Editing Hope:

Gene Therapy in Duchenne Muscular Dystrophy

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Disclosures

- The planners and speakers have indicated that there are no relevant financial relationships with any ineligible companies to disclose.

Learning Objectives

Recall

Recall pathophysiology and genetic mutations associated with Duchenne Muscular Dystrophy

Classify

Classify medications used for Duchenne Muscular Dystrophy based on mechanism of action

Select

Select a treatment plan for a patient with newly diagnosed Duchenne Muscular Dystrophy

Identify

Identify barriers to gene therapy access for patients and health systems

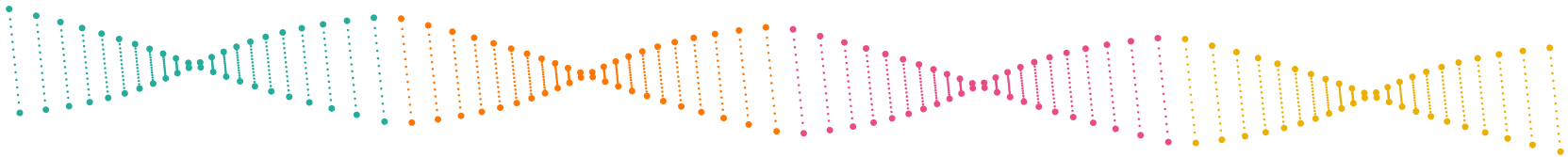
Presentation Outline

01
What is Duchenne Muscular Dystrophy (DMD)?

02
Treatment for DMD

03
Practical Considerations

04
Future Directions & Current Research

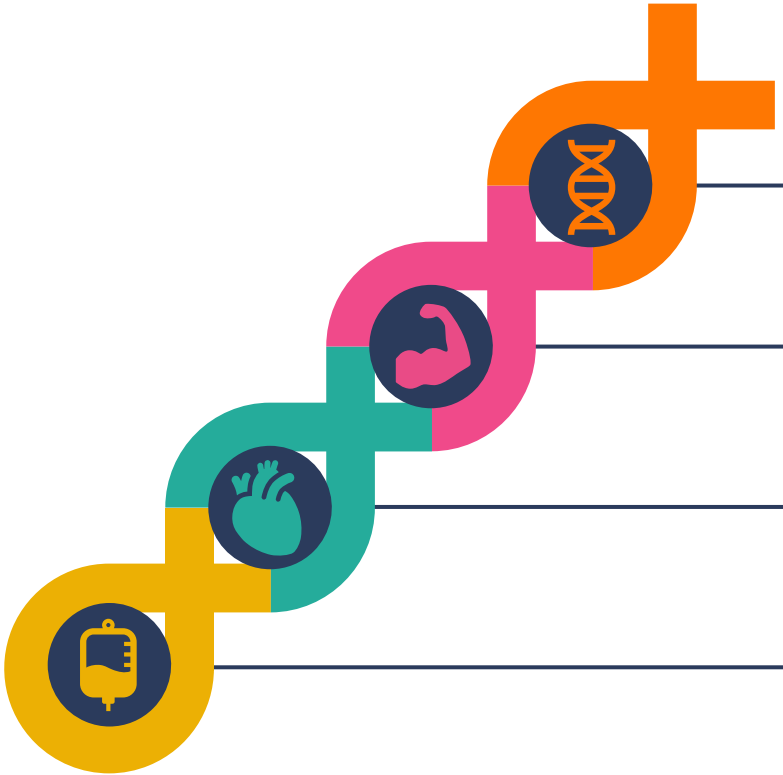


Abbreviation Guide

- 6MWT – 6-minute walk test
- AAV – adeno-associated virus
- AAVrh74 – a naturally occurring AAV serotype
- ACEi – angiotensin converting enzyme inhibitor
- AE – adverse event
- ARB – angiotensin II receptor blocker
- AWP – average wholesale price
- BMD – Becker Muscular Dystrophy
- CRISPR – clustered regularly interspaced short palindromic repeats
- DAPC – dystrophin-associated protein complex
- DCM – dilated cardiomyopathy
- DMD – Duchenne Muscular Dystrophy
- *DMD* – gene associated the Duchenne Muscular Dystrophy
- DelMox – delandistrogene moxeparvovec
- DFZ – deflazacort
- GC – glucocorticoid
- GDMT – guideline directed medical therapy
- HAT – histone acetyltransferase
- HDAC – histone deacetylase
- MDA – Muscular Dystrophy Association
- MRC – Medical Research Council
- mRNA – messenger ribonucleic acid
- MuSC – muscle satellite cells
- NF-κB - nuclear factor kappa-light-chain-enhancer of activated B cells
- NMJ – neuromuscular junction
- NOS – nitric oxide synthase
- nNOSμ – neuronal NOS isoform mu
- NSAA – North Star Ambulatory Assessment
- PFT – pulmonary function testing
- PRED – prednisone
- ROS – reactive oxygen species
- TQSM – Treatment Satisfaction Questionnaire for Medication
- ULN – upper limit of normal
- VLFF – vastus lateralis fat fraction

What is Duchenne Muscular Dystrophy?

Overview: Duchenne Muscular Dystrophy



01

X-Linked

Mutation in *DMD* gene located on chromosome 21

02

Neuromuscular

Dystrophin protein is critical for myocyte stabilization

03

Multiorgan Dysfunction

Myocytes all over the body are affected

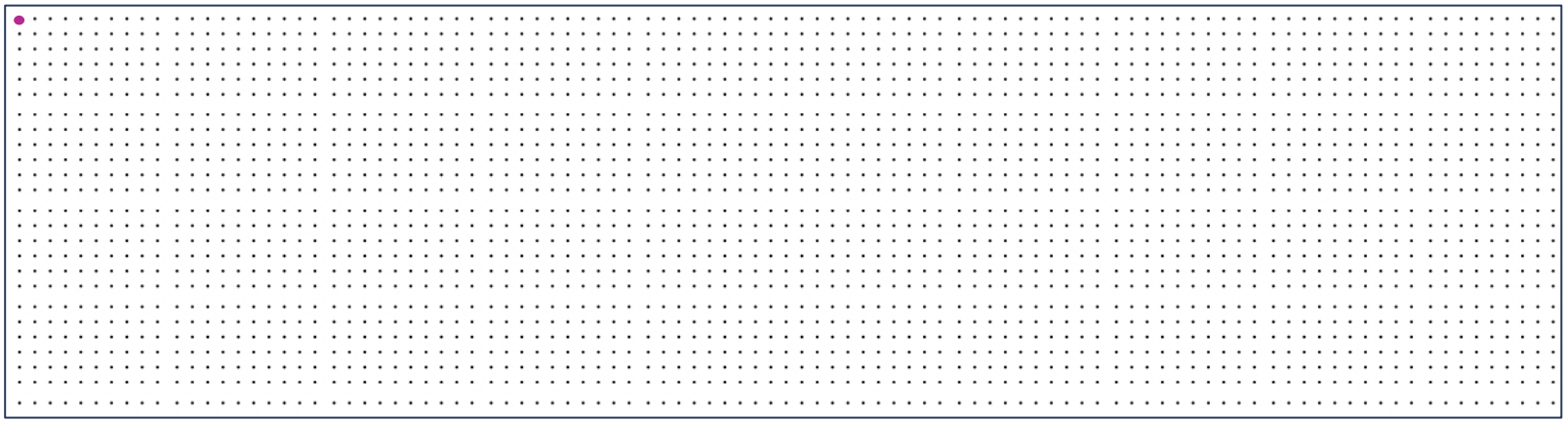
04

Cornerstone Therapies

Corticosteroids, exon skipping therapies, histone deacetylase inhibitors, and gene editing

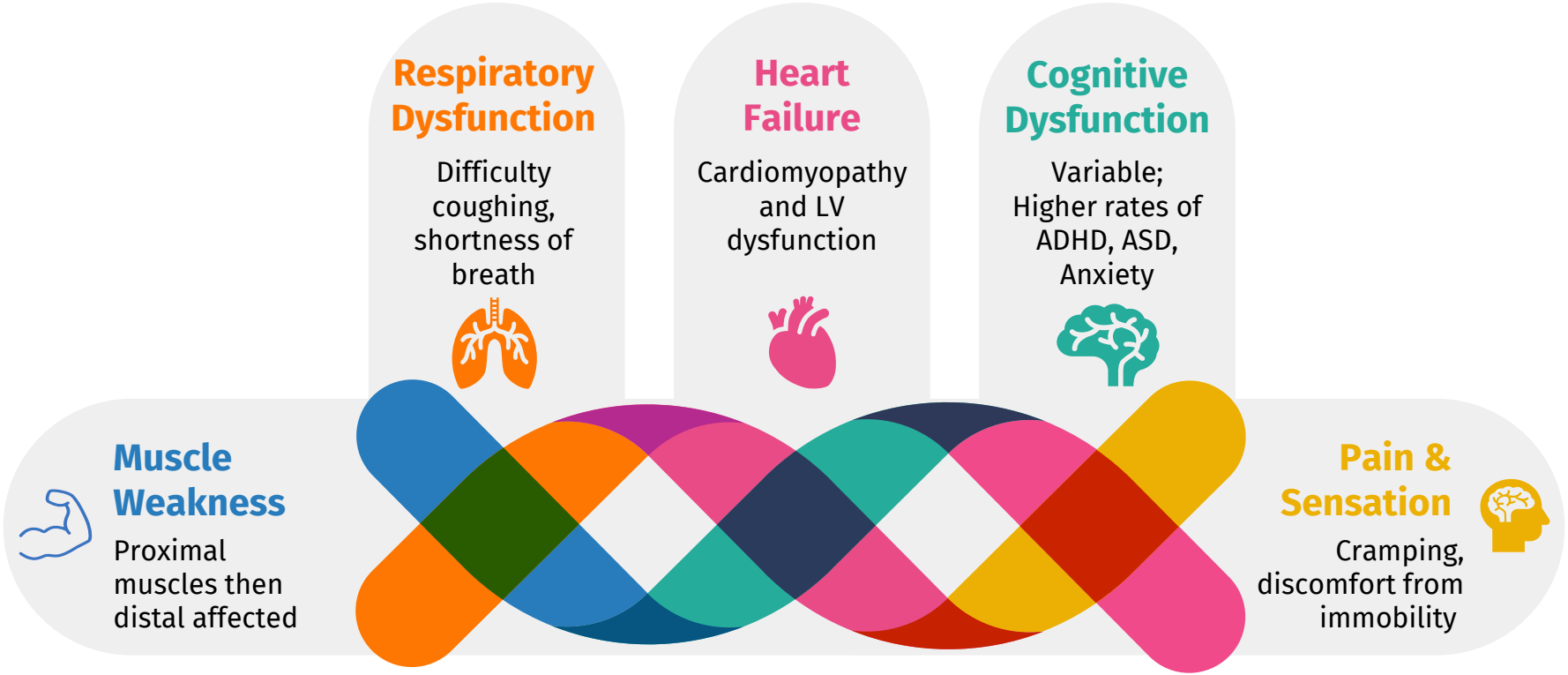
Epidemiology

- Worldwide prevalence of DMD is about **7 cases per 100,000 XY individuals**
  - In the United States, prevalence of DMD or BMD is about 1.4 per 10,000 XY individuals between ages of 5-24 years
- Incidence of about **1 per 5,000 live XY births**
- Carrier frequency: 7.3 per 10,000
- Average age of diagnosis in hemizygous XY individuals is **4.1 years**
  - Symptoms are first noted at 2.6 years, on average



Pickart AM, et al. *J Genetic Counseling*. 2024; 34(1): e1892

Signs & Symptoms of DMD



Chrzanowski S. *Muscular Dystrophy Association*. 2025.

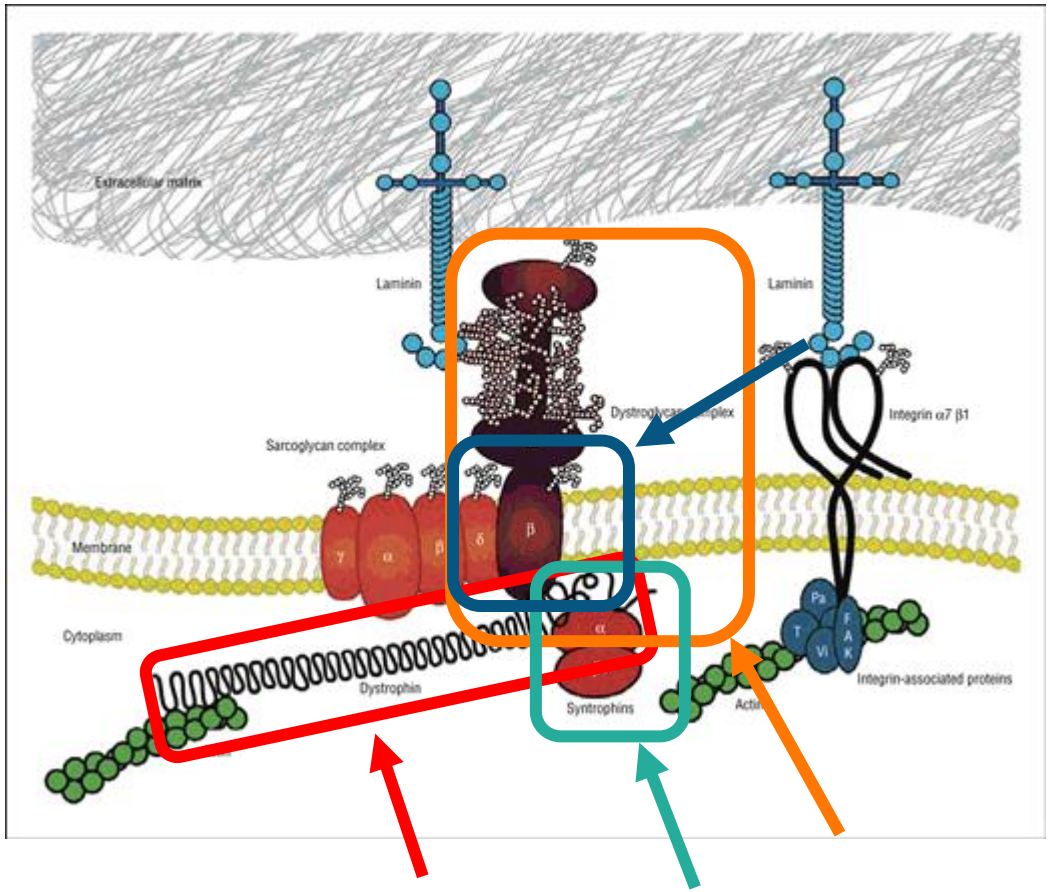
Progression of Disease

Age 2	Gross motor delays may begin to be noticeable
Age 3-4	Muscle weakness becomes clinically apparent
Age 7	Onset of plateau phase
Age 10-12	Loss of ambulation in patients not treated with corticosteroids. This can be delayed 1-2 years with corticosteroid use
Age 30s	Average life expectancy for a patient with DMD

Pickart AM, et al. *J Genetic Counseling*. 2024; 34(1): e1892
Chrzanowski S. *Muscular Dystrophy Association*. 2025.

Pathophysiology

- Mutation in *DMD* gene leads to inability to form functional dystrophin
  - Frameshift or nonsense mutations lead to absence of dystrophin
  - Missense mutations may lead to partially functional dystrophin, causing BMD
- Dystrophin protein normally links dystrophin-associated protein complex (DAPC) to intracellular γ-actin in myocyte cells
- Portions of dystrophin protein
  - N-terminal binds actin
  - Cysteine-rich region binds DAPC
  - Rod-shaped domain of spectrin-like repeats (R1-R24)
  - C-terminal



Rodino-Klapac LR, et al. *JAMA Neurol*. 2007; 64(9): 1236-12341.

Consequences of DAPC Damage

1 Oxidative Stress

2 Dysregulated Calcium Homeostasis

3 Neuromuscular Junction Impairment

4 Abnormal Differentiation of Muscle Satellite Cells

Consequences of DAPC Damage

Oxidative Stress	Dysregulated Calcium Homeostasis
• Nitric oxide synthase mis-localization leads to lack of protective vasodilation during muscle contraction ○ Basis for micro- and mini-dystrophin therapies containing R16/R17 structures • Overproduction of reactive oxygen species leads to oxidative stress	• Structural abnormalities in DAPC cause abnormal Ca^{2+} entry into myocytes • Oxidative stress and abnormal signaling leads to Ca^{2+} leakage from sarcoplasmic reticulum into cytoplasm • Elevated cytoplasmic Ca^{2+} leads to activation of calcium-dependent enzymes and cellular apoptosis

Chang M, et al. *J Neurol*. 2023; 270: 3733-3749.

Consequences of DAPC Damage

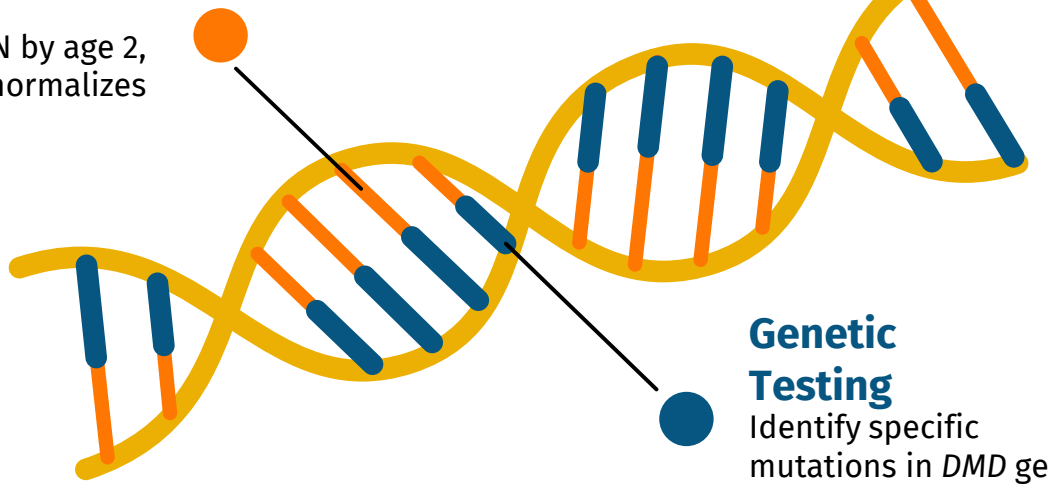
Neuromuscular Junction (NMJ) Impairment	Abnormal Differentiation of Muscle Satellite Cells (MuSCs)
• Normally, simultaneous release of multiple ACh from a single nerve impulse causes postsynaptic sarcolemma depolarization • Absence of function DAPC hinders clustering of AChR • Endplate potential cannot reach threshold for signal transmission	• Muscle satellite cells are partially differentiated and live around myofibers, entering cell cycle when myofibers are damaged • Structural abnormalities of DAPC impair asymmetric division of MuSCs

Chang M, et al. *J Neurol*. 2023; 270: 3733-3749.

Newborn screening

Diagnosis & Screening

Federal: CK was added to the Recommended Uniform Screening Panel (RUSP) in December 2025



Creatine Kinase

10-20x ULN by age 2, then normalizes

Muscle Biopsy

Rarely done; can be used if clinical suspicion remains high

Genetic Testing

Identify specific mutations in *DMD* gene

Chrzanowski S. *Muscular Dystrophy Association*. 2025.
HRSA. Recommended Uniform Screening Panel. 2024.

DMD Compared to Other Muscular Dystrophies

1 per 5,000 XY

Duchenne Muscular Dystrophy (DMD)

X-linked mutation in *DMD* gene on chromosome 21 leading to dysfunctional dystrophin; onset age 2-3

1 per 20,000 XY

Becker Muscular Dystrophy (BMD)

X-linked mutation in *DMD* gene on chromosome 21 leading to partially functional dystrophin; onset age 5 to 60

1 per 10,000

Myotonic Dystrophy (DM)

Mutation on chromosome 19 (Type 1) or chromosome 3 (Type 2); adult-onset

1 per 25,000

Fascioscapulohumeral Muscular Dystrophy

Inappropriate expression of *DUX4* gene on chromosome 4; onset age 20

1 per 123,000

Limb-Girdle Muscular Dystrophy (LGMD)

Multiple implicated genes; onset varies widely based on subtype

1 per 100,000

Emery-Dreifuss Muscular Dystrophy (EDMD)

Multiple implicated genes; onset around age 10

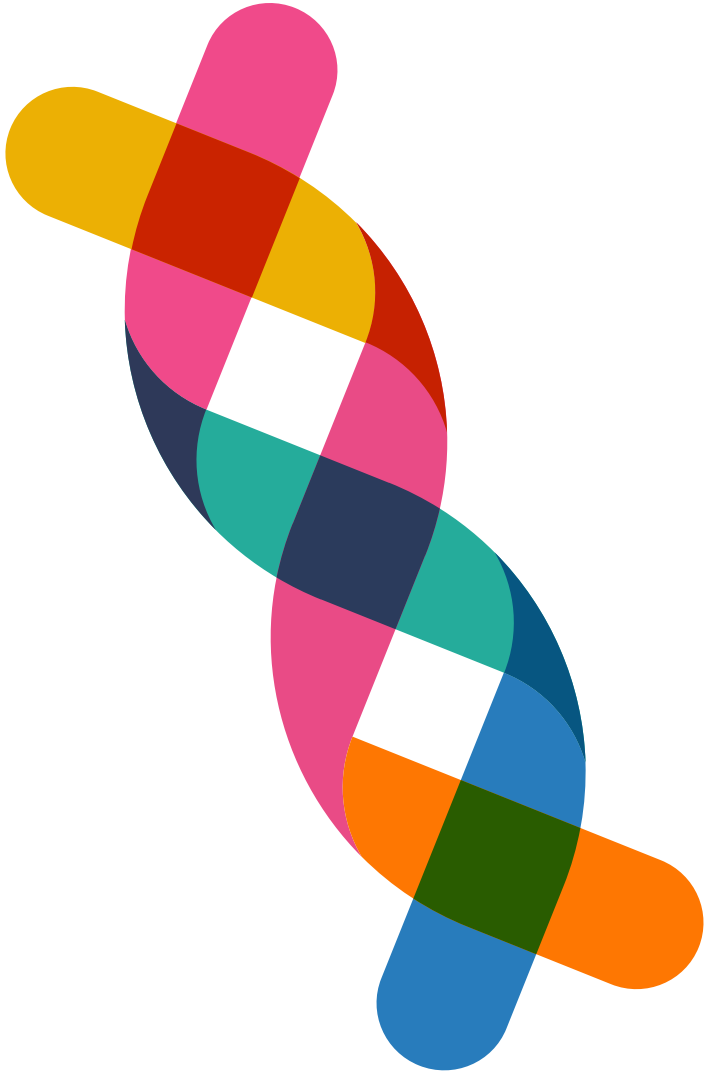
Neuromuscular Diseases. *Muscular Dystrophy Association*. 2026.

Assessment Question #1

Duchenne Muscular Dystrophy results from which of the following pathophysiologic pathways?

A. Missense mutation in *DMD* gene leads to absence of dystrophin
B. Inappropriate over-expression of the *DMD* gene leads to absence of dystrophin
C. Mutation in Y-linked *DMD* gene leads to absence of dystrophin
D. Frameshift mutation in *DMD* gene leads to absence of dystrophin

Treatment of Duchenne Muscular Dystrophy



Guideline Overview

Neuromuscular

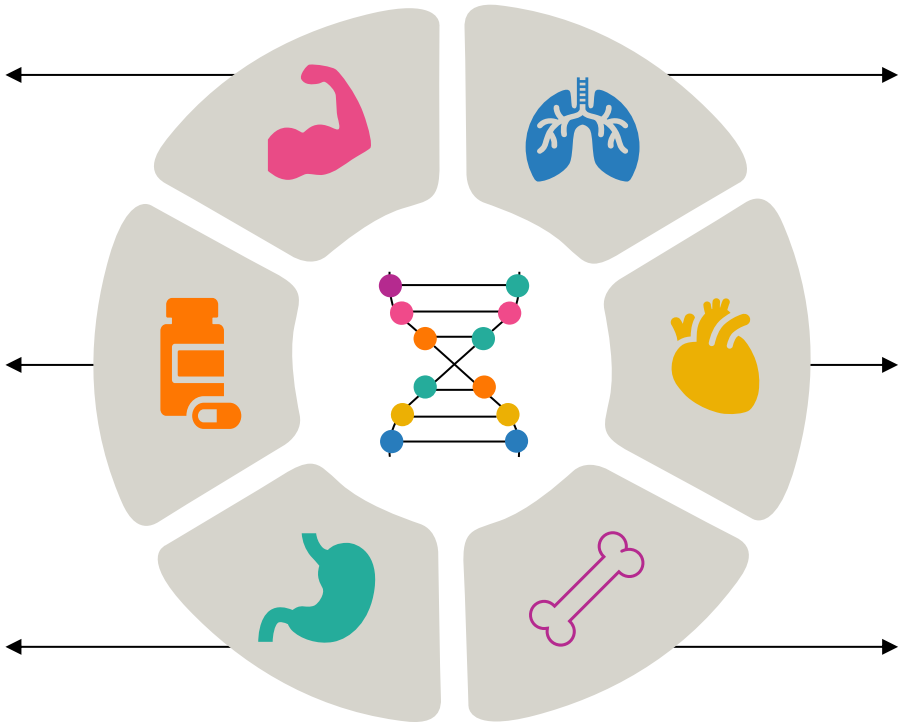
Initiate glucocorticoids at early ambulatory stage

Endocrine

Stress dose steroids as needed for adrenal crisis

Gastrointestinal

Swallowing function, constipation, GERD, & gastroparesis



Respiratory

Frequent spirometry & ventilation support

Cardiac

Initiate ACEi or ARB by age 10, standard GDMT for heart failure

Bone Health

Treat calcium/vitamin D deficiencies; consider IV bisphosphonates

Birnkrant DJ, et al. *Lancet Neurol*. 2018.

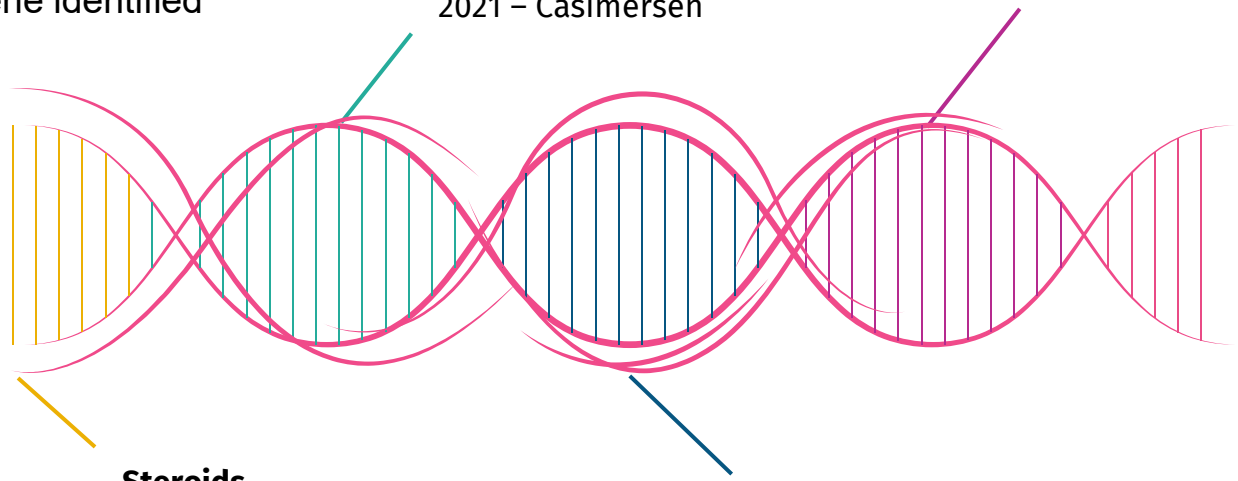
Timeline of Therapies

1860s: DMD first described by French neurologist Guillaume Benjamin Amand Duchenne

1986: *DMD* gene identified

Exon Skipping
2014 – Ataluren (Europe)
2016 – Eteplirsen
2019 – Golodirsen
2020 – Vitolarsen
2021 – Casimersen

Histone Deacetylase Inhibitor
2024 – Givinostat



Steroids
1980s – Glucocorticoids
2017 – Deflazacort
2023 – Vamorolone

Micro-Dystrophin Gene Therapy
2023 – Delandistrogene moxeparvovec

Chrzanowski S. *Muscular Dystrophy Association*. 2025.

Glucocorticoids

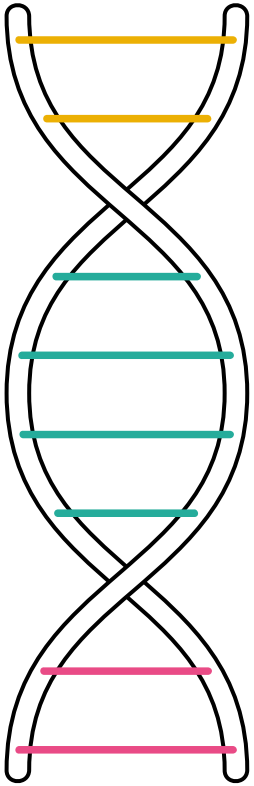
Glucocorticoids in DMD

- Mechanism of Action
  - Activation of glucocorticoid receptor leads to alteration of gene expression, specifically **inhibiting the transcription factor NF-κB**, that is overexpressed in both muscle and immune cells in dystrophic muscle
    - Prednisone is the classic glucocorticoid with additional mineralocorticoid activity
    - Deflazacort is a heterocyclic glucocorticoid prodrug
    - Vamorolone is a first-in-class dissociative steroidal anti-inflammatory drug that acts as a glucocorticoid agonist and a mineralocorticoid antagonist

	Prednisone (PO)	Deflazacort (PO)	Vamorolone (PO)
Starting Dose	0.75 mg/kg/day	0.9 mg/kg/day	6 mg/kg/day
Stress dose IM hydrocortisone: - Age <2: 50 mg - Age ≥2: 100 mg			

Birnkrant DJ, et al. *Lancet Neurol*. 2018.

Comparison of Glucocorticoids Used in DMD



1

Prednisone

- **Most pronounced weight gain**
- Common behavioral effects, moderate growth suppression, elevated fracture risk
- AWP: tablet ~$0.08 per mg; solution ~$0.80 per mg

2

Deflazacort

- **Most pronounced growth suppression**
- Less weight gain, common behavioral effects, risk of cataracts, elevated fracture risk
- AWP: tablet ~$18 per mg; suspension ~$25.60 per mg

3

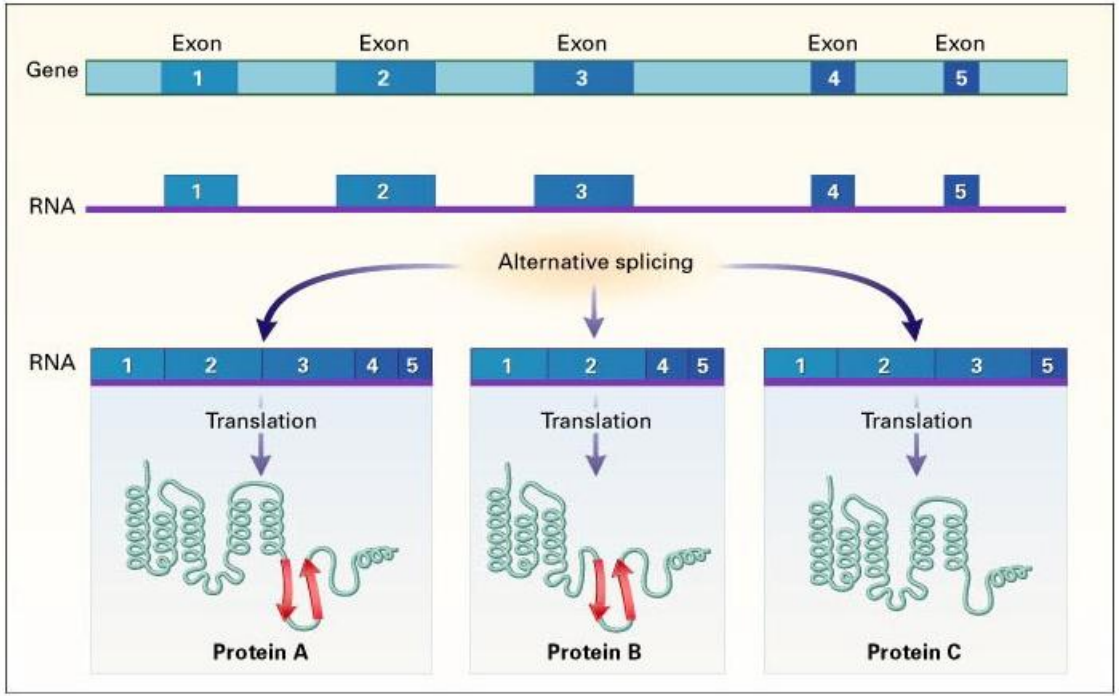
Vamorolone

- Preservation of linear growth, similar weight gain to DFZ
- Less common cushingoid appearance, potentially lower behavioral effects and fracture risk
- AWP: suspension ~$3.25 per mg

Guglieri M, et al. *JAMA Neurol*. 2022.
Prednisone. In: UpToDate Lexidrug. 2026.
Deflazacort. In: UpToDate Lexidrug. 2026.
Vamorolone. In: UpToDate Lexidrug. 2026.

Exon Skipping Therapies

What are Exons?

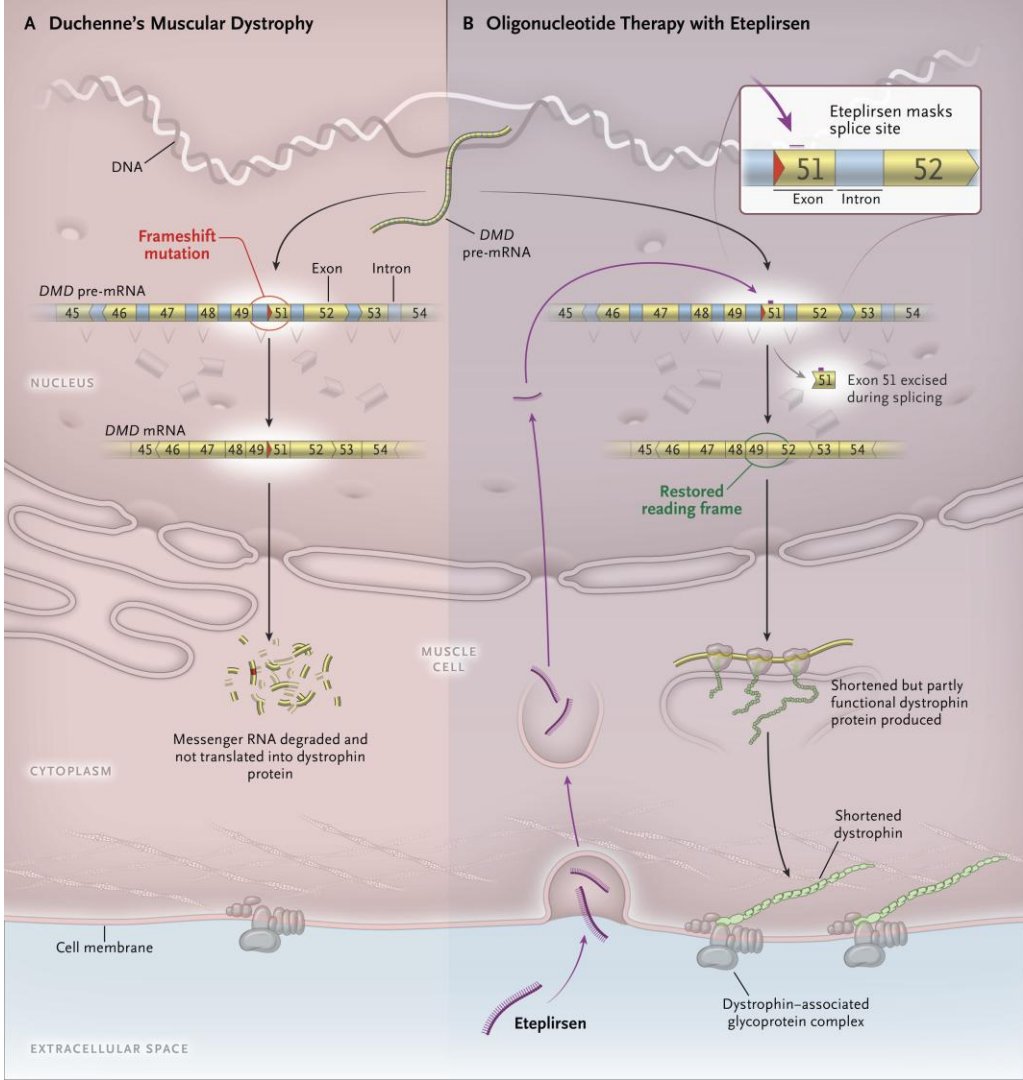


- **Exons** are the coding segments of a gene that are retained in the final mRNA
- **Introns** are non-coding intervening sequences
- After a gene is transcribed into precursor mRNA, **splicing** removes introns and joins exons together to form mature mRNA
- Mature mRNA is **translated** into protein

Guttmacher AE, et al. *NEJM*. 2002.

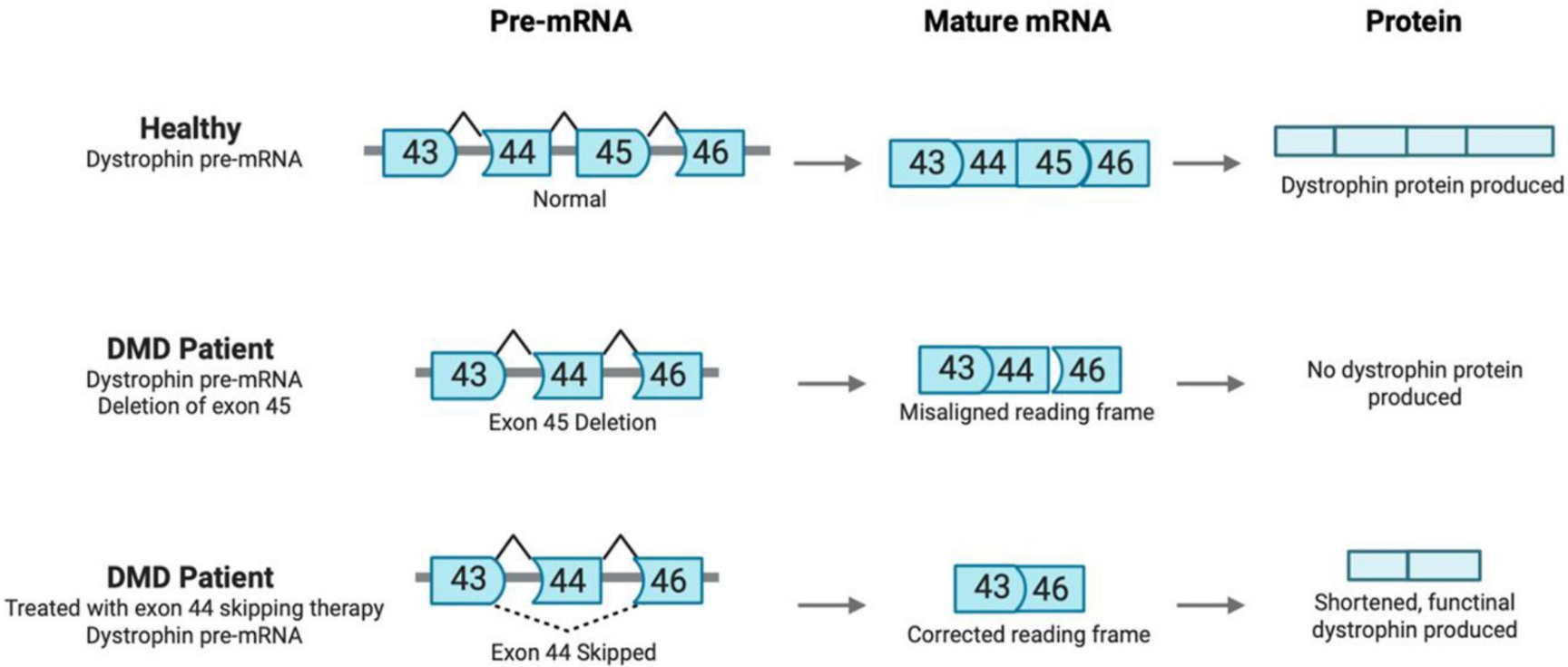
Exon Skipping

- The *DMD* gene contains 79 exons
- Exon skipping therapies are **oligonucleotides** that bind specific exons associated with a frameshift mutation
- Oligonucleotide binding prevents spliceosome from splicing at the frameshift mutation, effectively "skipping" the mutation
- Resultant protein is **shortened** but still partially functional



Levin AA, et al. *NEJM*. 2019.

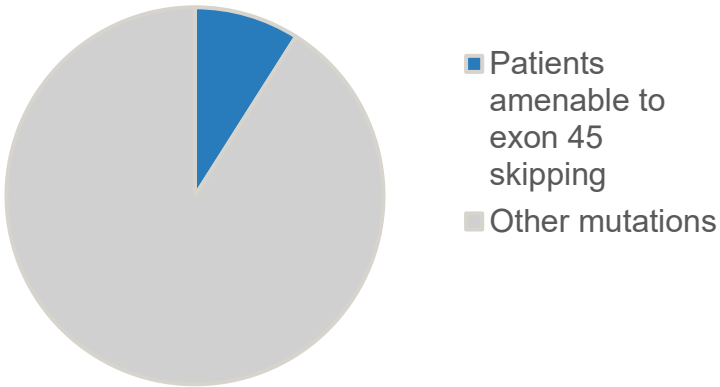
Exon Skipping



Patterson G, et al. *Eur J Pharmacol*. 2023.

Exon Skipping

- Exon 45 skipping therapy
  - Casimersen (Amondys 45): 30 mg/kg IV infusion once weekly
  - **About 9%** of DMD patients have deletions and mutations that are amenable to exon 45 skipping



Patterson G, et al. *Eur J Pharmacol*. 2023.

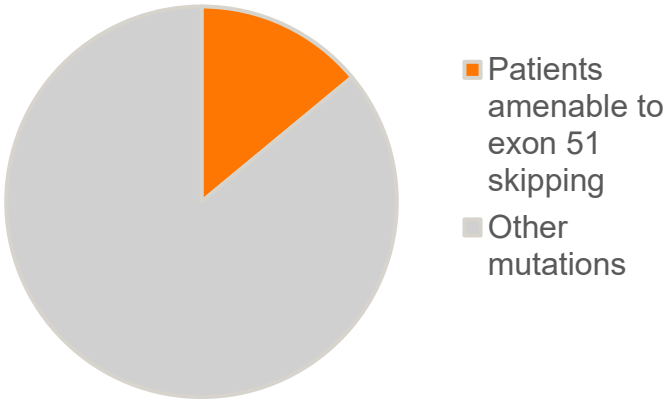
Casimersen in patients with Duchenne muscular dystrophy amenable to exon 45 skipping: Interim results from the Phase 3 ESSENCE trial

Population	Males age 7-13 years with *DMD* deletion amenable to exon 45 skipping who are on a stable dose of oral corticosteroids for at least 24 weeks prior to enrollment; n=43
Study Design	Randomized 2:1 to receive active treatment or placebo (weeks 0-96) • Casimersen 30 mg/kg IV weekly • Placebo IV weekly
Endpoints	**Interim muscle biopsy results:** mean dystrophin levels, rates of exon 45 skipping, de novo dystrophin production, percent of dystrophin-positive muscle fibers, dystrophin localization
Results	• Casimersen demonstrated significant increases in exon 45 skipping compared to placebo (between group difference 1.60%, p<0.001) ○ Placebo group did not demonstrate increased exon skipping (p=0.808) • Casimersen significantly increased mean dystrophin from baseline to 48 weeks and compared to placebo (between group difference 0.59%, p=0.004) • Casimersin significantly increased percentage of dystrophin-positive muscle fibers (between group difference 8.29%, p=0.002)
Conclusions	Interim analysis shows promising results for casimersen, but a forthcoming functional outcomes analysis will give a better idea of efficacy

Iannaccone S, et al. *Neuromuscular Disorders*. 2022.

Exon Skipping

- Exon 51 skipping therapy
  - Eteplirsen (Exondys 51): 30 mg/kg IV infusion once weekly
  - **About 14%** of DMD patients have mutations amenable to exon 51 skipping



Patterson G, et al. *Eur J Pharmacol*. 2023.

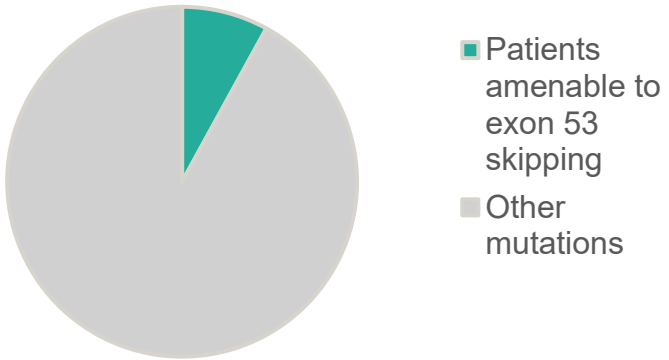
Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy

Population	Ambulatory boys aged 7-13 years with DMD deletion amenable to exon 51 skipping who are on a stable dose of oral corticosteroids for at least 24 weeks prior to enrollment; n=13	
Study Design	Phase 1 (weeks 0-24), randomized 1:1:1 • Placebo • Eteplirsen 30 mg/kg IV weekly • Eteplirsen 50 mg/kg IV weekly	Phase 2 (week 24 – month 36) • Patients who received placebo in phase 1 randomly assigned 1:1 to an eteplirsen dose
Endpoints	**Primary endpoint:** change in 6-minute walk test (6MWT) **Secondary endpoints:** loss of ambulation, pulmonary function decline, AEs	
Results	• At 36-month follow-up, patients treated with eteplirsen had a 151 m difference in 6MWT distance compared to historical controls ($p<0.01$) • Eteplirsen resulted in less ambulation loss compared to historical controls (16.7% vs to 46.2%) at 3 years • Percentage of predicted FVC declined 9.4% over 36 months compared to an expected ~15% decline based on natural history data	
Conclusions	Eteplirsen is safe and effective to delay loss of ambulation, improve 6MWT distance, and preserve pulmonary function	

Mendell JR, et al. *Ann Neurol*. 2016.

Exon Skipping

- Exon 53 skipping therapy
  - Golodirsen (Vyondys 53): 30 mg/kg IV infusion once weekly
  - Vitolarsen (Viltepso): 80 mg/kg IV infusion once weekly
  - **About 8%** of DMD patients have mutations amenable to exon 53 skipping



Patterson G, et al. *Eur J Pharmacol*. 2023.

Long-Term Safety and Efficacy Data of Golodirsen in Ambulatory Patients with Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping

Population	Ambulatory males aged 6–15 years with DMD and confirmed mutations amenable to exon 53 skipping on stable oral corticosteroids for at least 24 weeks; n=25	
Randomization	Part 1 (weeks 0-12), randomized 2:1 • Golodirsen with escalating weekly IV dosing (4, 10, 20, then 30 mg/kg) • Placebo	Part 2 (weeks 13-168) • All part 1 patients + an additional 13 patients received golodirsen 30 mg/kg IV weekly
Endpoints	**Primary endpoint:** dystrophin protein expression at week 48 and 6MWT change from baseline at week 144 **Secondary endpoints:** loss of ambulation, pulmonary function, other biomarkers	
Results	• Biologic efficacy: golodirsen produced a 16.0-fold increase in dystrophin protein (from 0.095% to 1.019% of normal; P<0.001) • Clinical efficacy: At 3 years, mean 6MWT decline was -99.0 m for golodirsen-treated patients versus -181.4 m for matched external controls (difference 82.4 m; P=0.067)	
Conclusions	Golodirsen is safe and effective in delaying decline in 6MWT and maintaining pulmonary function, as well as demonstrates favorable biomarker outcomes	

Servais L, et al. *Nucleic Acid Ther*. 2022.

Safety, Tolerability, and Efficacy of Viltolarsen in Boys With Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping

Population	Ambulatory males aged 4-9 years with DMD amenable to exon 53 skipping on stable glucocortioids for at least 3 months; n=16	
Study Design	Phase 1 (weeks 0-4); randomized 3:1 • Placebo • Vitolarsen 40 mg/kg IV weekly or 80 mg/kg IV weekly by cohort	Phase 2 (weeks 5-24) • All patients who received placebo crossed-over to low or high dose vitolarsen depending on cohort
Endpoints	**Primary endpoint:** *de novo* dystrophin protein production **Secondary endpoints:** dystrophin characterization, time to standing from supine, time to run/walk 10m, time to climb 4 stairs, 6MWT, NSAA	

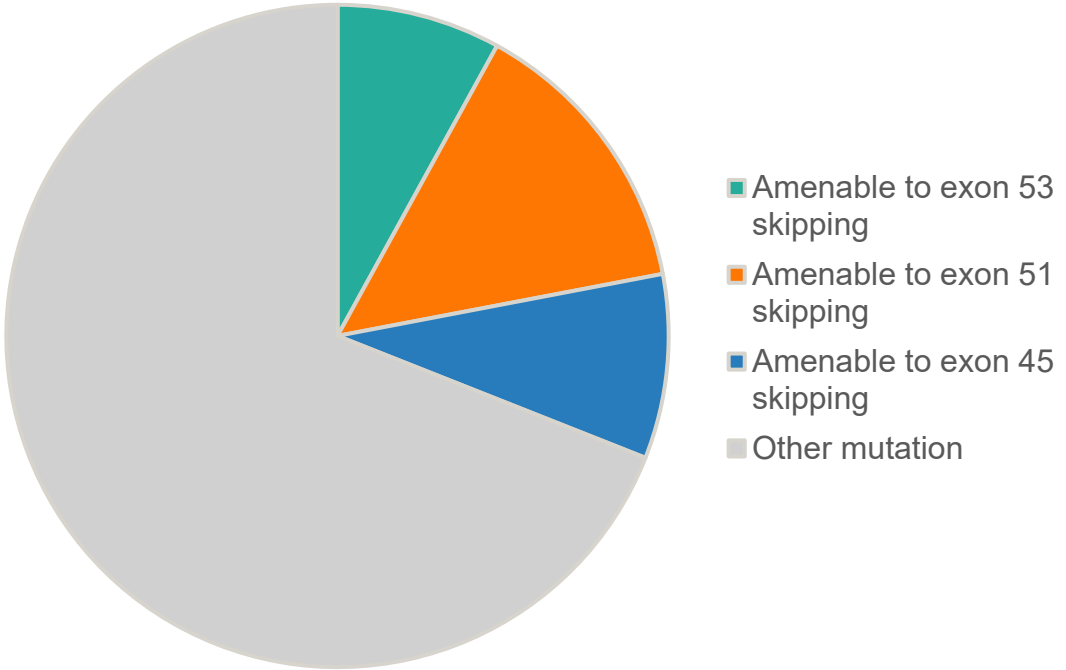
Results	• Both dose groups showed significant dystrophin induction (mean 5.7% of normal in low-dose group, 5.9% in high-dose group, p<0.001 and p=0.01)
	• Viltolarsen-treated patients demonstrated significant improvements in timed function tests at week 25
	  ○ Time to run/walk 10 m velocity improved 0.23 m/s vs. decline of 0.04 m/s in placebo group (p=0.003)
	  ○ 6MWT improved 28.9 m compared to decline of 65.3 m (p=0.047)	

Conclusions	Vitolarsen is safe and effective in *de novo* dystrophin protein production, and facilitates delaying decline in 6MWT and other functional outcomes	

Clemens PR, et al. *JAMA Neurol*. 2020.

Exon Skipping Therapies Summary

- Exon skipping therapies are overall **well-tolerated** and have shown promising outcomes in DMD
- **Long-term data is needed** to verify safety and assess how they impact progression of disease
- About **69% of patients** with DMD have a mutation other than one that would make them eligible for a currently-approved exon-skipping therapy



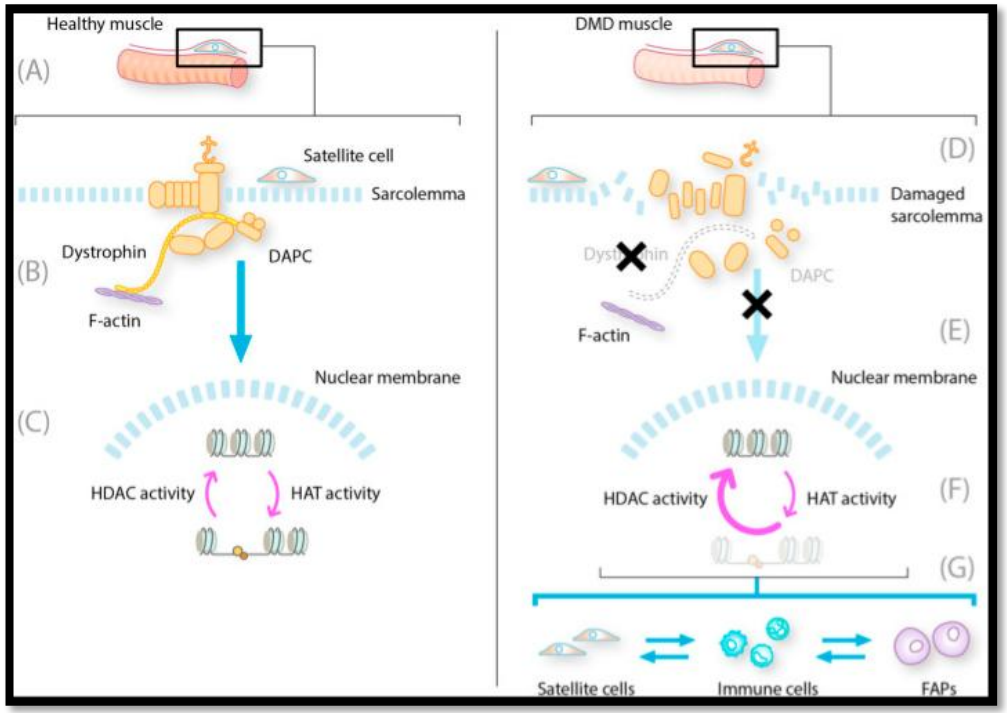
Assessment Question #2

Which medication used in DMD is **incorrectly** matched with its mechanism of action?

A. Casimersen – exon 45 skipping
B. Vamorolone – glucocorticoid & mineralocorticoid receptor agonism
C. Golodirsen – exon 53 skipping
D. Deflazacort – glucocorticoid receptor agonism

Histone Deacetylase Inhibitors

Histone Deactylase Inhibitors



- Intact DAPC regulates activity of histone deacetylase (HDAC) to allow translation of muscle regeneration factors
- Absent or mutated dystrophin leads to **disruption of DAPC** with multiple consequences for muscle repair
- Increased HDAC activity results in **repressed translation and transcription of muscle repair factors**
  - These changes lead to prolonged inflammatory state and impaired production of new muscle fiber cells

Aartsma-Rus A, *Front Cell Dev Biol.* 2025.

EPIDYS Trial: Safety and efficacy of givinostat in boys with Duchenne muscular dystrophy

Population	Ambulatory males aged 8-11 years with DMD on systemic corticosteroids for at least 6 months prior to enrollment; n=179
Study Design	Randomized 2:1 to receive either givinostat or placebo twice a day for 72 weeks Givinostat (n= 120) or Placebo (n= 59), and stratified by VLFF • Group A: VLFF >5% to ≤30%, Group B: ≤5% or >30%
Endpoints	**Primary endpoint:** Change in four-stair climb test from baseline to 72 weeks in the Group A population. **Secondary endpoints:** Change from baseline after 72 weeks in NSAA total score, NSAA cumulative loss-of-function, time-to-rise, 6MWT, muscle strength assessments, and MRI evidence of reduced muscle fat infiltration
Results	• Among 120 males in Group A, givinostat demonstrated less functional decline when compared to placebo in four-stair climb test (ratio 0.86, p=0.035) and total NSAA score (lease squares mean difference 1.91, 95%CI 0.295-3.533) • Most common adverse events were diarrhea (36% givinostat v. 18% placebo) and vomiting (29% givinostat v. 13% placebo)
Conclusions	• Over the 72-week study period, givinostat improved muscle function and strength compared to placebo • Ongoing extension study will evaluate long-term safety and efficacy

Mercuri E, et al. *Lancet Neurol*. 2024.

Micro-Dystrophin Gene Therapies

Micro-dystrophin Gene Therapy

Currently approved: delandistrogene moxeparvovec (Elevidys®)

Mechanism of Action

- Nonreplicating recombinant adeno-associated virus (AAV) rhesus isolate serotype 74 (rAAVrh74) vector containing a micro-dystrophin transgene, producing a truncated micro-dystrophin protein
- This shortened dystrophin protein is intended to address the **genetic root cause** of DMD

Indications	**Contraindications**
• Patient ≥4 years old • Anti-AAVrh74 total binding antibody titers <1:400 • Up to date on vaccines	• Mutations involving exon 8 and/or exon 9 in the *DMD* gene • Mutations in exons 1-17 and/or exons 59-71 • Preexisting immunity against AAVrh74 indicated by total binding antibody titers ≥1:400

Mendell J, et al. *Nature Medicine*. 2024.
Elevidys [Package Insert]. Sarepta Therapeutics. 2024.

Micro-dystrophin Gene Therapy

- Considerations for postponing treatment
  - Active or clinical signs & symptoms of infection
  - Preexisting liver impairment, chronic hepatic condition, or acute liver disease
    - ❖ Postpone until resolved or controlled
- Monitoring
  - Liver function at baseline and weekly for the first 3 months after infusion
  - Troponin-I prior to infusion and weekly following infusion for 4 weeks
  - Platelets prior to infusion and weekly for 2 weeks

FDA Investigating Deaths Due to Acute Liver Failure in Non-ambulatory Duchenne Muscular Dystrophy Patients Following ELEVIDYS

U.S. Food & Drug Administration. FDA Safety Communication. June 24, 2025.
Elevidys Treatment Guide. Sarepta Therapeutics. 2024.

Clinical Trials of Delandistrogene Moxeparvovec (SRP-9001) in Patients with DMD

SRP-9001-101

COMPLETED Open label phase 1/2a single site study evaluating safety

SRP-9001-102

COMPLETED Phase 2: Randomized, double-blind, placebo-controlled, multicenter, 3-part study evaluating efficacy at week 12 & 48

SRP-9001-301 (EMBARK)

COMPLETED Phase 3: Randomized, double-blind, placebo-controlled, multinational, 2-part study evaluating efficacy at week 52

SRP-9001-103 (ENDEAVOR)

ONGOING Open-label phase 1b study evaluating efficacy at week 12

SRP-9001-302 (ENVOL)

ONGOING Phase 2: Open-label study evaluating safety

SRP-9001-303 (ENVISION)

ONGOING Phase 3: Randomized, double-blind, placebo-controlled, multinational study evaluating efficacy at week 72

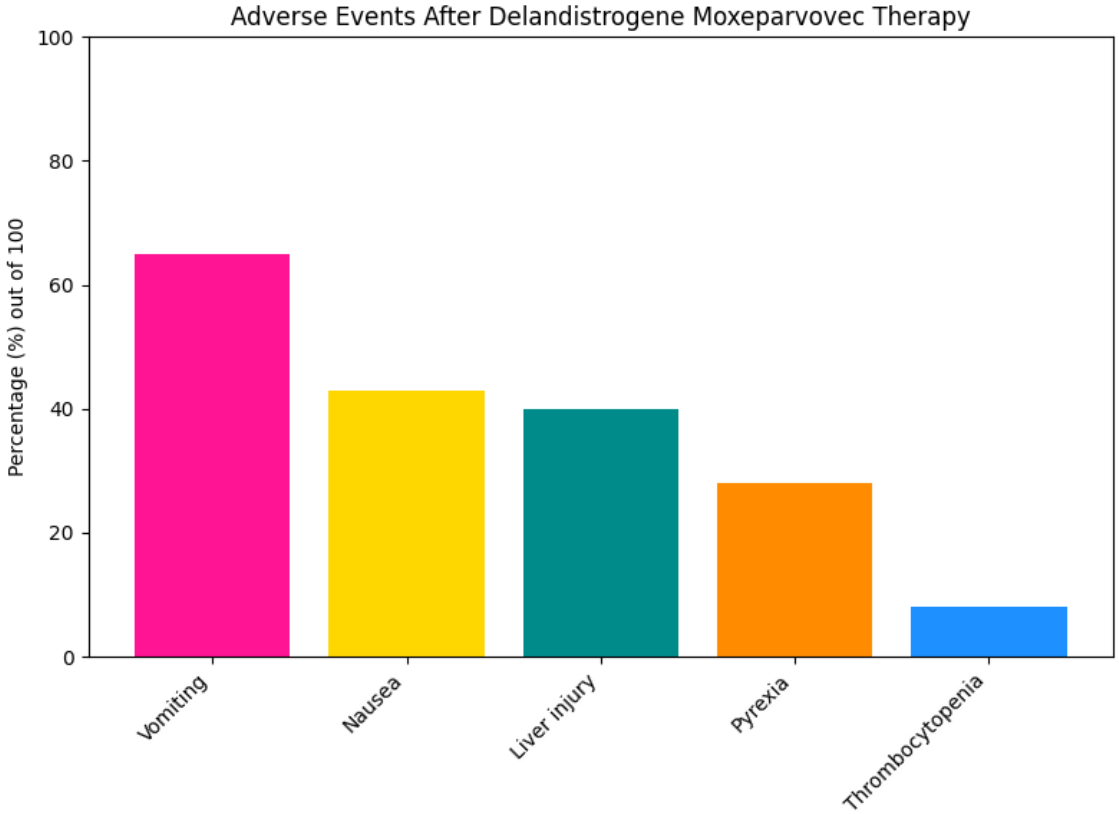
Oskoui M, et al. Neurology. 2025.

EMBARK trial: Assessing the efficacy and safety of delandistrogene moxeparvovec

Population	Ambulatory males with DMD who were ≥4 years to <8 years of age (n = 125)	
Study Design	Part 1 (52 weeks): • Stratified by age group and NSAA score to intervention (single dose DelMox 1.33×10^{14} vg/kg IV infusion) or placebo	Part 2 (>52 weeks): • Placebo group from part 1 received the intervention
Endpoints	**Primary endpoint:** change in NSAA score from baseline to week 52. **Secondary endpoints:** mean micro-dystrophin expression at week 12, Time to Rise, 10-meter Walk/Run, stride velocity 95th percentile, time to ascend 4 steps, PROMIS Mobility and Upper Extremity, and number of NSAA skills gained/improved	
Results	• At week 52, the primary endpoint was not met (least squares mean 2.57 DelMox versus 1.92 in placebo group; between-group difference, 0.65; P = 0.2441) • Some of the secondary endpoints favored treatment, none statistically significant • Safety was manageable and consistent with previous delandistrogene moxeparvovec trials	
Conclusions	At 52 weeks, delandistrogene moxeparvovec demonstrated no concrete benefits over placebo. The safety profile was manageable: there were no deaths, discontinuations or clinically significant adverse events.	

Mendell J, et al. *Nature Medicine*. 2024.

EMBARK Trial: Most Common Adverse Events



Mendell J, et al. *Nature Medicine*. 2024.

Assessment Question #3

A 5-year-old boy, AJ, presents to a pediatric neuromuscular clinic after genetic testing confirms a diagnosis of Duchenne Muscular Dystrophy. AJ is ambulatory, demonstrates mild weakness, and has no significant cardiac or hepatic abnormalities at baseline. His parents ask if there are any treatments available that could help target the root cause of DMD to prolong AJ's ambulatory status. Select the most appropriate therapy to consider for AJ:

A. Initiate prednisone as monotherapy and defer all gene-targeted therapy until AJ turns 6 years old
B. Begin eteplirsen exon-skipping therapy
C. Administer Delandistrogene moxeparvovec (Elevidys®) micro-dystrophin gene therapy
D. There is no FDA approved therapy that targets the root cause. They should consider enrolling in a clinical trial.

Practical Considerations

Delandistrogene moxeparvovec: Preparation

Dosing

- Patient weight < 70 kg: 1.33×10^{14} vector genomes per kilogram (vg/kg) (or 10 mL/kg) IV infusion
- Patient weight > 70 kg: 9.31×10^{15} vg total fixed dose IV infusion

Kit details

- Suspension for intravenous infusion
- Customized to meet the dosing for each patient
- Anywhere between 10 and 70 single dose vials per kit
- **Price:** WAC $3.2 million and 340b ~ $2.6 million

Storage & Preparation

- Shipped at **ultra-low temperature** (≤-60°C)
- Thaw vials over ~2 hours at room temperature
- When thawed swirl gently, do not shake, do not refreeze, do not place back in refrigerator after exposure to room temperature

Elevidys [Package Insert]. Sarepta Therapeutics. 2024.
Elevidys. Medical Professionals Reference. 2026.

Delandistrogene moxeparvovec: Premedication

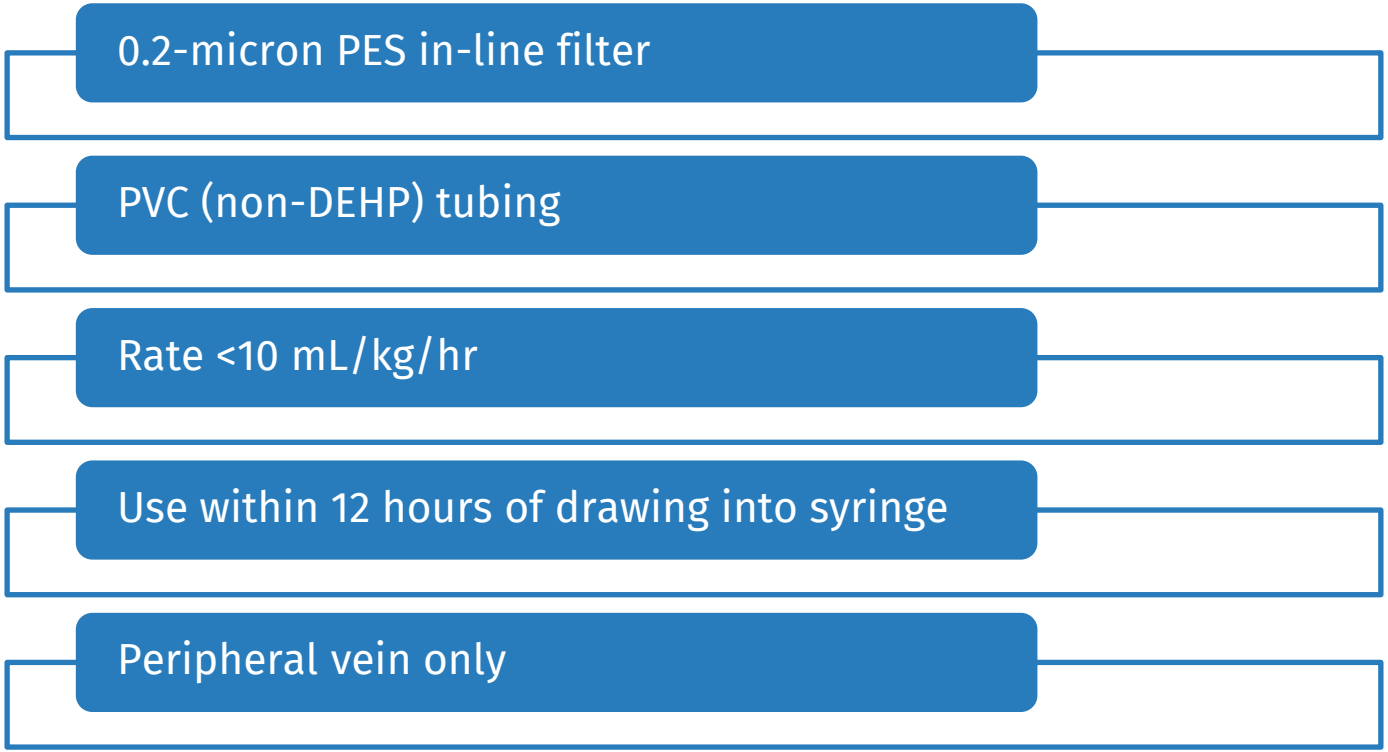
Premedication

- Corticosteroids via oral or parenteral route should be administered 1 day prior to infusion and continued daily for ≥ 60 days after the infusion

Baseline Corticosteroid Dosing	Peri-infusion corticosteroid dose (prednisone-equivalent)
Daily or intermittent dose	Start 1 day prior to infusion: 1 mg/kg/day (and continue baseline dose)
High dose for 2 days per week	Start 1 day prior to infusion: 1 mg/kg/day taken on days without high-dose corticosteroid treatment (and continue baseline dose)
Not on corticosteroids	Start 1 week prior to infusion: 1.5 mg/kg/day

Elevidys [Package Insert]. Sarepta Therapeutics. 2024.
Elevidys (Delandistrogene moxeparvovec) [Package insert]. Cambridge, MA: Sarepta Therapeutics; 2023.

Delandistrogene moxeparvovec: IV Administration



Elevidys [Package Insert]. Sarepta Therapeutics. 2024.
Elevidys Treatment Guide. Sarepta Therapeutics. 2024.

Assessment Question #4

What barriers might patients or healthcare systems experience to access micro-dystrophin gene therapies?

A. Insurance approval & cost
B. Patient proximity to administration facility
C. Storage in ultra-low temperature freezers
D. All of the above

Future Directions in Therapy

Studies in Progress

Exon Skipping

Surrogate Gene Therapy

Replacement Gene Therapy

Phase I

- Insmed Gene Therapy

Phase I/II

- Entrada Therapeutics
- Nationwide Children's Hospital
- Nationwide Children's Hospital
- Wave Life Sciences
- Avidity Biosciences
- Biomarin
- Dyne Therapeutics
- NS Pharma
- Entrada Therapeutics

Phase II

- NS Pharma
- PepGen

Phase III

- REGENXBIO
- Solid Biosciences

Duchenne Drug Development Pipeline. Parent Project Muscular Dystrophy. 2026.

CRISPR-based Gene Editing

CRISPR: clustered regularly interspaced short palindromic repeats

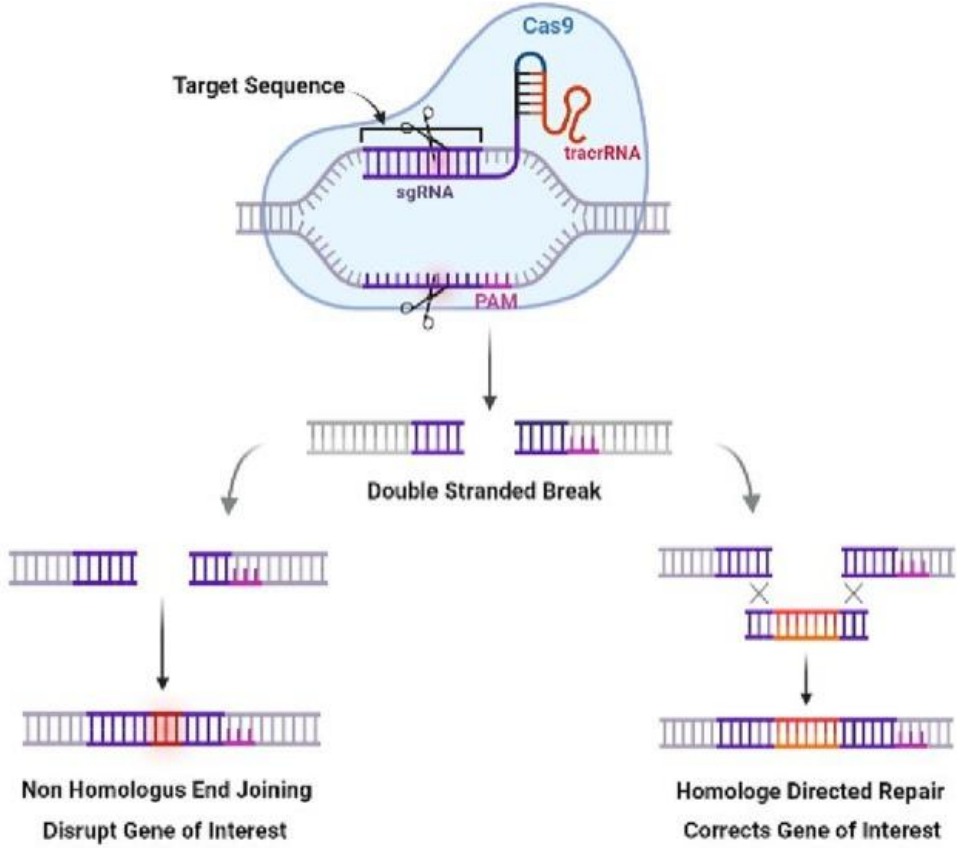
Mechanism

- The CRISPR-Cas9 system makes targeted cuts in the genome to enable editing of the underlying genetic defect

Comparison to Current Therapies

- Exon-skipping therapies force alternative splicing resulting in truncated dystrophin protein, but they do not change the underlying *DMD* sequence

- Delandistrogene moxeparvovec is a gene replacement therapy that delivers an external copy of a truncated version of the therapeutic gene



Calos MP. *NEJM*. 2016.
Eslahi A, et al. *Gene*. 2023.

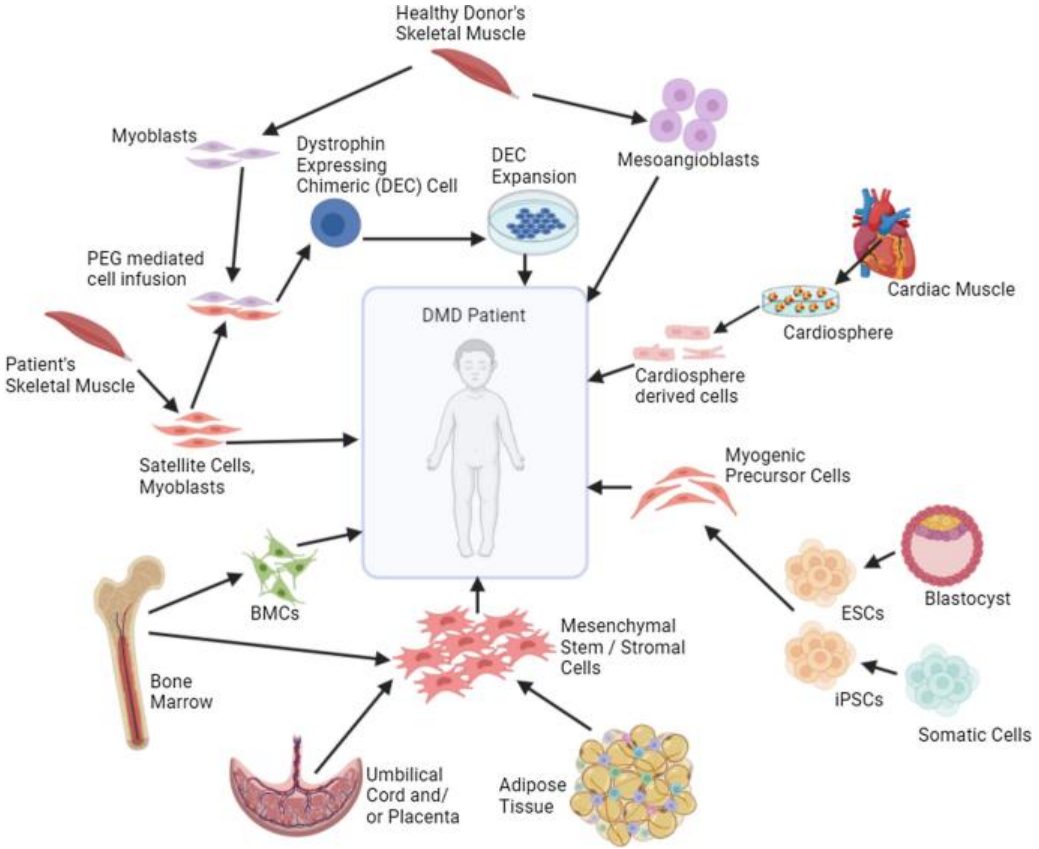
Muscle Stem Cell Therapies

Mechanism

- Transplantation of allogeneic or autologous stem cells can engraft into dystrophic muscle and fuse with existing fibers or form new ones

- Several cell types are being investigated:
  - Myogenic stem/progenitor cells
  - Induced pluripotent stem cell-derived muscle stem cells
  - Mesenchymal stromal cells

- Cardiosphere-derived cells are being investigated to reduce cardiac scar size in DMD patients with cardiomyopathy



Tominari T, et al. *Front Cell Dev Biol*. 2025.
Markati T, et al. *Lancet Neurol*. 2022.
Akat A, et al. *Stem Cell Reviews and Reports*. 2023.

Summary/Conclusion

- Duchenne Muscular Dystrophy is a rare, X-linked genetic disorder that results in progressive neuromuscular decline and is ultimately fatal
- Historically, glucocorticoids have been used to delay loss of ambulation
- Exon skipping therapies are options for patients with specific *DMD* mutations, but require weekly transfusions
- Delandistrogene moxeparvovec is a novel micro-dystrophin therapy that provides a replacement transgene aimed at addressing the root pathophysiology in DMD
- Future directions in management include CRISPR-based gene editing and stem cell therapies
- There are still significant barriers that exist for both patients and health systems in accessing newer therapies

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