Evolutions in the Management of

DUCHENNE MUSCULAR DYSTROPHY:

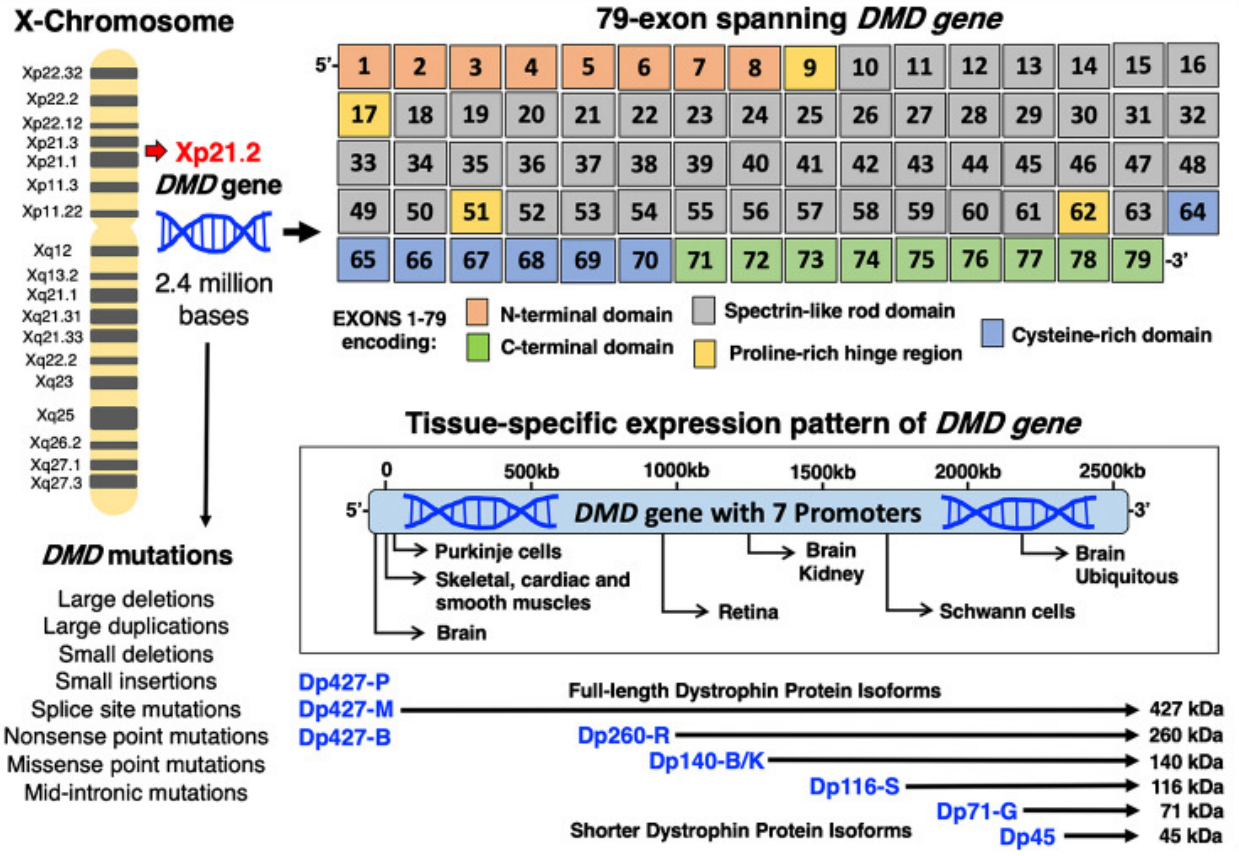
Treatment Implications for the Present and Future

RAPID RECAP

Learning Objectives

- Describe the role of dystrophin disruption and restoration in the progression and management of Duchenne muscular dystrophy (DMD)
- Assess the latest clinical trial results across various treatment modalities for DMD
- Examine emerging approaches to DMD management that seek to align patient selection, treatment choice, and optimal initiation of therapy

Dystrophin[1,2]



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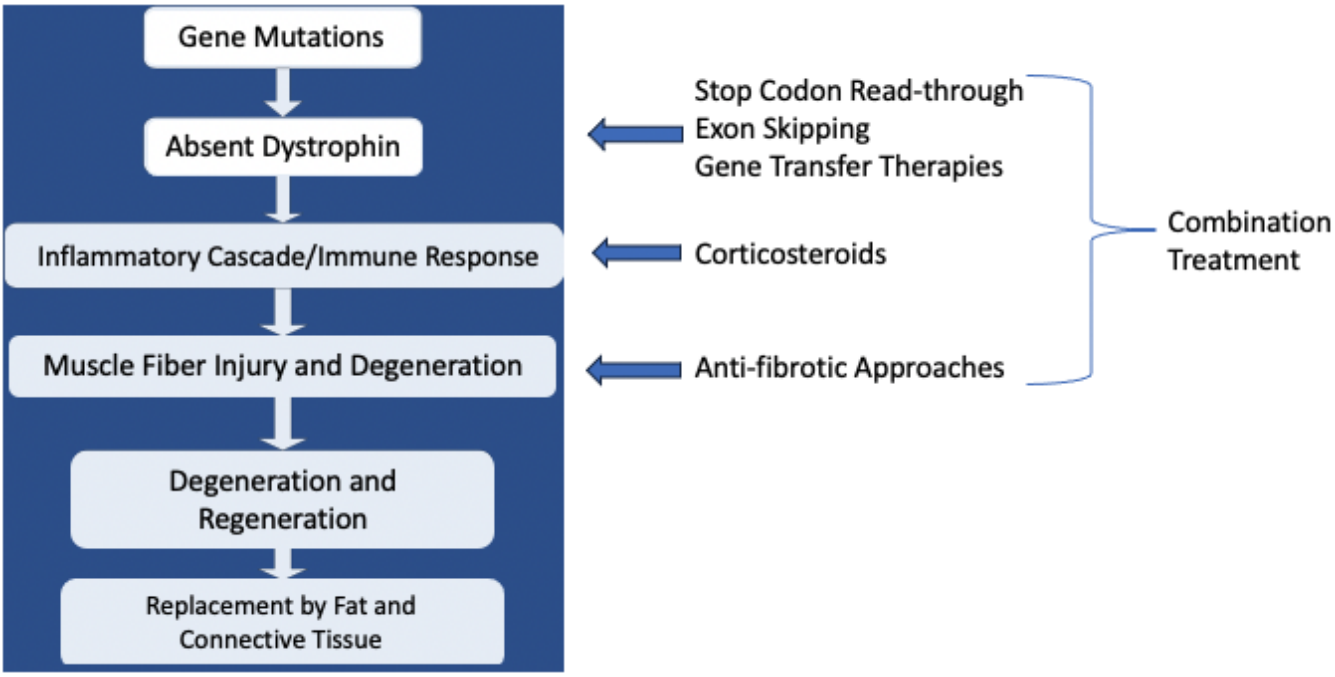
Therapeutic Strategies for DMD

Genetic supplementation of dystrophin utilizes gene therapy technology, including:[3,4]



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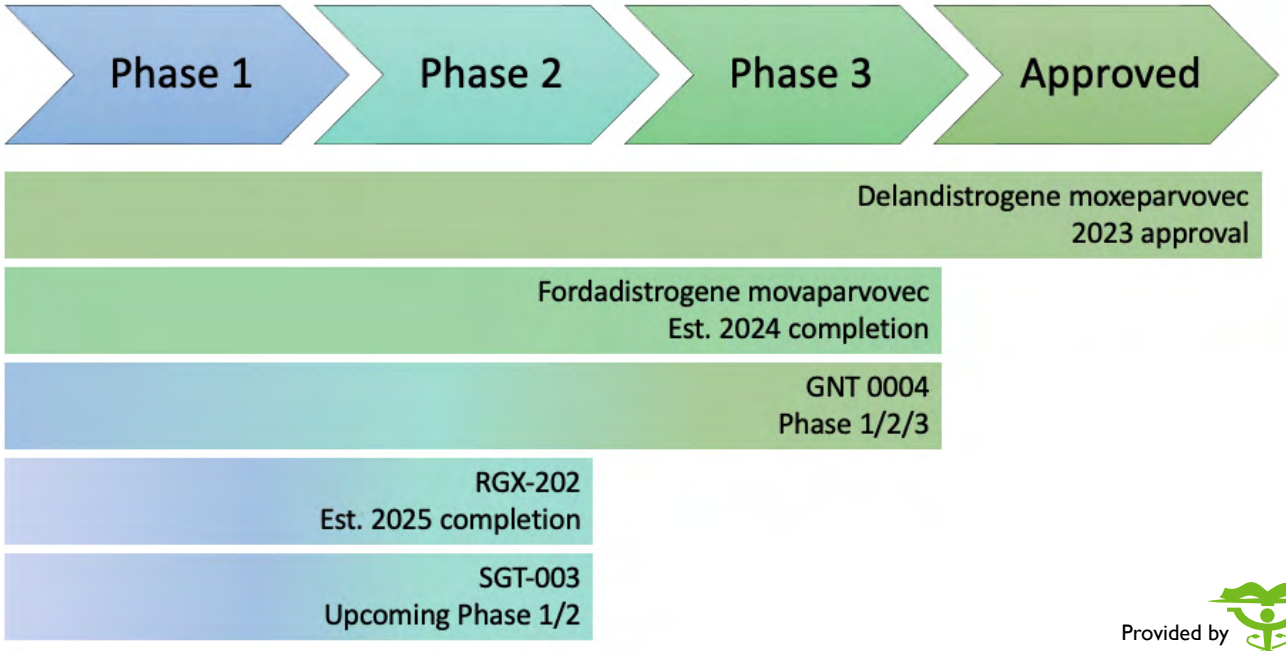
Dystrophin-restoring Therapies

Exon-Skipping Therapies[4,5]

ETEPLIRSEN Exon 51 2016 approval	**GOLODIRSEN** Exon 53 2019 approval	**VILTOLARSEN** Exon 53 2020 approval	**CASIMERSEN** Exon 45 2021 approval
VESLETEPLIRSEN Exon 51 Phase 2 (est. 2025 completion)	**PGN-EDO51** Exon 51 Phase 2 (est. 2025 completion)	**AOC 1044** Exon 44 Phase 1/2 (est. 2025 completion)	**DS-5141** Exon 42 Phase 2 (est. 2027 completion)

Gene Therapies[4,5]



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Pros and Cons of DMD Therapies[4,5]

Therapeutic Approach	Pros	Cons
Glucocorticoids	• Applicable to all patients with DMD, regardless of mutation • Prolonged time to loss of ambulation • Reduced requirement for scoliosis surgery • Improved cardiopulmonary function	• Weight gain • Changes in mood/behavior • Reduced bone health • Pubertal suppression • Adrenal insufficiency risk • Risk for cataracts • Frequent dosing (daily or intermittent)
Exon Skipping	• Prolonged time to loss of ambulation • Improved pulmonary function compared to natural history	• Requires frequent dosing intravenously • Only applicable to a subset of patients (mutation specific) • Requires monitoring of renal function • Low dystrophin protein production on biopsy
Gene Transfer Therapy	• Minimal genetic restrictions (exclusion of only deletions of exons 8/9) • Significant microdystrophin protein production on biopsy • Improved functional outcomes • Single administration	• Only FDA-approved currently for 4- to 5-year-old boys • Risk for hepatotoxicity, myocarditis, immune-mediated myositis, nausea/vomiting, thrombocytopenia, complement activation • Subset of patients will be excluded from treatment due to antibody positivity for vector

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Conclusions

- There are several approved therapies for DMD, including glucocorticoids, exon skipping, and gene transfer
- There are many therapeutics in the pipeline for DMD, including small molecules, cell-based treatments, more exon-skipping interventions, and gene transfer therapies
- Since each therapy is associated with specific risks and benefits, it is important to align patients, their medical history, and their specific goals with the right treatment
- The future will investigate the impact of combination therapies in patients with DMD. Preclinical and clinical studies are currently in progress

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