized by progressive skeletal, cardiac muscle loss and scoliosis
- Progressively go from walking to wheelchair and without treatment expected to not live beyond teenage years
- Estimated prevalence is around 16 in 100,000 live male births in the United States

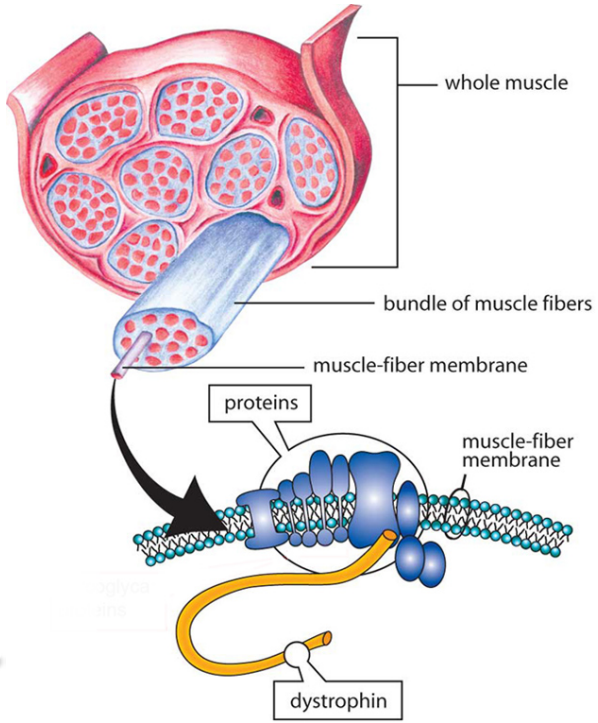
Pathophysiology



- DMD derives from mutations in the DMD gene located only on the X-chromosome. Boys only have one X chromosome, so they will show the most muscle loss and symptoms versus girls who will show little to no symptoms but are carriers of the disease

Pathophysiology

- DMD gene has 79 exons that code for dystrophin, a protein used to protect the glycoprotein complex of muscle fibers from degradation by endogenous proteases and allow its binding to the extracellular matrix of the sarcolemma
  - A mutation in the DMD gene causes the DMD disease as <3% of normal dystrophin levels lead to severe muscle instability as connections to other muscle fibers are lost and deforms the surrounding tissue, losing muscle stiffness and strength. Other lab markers include creatinine kinase greater than 10-100 ULN



Complications and Impact

- Daily Rehabilitation Management:
  - Daily stretching 4-6 times per week of joints and areas of motion; especially in areas of deformity and contractures
  - Exercise with aerobic swimming or cycling without overexertion paying attention to falls and fractures
  - Work on physical, occupational and speech/language continued through adulthood to avoid social isolation and obesity
- Endocrine Management:
  - Measure bone and arm span to get the growth velocity to measure progression of DMD; <4cm/year is impaired growth
  - Delayed puberty by 14 yo from glucocorticoid therapy may need testosterone replacement therapy and titrated to adult doses or until intolerable

Complications and Impact

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- Nutrition Management:
  - Dysphagia and mandible contracture can lead to malnutrition; refer to SLP
  - Focus on Calcium and Vit-D that can affect other organ systems and steroid therapy
  - Immobility frequently leads to constipation, abdominal muscle weakness and dehydration: use laxative and PEG or lactulose
  - GERD use H2A or PPI, but watch for fracture risks
- Respiratory Management:
  - Use of lung volume recruitment, assisted coughing, ventilation day and night to improve QOL, and recommend pneumococcal and flu shots
  - Assess spirometry, like FVC, and Oxygen saturation and signs of pneumonia, dyspnea, fatigue, and difficulty concentrating as back support muscles fail

Complications and Impact

- Cardiac Management:
  - Dystrophin deficiency leads to cardiomyopathy, arrhythmias and heart failure
  - Assess with echocardiogram/imaging, LVEF that may range from 80% to 40% by mid-20s; may use a mechanical ventricular assist device
  - Arrhythmia come from failing muscles and cannot respond to the nodal signals
- Bone Health Management:
  - Symptom of DMD worsened with glucocorticoid use and found with lateral spine radiograph whenever suspect spine fractures and back pains;
  - Any signs of bone fragility would start IV bisphosphonates even when asymptomatic; monitor for symptoms and height loss

Complications and Impact

- Psychosocial Management:
  - Being unable to participate in normal activities and disease-related intellectual and behavioral impairment such as explosive tempers, autism, ADHD, OCD, anxiety, and depression
  - Use group therapy, behavioral training for patient and family or pharmacologically manage with SSRIs, mood stabilizers, or stimulants
  - slow language/learning development that may require special education and training programs

Stages of Management

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Care Considerations Working Group: Guidelines for Diagnosis and Management of DMD

	Stage 1 Diagnosis	Stage 2 Early Ambulation	Stage 3 Late Ambulatory	Stage 4 Early Non-Ambulatory	Stage 5 Late Non-Ambulatory
Neuromuscular		• Initiate and manage use of glucocorticosteroids			
Rehabilitation	• Provide orthoses, equipment, learning support		• Provide mobility devices, seating, supported standing devices, assistive technology		
Endocrine		• Provide family education and stress dose steroid prescription if on glucocorticosteroids			
Gastrointestinal & Nutritional			• Initiate annual discussion of gastrostomy tube as part of usual care		
Respiratory				• Initiate use of lung volume recruitment • Begin assisted cough/nocturnal ventilation	• Add daytime ventilation
Cardiac		• Assess cardiac function annually • Initiate ACEI/ARB by 10 years of age	• Use standard heart failure interventions with deterioration function		
Bone Health		• Assess lateral spine X-rays (every 1-2 years with glucocorticoid therapy; every 2-3 years without glucocorticoid therapy) • Refer to bone health expert at earliest sign of fracture (Genant grade 1 or higher vertebral fracture, or first long-bone fracture)			
Orthopedic		• Select situations – refer for surgery on foot and Achilles tendon to improve gait		• Consider intervention for foot position for wheelchair positioning • Initiate intervention with posterior spinal fusion in defined situations	

DMD Pharmacologic Management

- Goal is to delay loss of ambulation at a later age, delay onset of heart failure, preserve upper limb/respiratory function and avoid scoliosis surgery
- 2 choices as standard of care:
  - Prednisone 0.75mg/kg/d
  - Deflazacort (Emflaza®, glucocorticoid prodrug) 0.9 mg/kg/d
- Side Effects
  - Cushing's syndrome (weight gain)
  - Osteoporosis (fractures)
  - HPA suppression (growth delay)
  - Behavioral changes

Duchenne Muscular Dystrophy Treatments

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FDA Approved	September 19, 2016	December 12, 2019	August 12, 2020
Route of Administration	Intravenous Infusion	Intravenous Infusion	Intravenous Infusion
Dosing	30 mg/kg once weekly	30 mg/kg once weekly	80 mg/kg once weekly
Estimated Annual Cost for 7 yo 50 lbs Boy	$680,727	$680,727	$639,883
AWP Medispan Per mL Cost	$960.00	$960.00	$338.40

Exondys 51® (eteplirsen)

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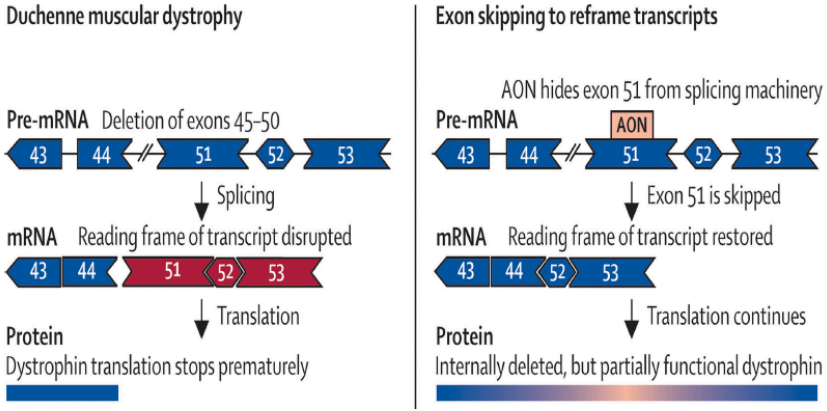
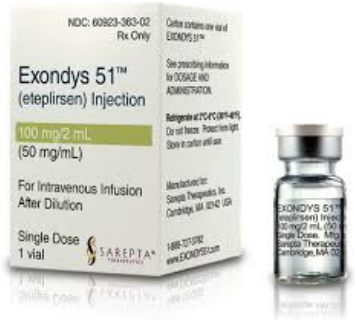
- **Mechanism of Action:** binds to exon 51 on dystrophin mRNA, skipping exon 51, and effectively frameshifting the mRNA when read to produce partially functional dystrophin
- **Indication**: antisense oligonucleotide therapy in DMD patients who have mutations amenable to exon 51 skipping
- **Dose:** 30 mg/kg once weekly intravenously
- **Side Effects:** balance problems, vomiting, skin irritation, allergic reactions





Summary of Clinical Trials – Exondys 51

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	Study 1: NCT01396239
Design	Phase 2, randomized, double-blind, placebo-controlled 24 wks+open-label 24 wks
# of patients	Confirmed DMD amenable to exon 51 skipping, N = 12
Patient Traits	Ages 7-13 years old, 6MWT approx. 200-400 meters, stable on steroid therapy prior for 6 months
Results	**6-minute Walk Test (6MWT)** • 30 mg/kg group showed no statistical significance compared to placebo group from baseline to week 48 • 50 mg/kg group showed statistical significance ($p<0.016$) compared to placebo group, showing an increase of 21 meters with Standard Error (SE) of 38.2 meters from baseline to week 48 **Percentage of Dystrophin Positive Muscle Fibers** • 30 mg/kg group increased to 52% from 18% and showed statistical significance ($p<0.001$) from baseline to week 48 • 50 mg/kg group increased to 47% from 11% and showed statistical significance ($p<0.008$) from baseline to week 48

Summary of Clinical Trials – Exondys 51

	Study 2: NCT01540409 (continuation of Study 1)
Design	Phase 2, randomized, open-label, case-controlled, longitudinal (24 wks + 4 years)
# of patients	Confirmed DMD amenable to exon 51 skipping, N = 12
Patient traits	Ages 7-13 years old, 6MWT approx. 200-400 meters, started steroid therapy prior, assigned to 30 mg/kg or 50 mg/kg vs historical data
Results	**6MWT after 36 months:** • Exondys treated group showed a favorable statistical difference of 151 meters compared to untreated historical data (data from Italian and Belgium DMD registry database) Respiratory Function: • Respiratory function of Exondys treated patients experienced less than 10% decline versus estimated DMD respiratory decline of approximately 11.5% or 4-5% per year FDA Label only: Average dystrophin protein level after 180 weeks of treatment with Exondys was 0.93% of normal dystrophin
Status	Completed

Summary of Clinical Trials – Exondys 51

	PROMOVI/pre-Study 3 NCT02255552
Design	Phase 3, non-randomized, open-label, multi-center, placebo-controlled
# of patients	Confirmed DMD with and without amenable to exon 51 skipping, N = 13
Age Range	Mean age of 8.9 years old (range 7-16 years old) and on steroid therapy 6 months prior
Results	**Dystrophin level:** • 12 subjects of the Exondys treated group showed an increase of 0.28% of normal at week 48 from 0.16% to 0.44%
Status	Ongoing/Merged into Vyondys ESSENCE trial

Vyondys 53™ (golodirsen)

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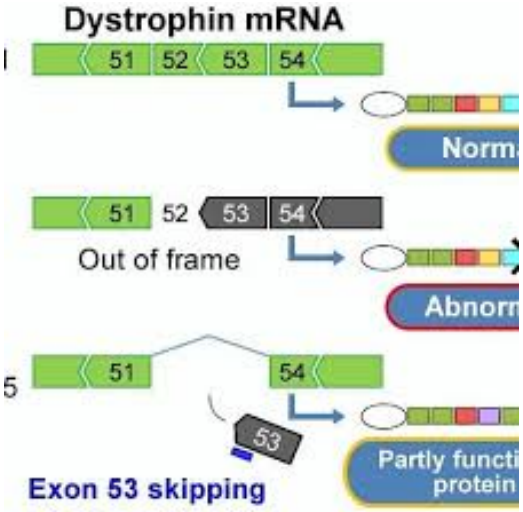
- **Mechanism of Action:** binds to exon 53 on dystrophin mRNA, skipping exon 53, and effectively frameshifting the mRNA when read to produce partially functional dystrophin
- **Indication**: antisense oligonucleotide for DMD patients who have mutations in DMD gene amenable to exon 53 skipping
- **Dose**: 30 mg/kg once weekly intravenously
- **Side Effects:** headache, fever, abdominal pain, falling, cough, common cold, nausea, vomiting, allergic reactions



Summary of Clinical Studies – Vyondys 53™

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	SKIP-NMD NCT02310906 Part 1	SKIP-NMD NCT02310906 Part 2
Design	Phase 1, Randomized, double-blind, placebo-controlled, multi-center, dose-finding, 12 wks	Phase 2, Randomized, open-label, multi-center, Efficacy and Safety Evaluation,168 wks
# of patients	Confirmed DMD amenable to exon 53 skipping, N = 12	Confirmed DMD amenable exon 53 skipping, N = 25
Avg. Age	6-15 years old	6-15 years old
Results	**Mean Dystrophin level:** • Statistical significant increase ($p<0.001$) from 0.095% to 1.019% of normal dystrophin protein level by week 48, a mean change from baseline of 0.88%	
	Complete	

Viltepso® (viltolarsen)

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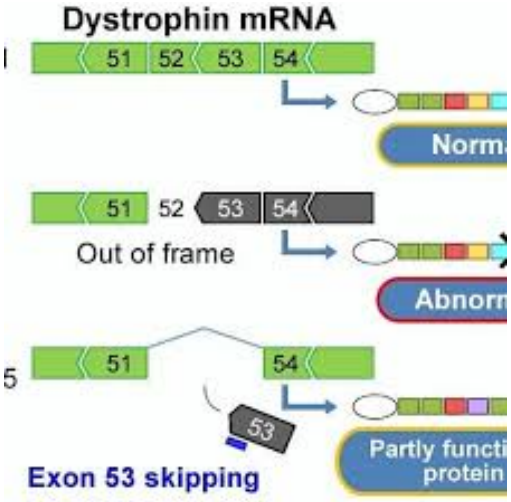
- **Mechanism of Action:** binds to exon 53 on dystrophin mRNA, skipping exon 53, and effectively frameshifting the mRNA when read to produce partially functional dystrophin
- **Indication**: antisense oligonucleotide for DMD patients who have mutations in DMD gene amenable to exon 53 skipping
- **Dose**: 80 mg/kg once weekly intravenously
- **Side Effects:** upper respiratory infections, injection site reactions, cough, fever, allergic reactions



Summary of Clinical Trials – Viltepso

	Safety and Dose Finding study of NS-065/NCNP-01 in Boys w/ DMD
Design	Phase 2, randomized, 4wk double-blind ten 20 wk open-label, multi-center, placebo/case-controlled, dose-finding
# of patients	Confirmed DMD with amenable to exon 53 skipping, N = 16
Age Range	range 4-9 years old and on steroid therapy prior for 3 months, ambulatory
Results	**Mean dystrophin level:** • High-dose (80 mg/kg) arm showed statistical significant ($p<0.05$) increase from 0.6% to 5.9% of normal dystrophin by week 25 • Low-dose (40mg/kg) arm showed statistical significant ($p<0.05$) increase from 0.3% to 5.7% of normal dystrophin by week 25 Motor functional tests: • Viltepso treated patients beat CINRG DNHS external control historic data in velocity to move 10 meters, 6MWT, and time to stand from supine
Status	Complete

Impact on Cost

- According the Muscular Dystrophy Association, the average Cost of Illness (COI) of DMD per patient:
  - Medical costs:$22,533/year
  - Nonmedical $12,939/year
  - Lost income $13,628/year
- The United States spends $362-488 million on DMD per year
- High Cost to society

Institute for Clinical and Economic Review (ICER) Analysis

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- Scenario 2 shows best case for deflazacort where it eliminated late-ambulatory and non-ambulatory stages, but incremental cost per QALY remains above $150,000 per QALY

Scenario	Treatment	Total Cost	QALYs	LYs	Incremental Cost per QALY
Scenario 1	Low dose: prednisone	$463,000	6.88	15.05	--
	Low dose: deflazacort	$892,000	8.40	16.64	$283,000
Scenario 2	Base-case value: prednisone	$464,000	6.88	15.05	--
	Early ambulatory and non-ambulatory: deflazacort	$1,010,000	8.77	16.64	$290,000

In the United States, thresholds of $100,000 or $150,000 per QALY gained have been suggested as a reasonable upper bound for an intervention to be deemed cost effective

Institute for Clinical and Economic Review (ICER) Analysis

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- Exondys and Vyondys are modelled the same due to insufficient historic data and showed an incremental cost per QALY of $450,000 per QALY where best case extended ambulation and delay mortality by 40 years with no SAE

Eteplirsen Scenarios	Incremental Costs	Incremental QALYs Gained	Incremental LYs Gained	Cost per QALY	Cost per LY Gained
10 year Shift	$12,670,000	4.70	5.15	$2,700,000	$2,460,000
20 Year shift	$17,510,000	8.20	8.63	$2,140,000	$2,030,000
40 Year Shift and Restore to Perfect Health	$23,350,000	28.00	16.07	$1,110,000	$1,450,000

In the United States, thresholds of $100,000 or $150,000 per QALY gained have been suggested as a reasonable upper bound for an intervention to be deemed cost effective

New Therapies in Pipeline

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- Gene Therapy (Sarepta Therapeutics)
  - SRP-9001
    - Adenovirus-based vector drug that will deliver micro-dystrophin DNA into muscle nucleus to make smaller functional dystrophin
  - GALGT2
    - Adenovirus-based vector drug that delivers GALGT2 gene into skeletal and heart muscles to build proteins that upregulate production of endogenous essential muscle proteins
- Allogenic Stem Cell Transplant (Capricor Therapeutics)
  - CAP-1002
    - Uses donor heart progenitor cells to release exosomes for macrophages and T-cells to encourage cellular regeneration

Conclusion

- Duchenne Muscular Dystrophy has a huge impact on utilization of health care services, durable medical equipment, and societal costs
- The development of disease modifying therapies that enhance the production of truncated dystrophin is a first step in addressing dystrophin deficiency
- Impact of gene therapies to be seen:
  - Different exon skipping like Casimersen (exon 45 skipping)
  - Gene editing w/ CRISPR and viruses
  - Life-long effects of therapies
  - More research on DMD pathophysiology aside from dystrophin

Glossary

- ACEI – Angiotensin converting enzyme inhibitor
- ARB – Angiotensin receptor blocker
- CINRG DNHS – Cooperative International Neuromuscular Research Group Duchenne Natural History Study
- CNS – Central Nervous System
- COI – Cost of Illness
- CRISPR – Clustered Regularly Interspaced Short Palindromic Repeats; a DNA technology to easily edit DNA sequences and modify gene function
- DMD – Duchenne Muscular Dystrophy
- ICER – Institute for Clinical and Economic Review
- LVEF – Left Ventricle Ejection Fraction
- NSAA – North Star Ambulatory Assessment
- MOA – Mechanism of Action
- QALY – Quality Adjusted Life Years
- QOL – Quality of Life
- SAE – Serious Adverse Effect
- SLP – Speech-Language Pathologist
- 6MWT – 6-Minute Walk Test

References

Exondys FDA approval clinical trials

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Study 2 or Study 202: NCT01540409
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Vyondys FDA approval clinical trials

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Viltepso FDA approval clinical trials

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