Provided by The France Foundation

Evolutions in the Management of

DUCHENNE MUSCULAR DYSTROPHY:

Treatment Implications for the Present and Future

MONDAY, MARCH 4, 2024

7:00–8:00 AM • Hilton Orlando

ORLANDO, FLORIDA

Disclaimer

This presentation is for educational purposes only. Opinions or points of view expressed in this presentation represent the view of the presenter, and does not necessarily represent the official position or policies of The France Foundation, Inc. Nothing in this presentation constitutes medical advice.

The France Foundation

Faculty Presenters

Craig McDonald, MD
Chair, Department of Physical Medicine & Rehabilitation
Professor, Departments of Pediatrics and Physical Medicine & Rehabilitation
UC Davis Health-Sacramento
Sacramento, CA

Crystal Proud, MD
Pediatric Neurologist
Children's Hospital of The King's Daughters
Norfolk, VA

Aravindhan Veerapandiyan, MD
Associate Professor
University of Arkansas for Medical Sciences
Arkansas Children's Hospital
Little Rock, AR

Disclosures

This activity is available for
ACCME, ANCC, AAPA, and ACPE credit.
Please review the full CME/CE information at this QR code.

- Dr. Craig McDonald does non-CE consulting for Avidity Biosciences, Capricor, Inc., Edgewise Therapeutics, Italfarmaco, PTC Therapeutics, Santhera Pharmaceuticals, Sarepta (Symbiotix), and Sarepta Therapeutics
- Dr. Crystal Proud does non-CE consulting for Biogen, Genentech/Roche, Novartis Gene Therapies, Sarepta, and Scholar Rock. She does contract research for Astellas, Biogen, CSL Behring, Fibrogen, Novartis Gene Therapies, Pfizer, PTC, Sarepta, and Scholar Rock, and is on the speakers bureau for Biogen.
- Dr. Aravindhan Veerapandiyan does non-CE consulting for AMO Pharma, AveXis, Biogen, Catalyst, Novartis, Pfizer, PTC Therapeutics, Sarepta Therapeutics, Scholar Rock, and UCB. He does contract research for AMO, Cure Duchenne, Fibrogen, Muscular Dystrophy Association, Parent Project Muscular Dystrophy, Pfizer, Octapharma, Regenxbio, Sarepta.
- **Content was reviewed by a non-conflicted content reviewer to ensure that it is not commercially biased, is fair and balanced, and is based on scientific evidence and/or clinical reasoning**

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

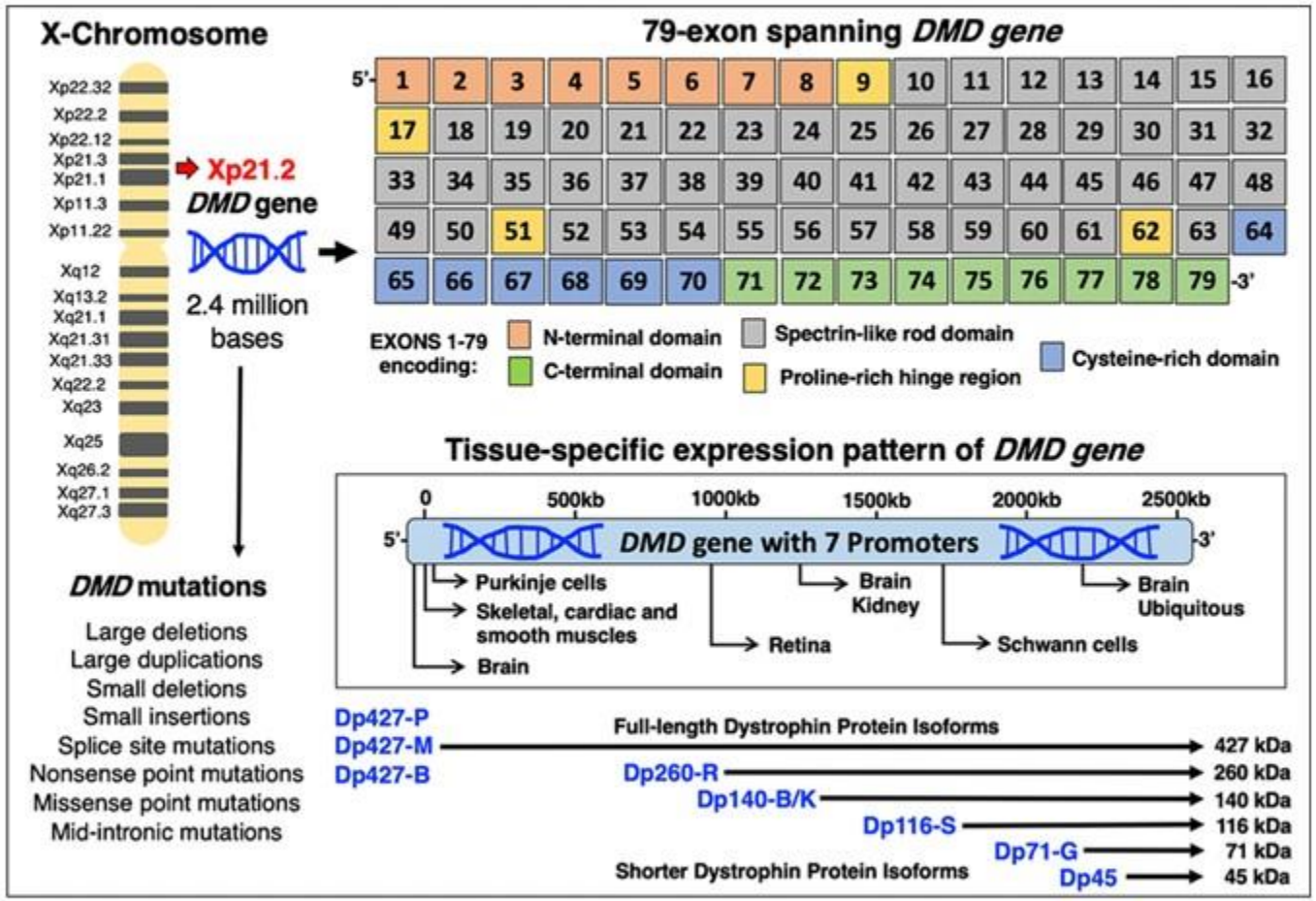
At the end of this activity, you will be able to:

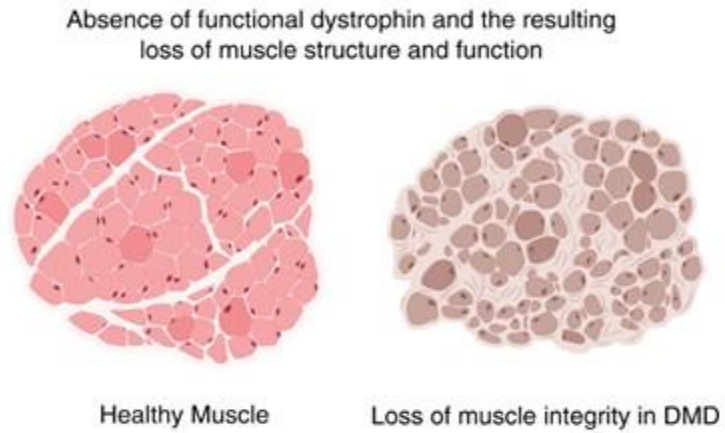
- Describe the role of dystrophin disruption and restoration in the progression and management of Duchenne muscular dystrophy (DMD)
- Assess the latest clinical trial results across various treatment modalities for DMD
- Examine emerging approaches to DMD management that seek to align patient selection,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

Introduction to Dystrophin

Dr. Craig McDonald

DMD Gene and Dystrophin Protein



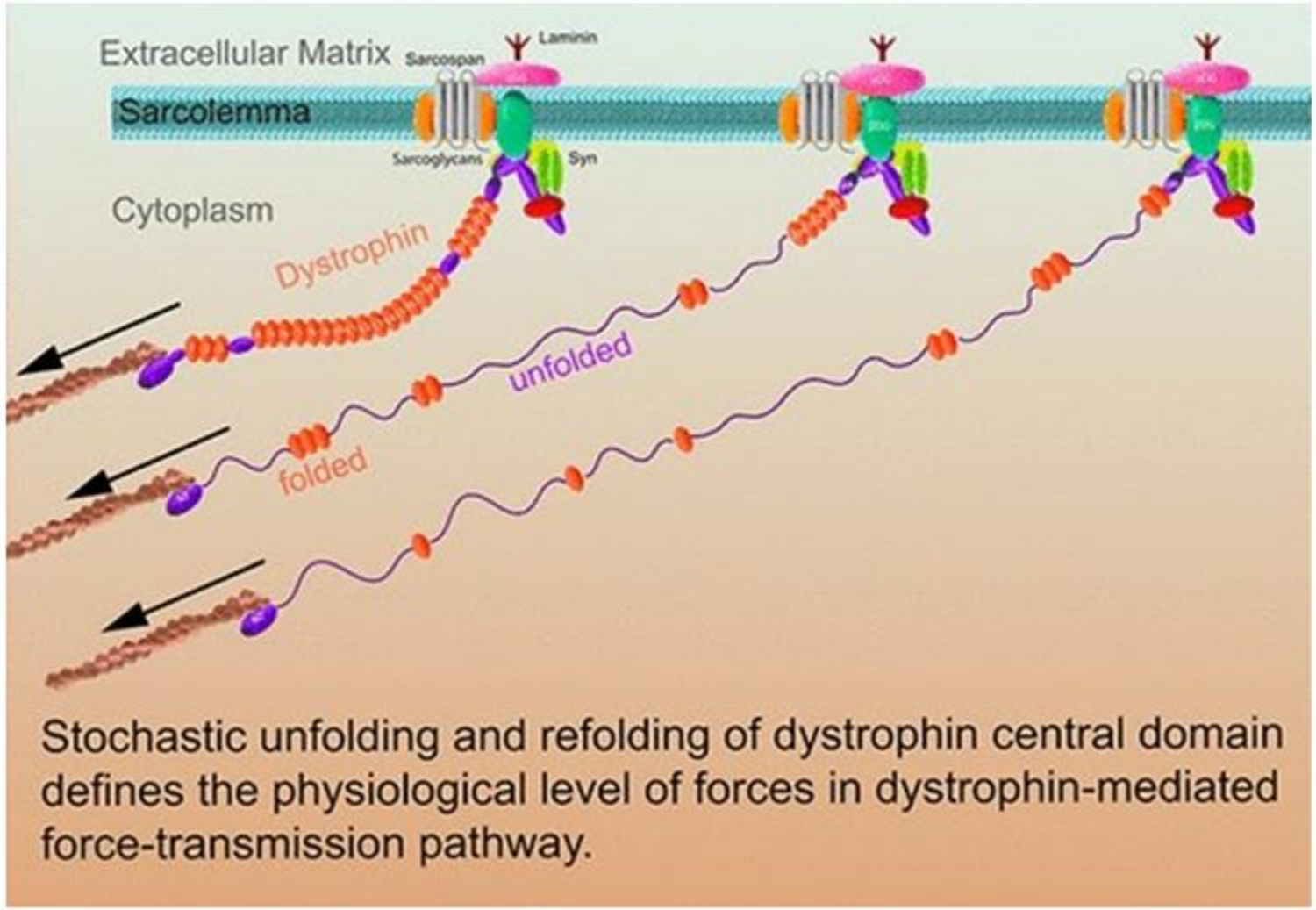


Dystrophin is expressed in various tissues, including skeletal, cardiac, and smooth muscle

mRNA = messenger RNA

Sun C, et al. *Genes*. 2020;11: 837; Himič V, et al. *Eur J Hum Genet*. 2021;29(9):1369-1376; Ohlendieck K, Swandulla D. *Pflugers Arch*. 2021;473(12):1813-1839.

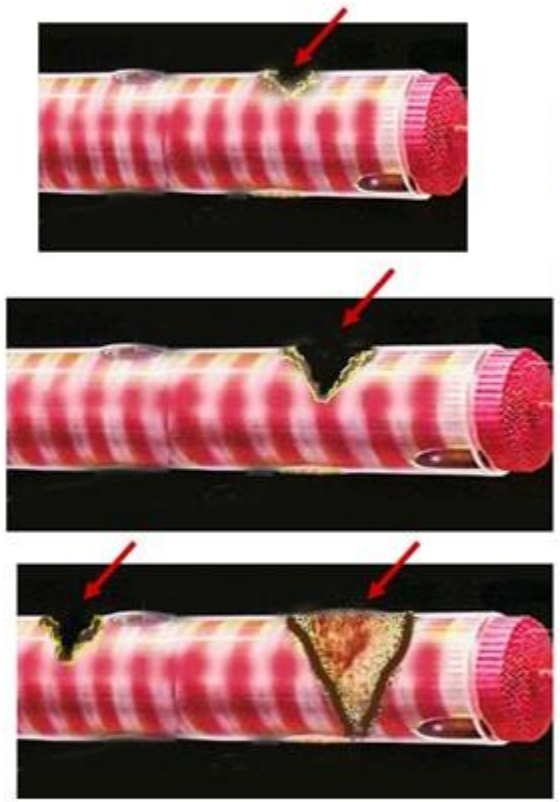
Dystrophin as a Molecular Shock Absorber



Stochastic unfolding and refolding of dystrophin central domain defines the physiological level of forces in dystrophin-mediated force-transmission pathway.

Le S, Yu M, Hovan L, Zhao Z, Ervasti J, Yan J. *ACS Nano*. 2018;12(12):12140-12148.

Lack of Dystrophin Protein Leads to Progressive Segmental Necrosis and Muscle Degeneration[1]



Reduced or absent dystrophin

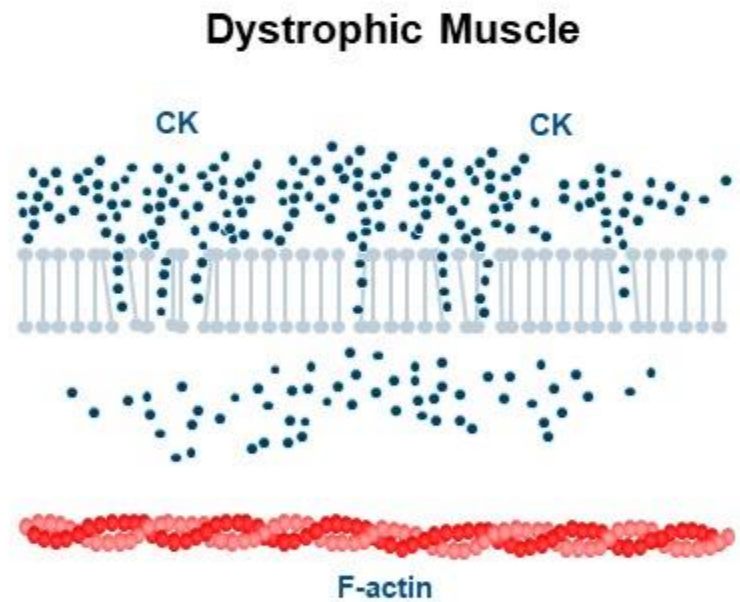
↓

Mechanically weakened plasma membrane, prone to focal tears during contractile activity

↓

Massive influx of extracellular calcium, activation of proteolytic enzymes

→ Segmental necrosis in muscle cell

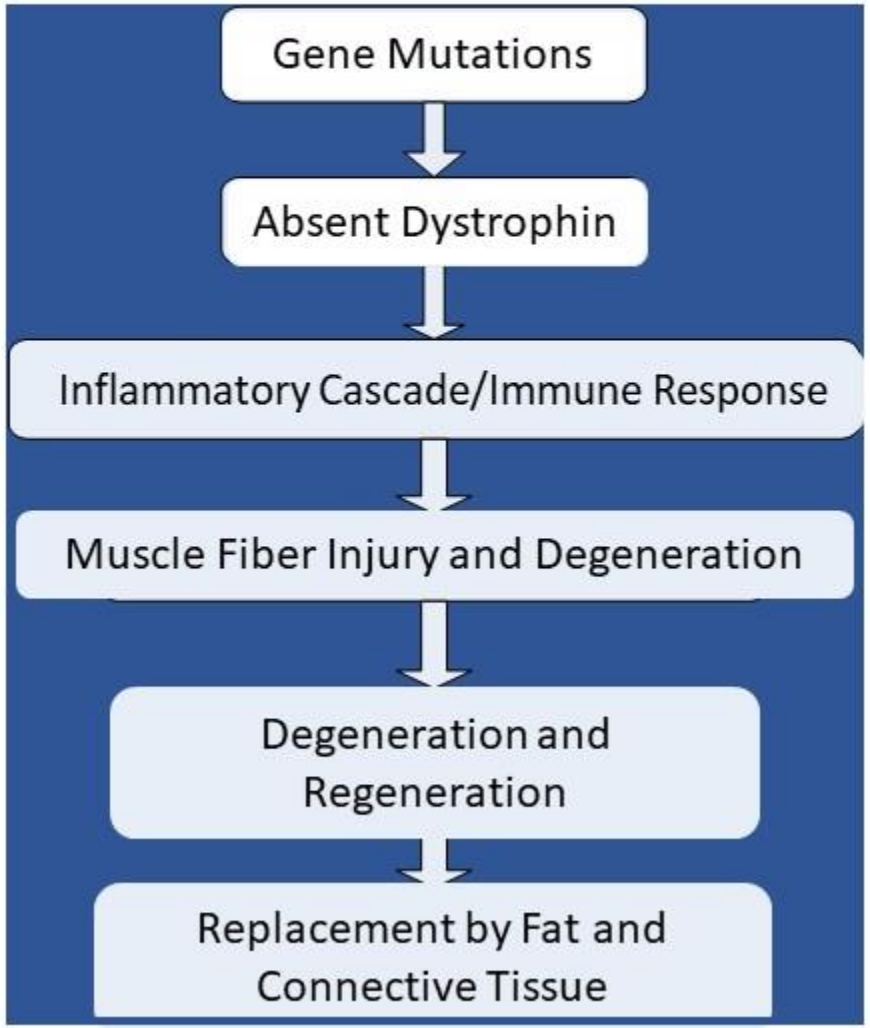


The DAPC is essential for muscle integrity and preventing damage during normal muscle contraction[2,3]

DAPC, dystrophin-associated protein complex. Images adapted from Zhao J, *et al. Hum Mol Genet.* 2016;25(17):3647–53.

1. Niks EH and Aartsma-Rus A. *Exp Opin Biol Ther.* 2017;17:225–36. 2. Kole R, *et al. Nat Rev Drug Discov.* 2012;11(2):125–40. 3.Verhaart IEC and Aartsma-Rus A. *Neuromuscul Disord.* InTech; 2012.

Therapeutic Strategies for DMD



- Stop Codon Read-through
- Exon Skipping
- Gene Transfer Therapies

- Corticosteroids
  - NFĶB Inhibition

- Other Approaches
  - Anti-fibrotic
  - Immunomodulatory
  - Improved Biogenesis
  - Type 2 Fiber Protection

Combination Treatment

NIH: National Center for Advancing Translational Sciences. Accessed December 4, 2023. https://rarediseases.info.nih.gov/diseases/6291/duchenne-muscular-dystrophy; Yao S, et al. *Front Cell Dev Biol.* 2021;9:689533.

Therapies for DMD

Non-genetic therapies

Genetic-based therapies

- Exon skipping
- Gene therapies

Glucocorticoid

Therapy	Approval Date	Indication
Deflazacort	2017	For the treatment of Duchenne muscular dystrophy (DMD) in patients 2 years of age and older
Vamorolone	October 2023	For the treatment of DMD in patients 2 years of age and older
Prednisone	Not specifically FDA approved for treatment of DMD but demonstrated to prolong independent ambulation	

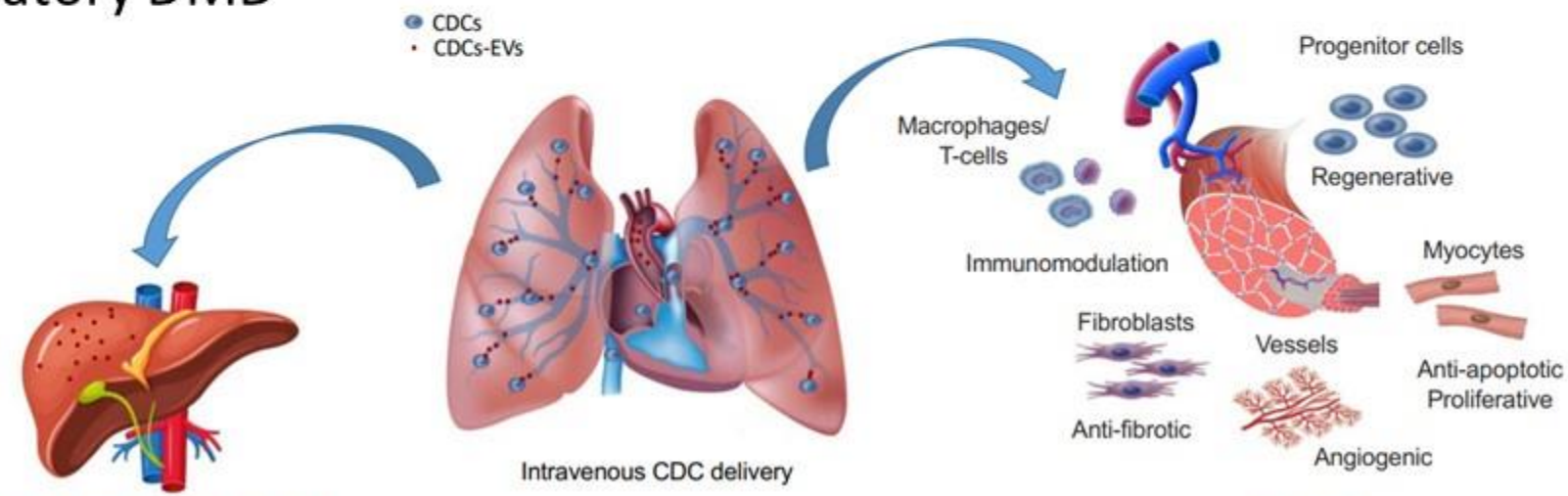
Small Molecule Therapies

Therapy	Approval Date	Mechanism of Action
EDG-5506	Phase 2 clinical trial (est. completion in 2026)	Prevent contraction-induced damage in dystrophic muscle
Givinostat	Phase 3 completed February 2022	Histone-deacetylase inhibitor that promotes expression of muscle cell regeneration genes

Russell AJ, et al. *J Clin Invest*. 2023;133(10):e153837; Vandenborne K, et al. Poster #99. *Poster* Presented at Muscular Dystrophy Association; March 2023. Dallas, TX.

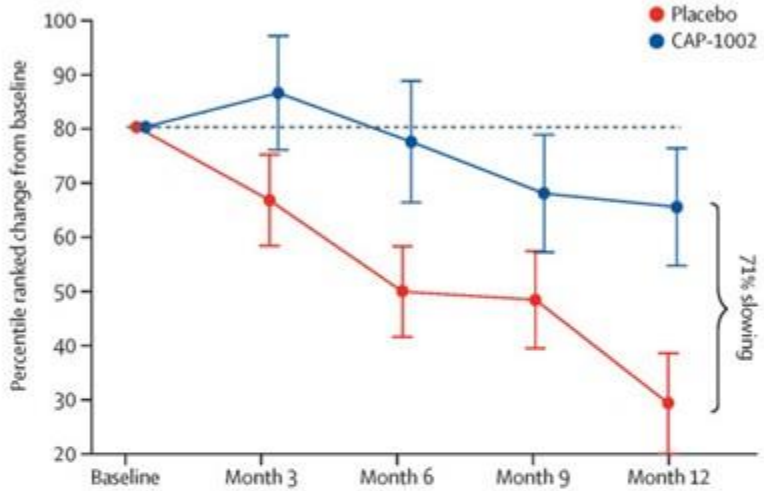
Cell Based Therapy

- CAP-1002 (Phase 3, NCT04126758) is a cell therapy that consists of allogeneic cardiosphere-derived cells (CDCs), a unique population of cells that contains cardiac progenitor cells
  - Intended to decrease inflammation, mitigate muscle degeneration, and promote muscle regeneration for extended muscle function in patients
- Trial is investigating efficacy in patients aged at least 10 years, with ambulatory and non-ambulatory DMD

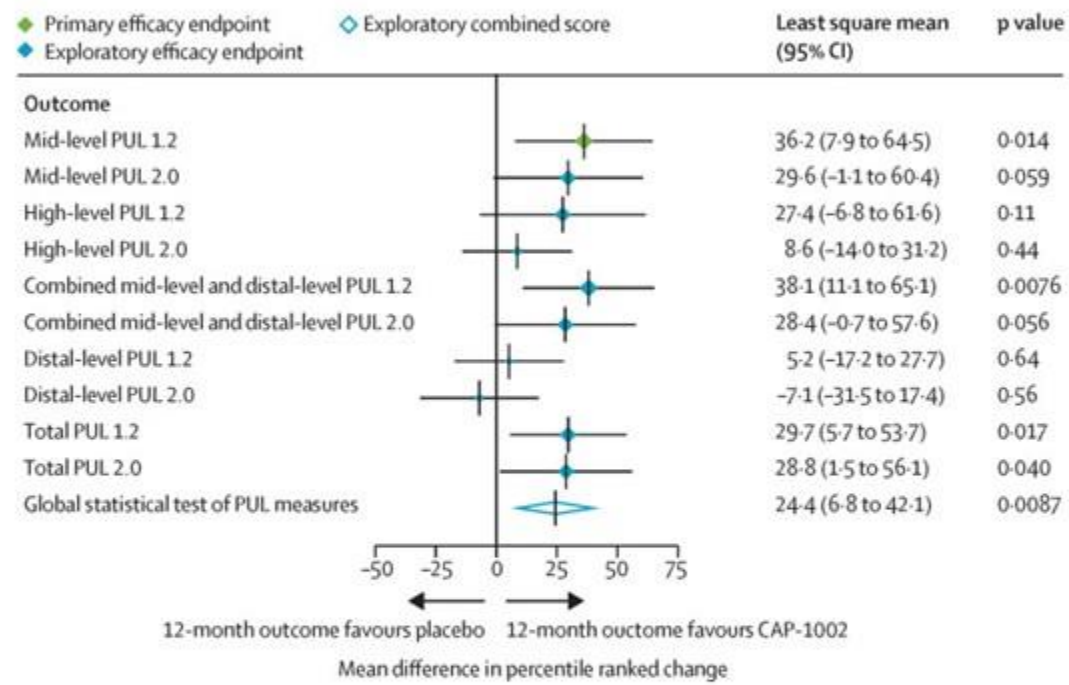


https://classic.clinicaltrials.gov/ct2/show/NCT05126758; P Furlong, et al. Parent Project Muscular Dystrophy Webinar. July 2018; YouTube.

CAP-1002



	Baseline	Month 3	Month 6	Month 9	Month 12
CAP-1002: least square mean (SE)	80·3	86·6 (10·5)	77·6 (11·2)	68·1 (10·8)	65·5 (10·8)
Placebo: least square mean (SE)	80·3	66·8 (8·4)	49·9 (8·4)	48·4 (9·0)	29·3 (9·2)
Difference (SE)	0·0	19·8 (12·8)	27·6 (13·3)	19·6 (13·6)	36·2 (13·8)
CAP-1002: converted	0·0	0·5	−0·1	−0·6	−0·8
Placebo: converted	0·0	−0·7	−1·7	−1·8	−3·4
Difference: converted	0·0	1·2	1·5	1·1	2·6
p value	..	0·13	0·047	0·16	0·014

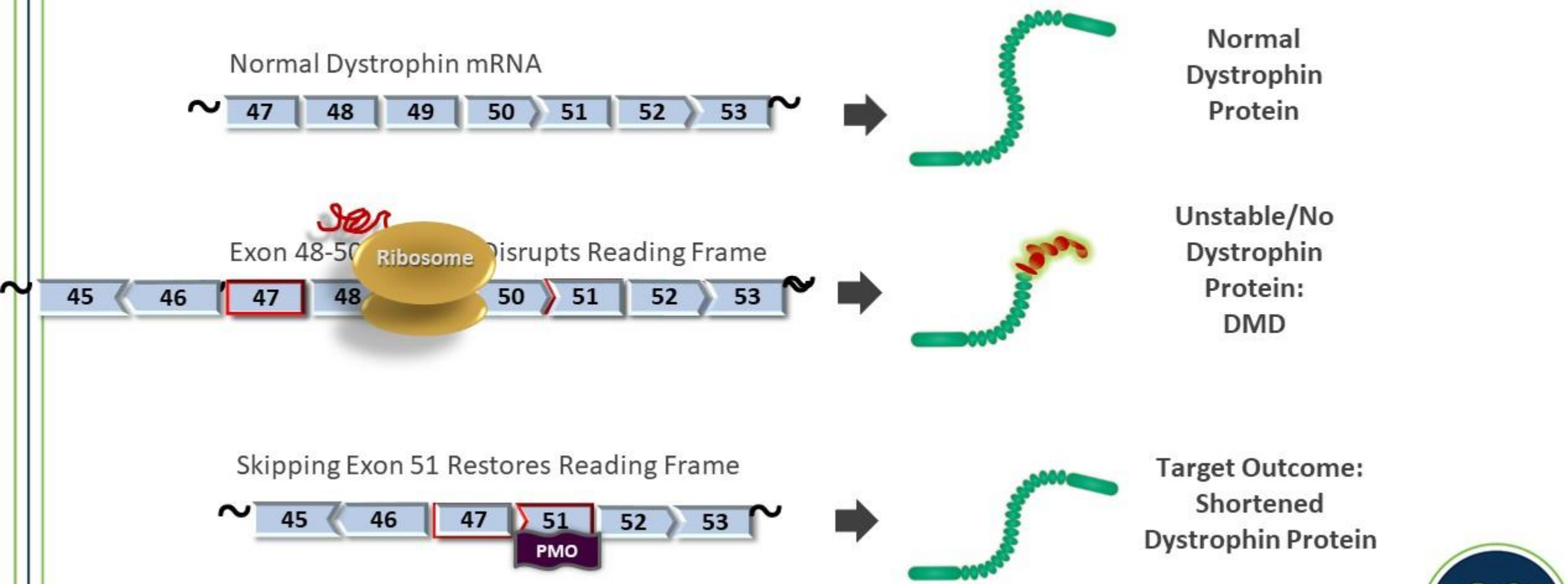


Longer-term studies are necessary to confirm the effectiveness and safety of CAP-1002 beyond 12 months in treating Duchenne muscular dystrophy

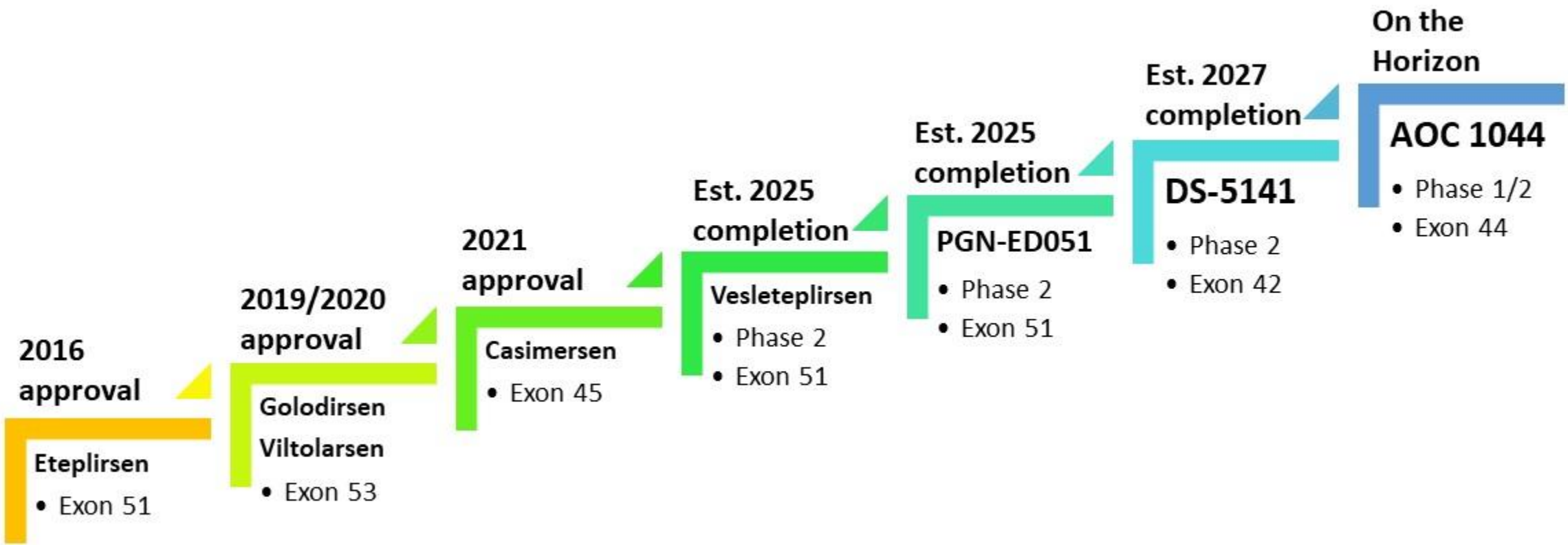
McDonald CM, et al. *Lancet*. 2022;399(10329):1049-1058.

Genetic-based Therapies for DMD

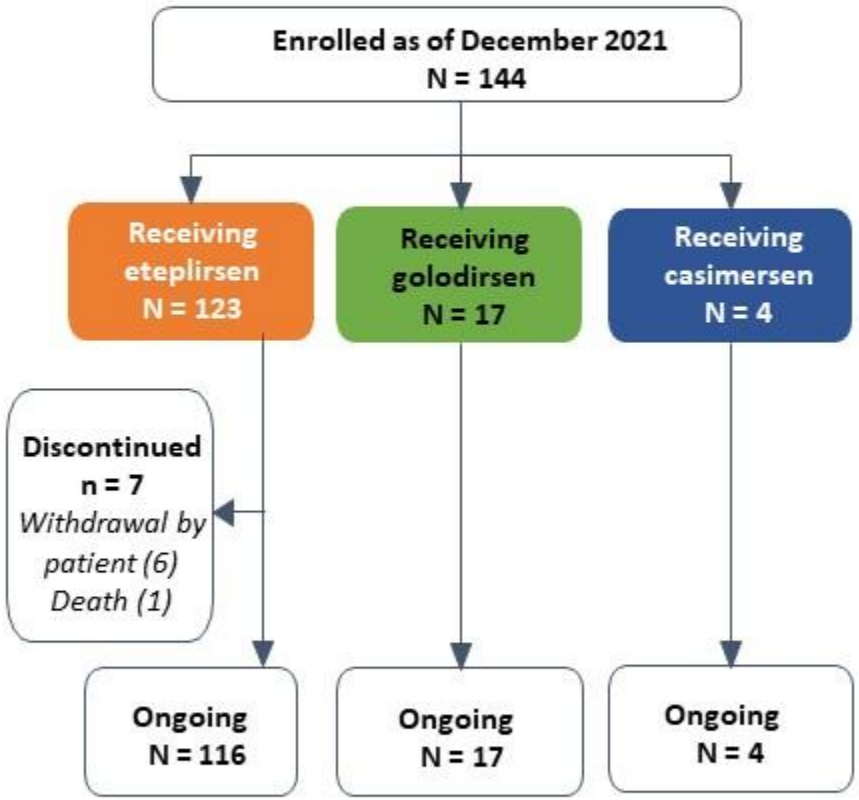
Exon Skipping Proposed Mechanism of Action e.g. Exon 51–amenable DMD Patients

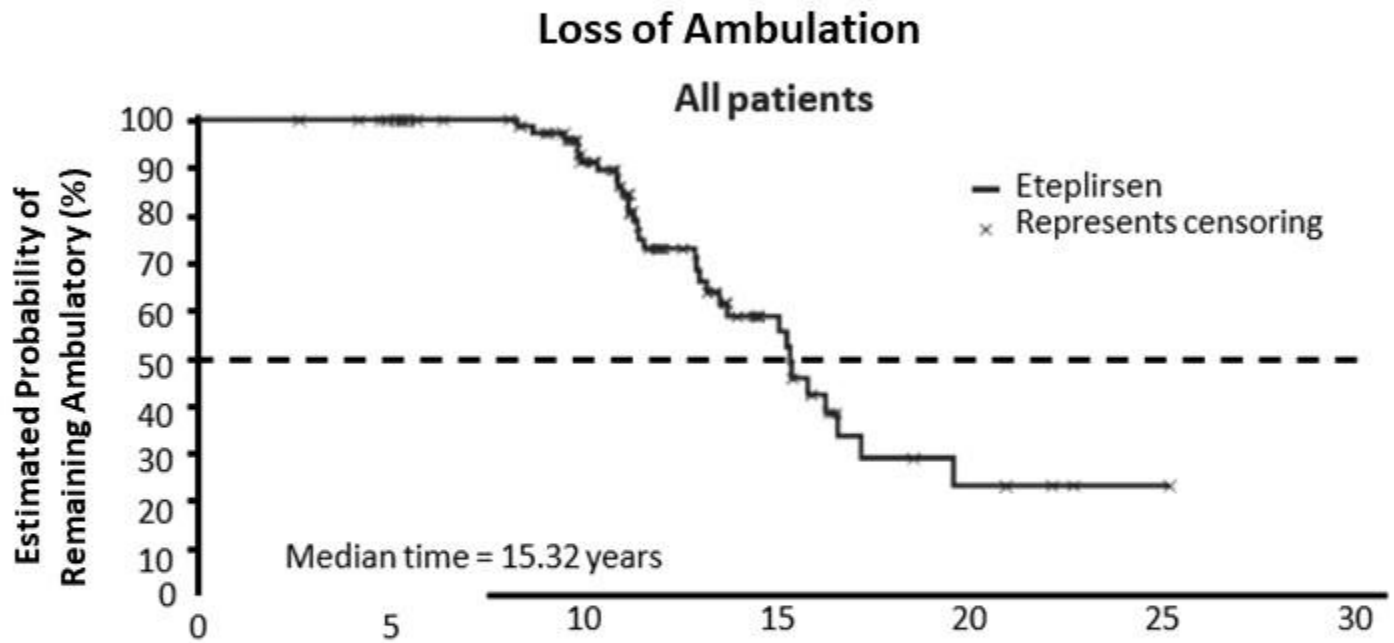


Exon Skipping Therapies



EVOLVE: Phase 4 Study





Median age at LOA for eteplirsen-treated patients was 15.32 years, which is consistent with past clinical trial results

Richetti-Masterson K, McDonald C, et al. Poster #185. Poster presented at: Muscular Dystrophy Association; March 19-22, 2023; Dallas, TX.

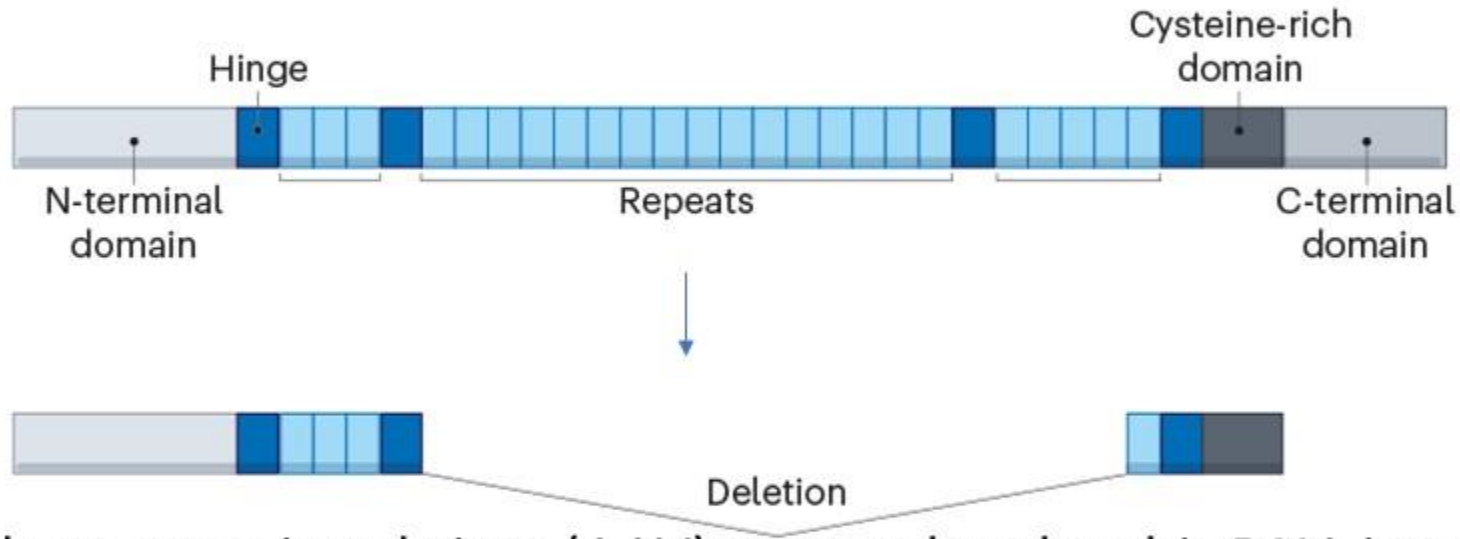
Gene Therapies

Dr. Crystal Proud

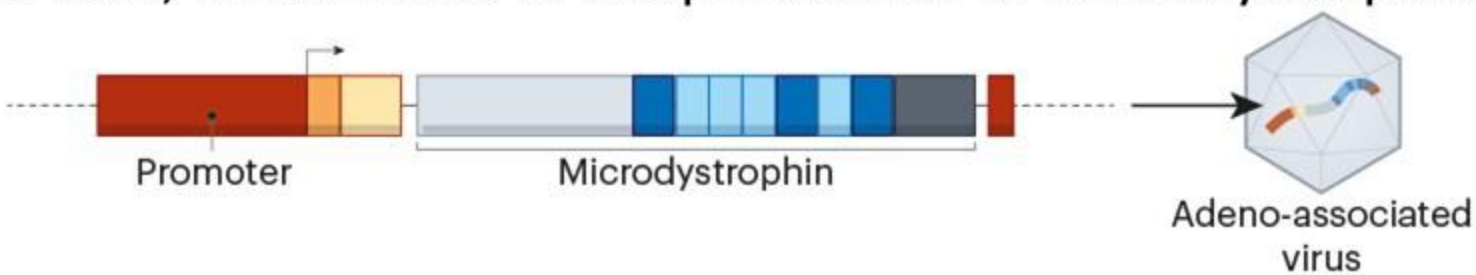
Dr. Aravindhan Veerapandiyan

Strategy for Delivery of a Miniaturized but Functional Dystrophin

Typical dystrophin contains 24 repetitive sections and four “hinge” regions



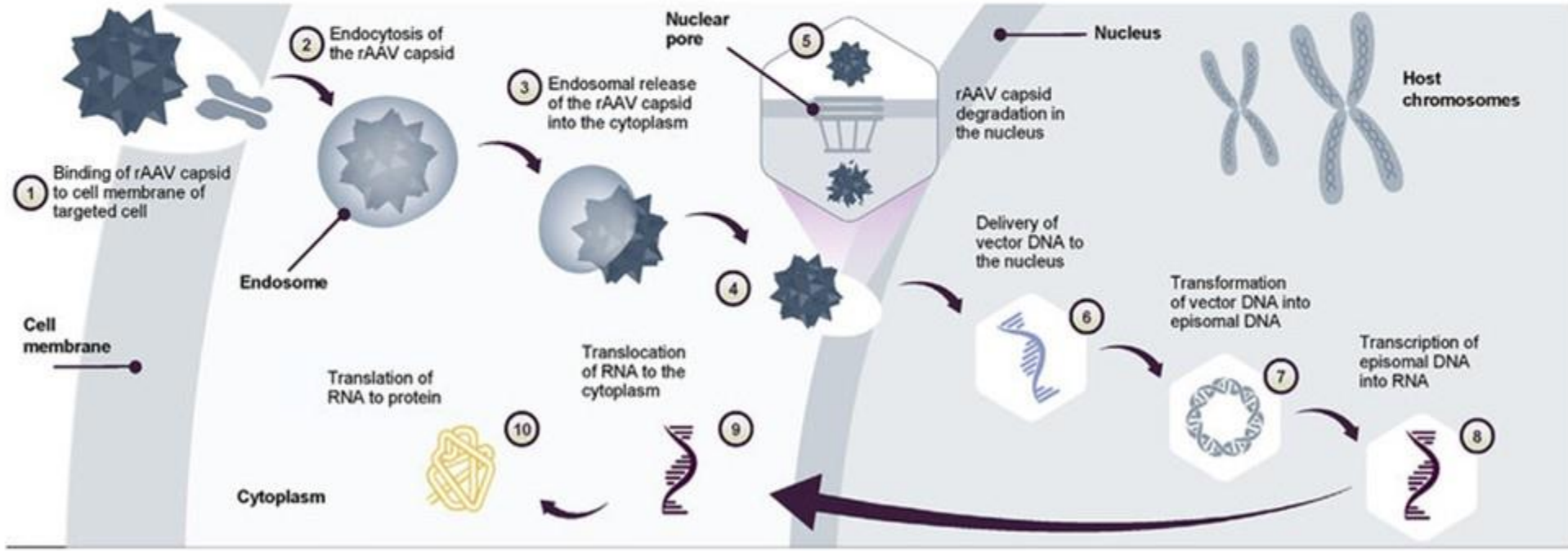
An adeno-associated virus (AAV) vector shuttles this DNA into the nucleus of muscle cells, which leads to the production of microdystrophin protein



Reardon S. *Nature*. 2023;618(7965):451-453.

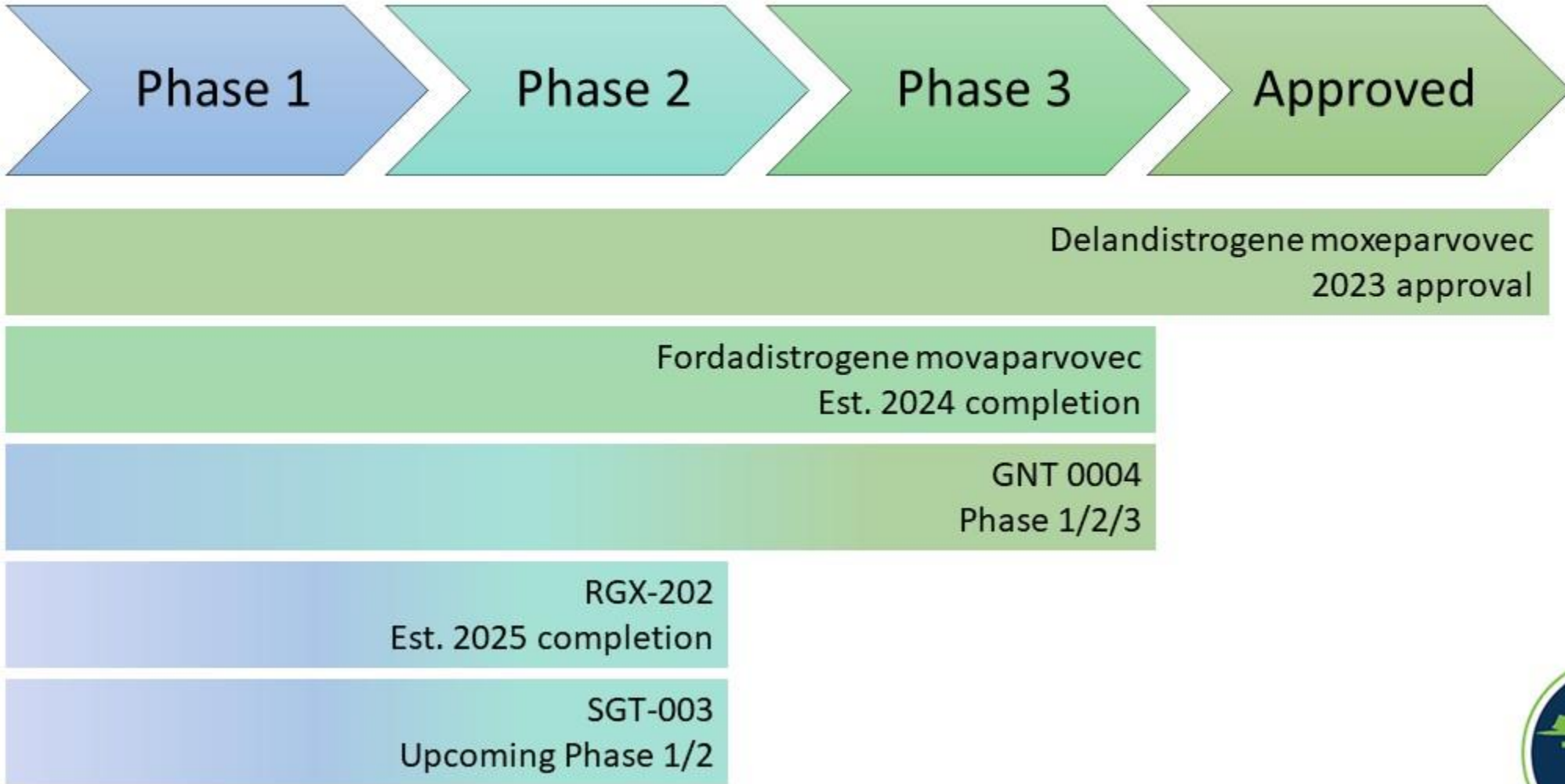
Gene Transfer Therapy for DMD

- Gene therapy consists of viral capsids containing a dystrophin trans gene injected intravenously into the patient
- Most commonly, an adeno-associated virus (AAV) vector is used

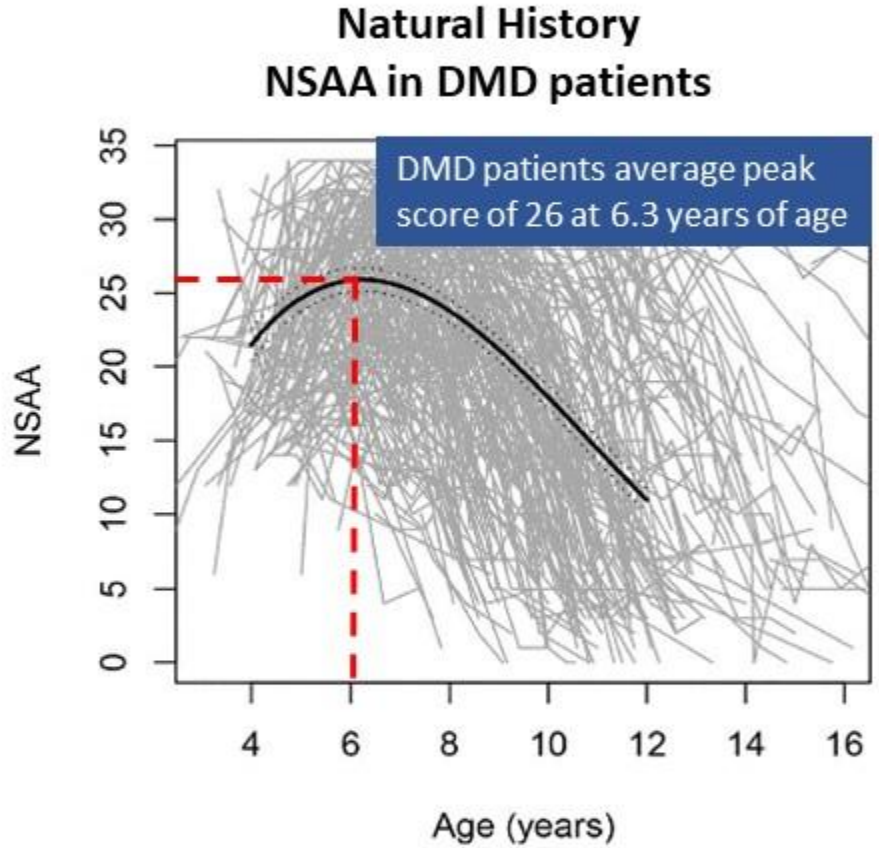


Naso MF, et al. *BioDrugs*. 2017;31(4):317-334; Ramos J and Chamberlain JS. *Expert Opin Orphan Drugs*. 2015;3:1255-66; Mendell JR, et al. *Mol Ther Methods Clin Dev*. 2022;25:74-83.

Gene Transfer Therapies



North Star Ambulatory Assessment (NSAA)

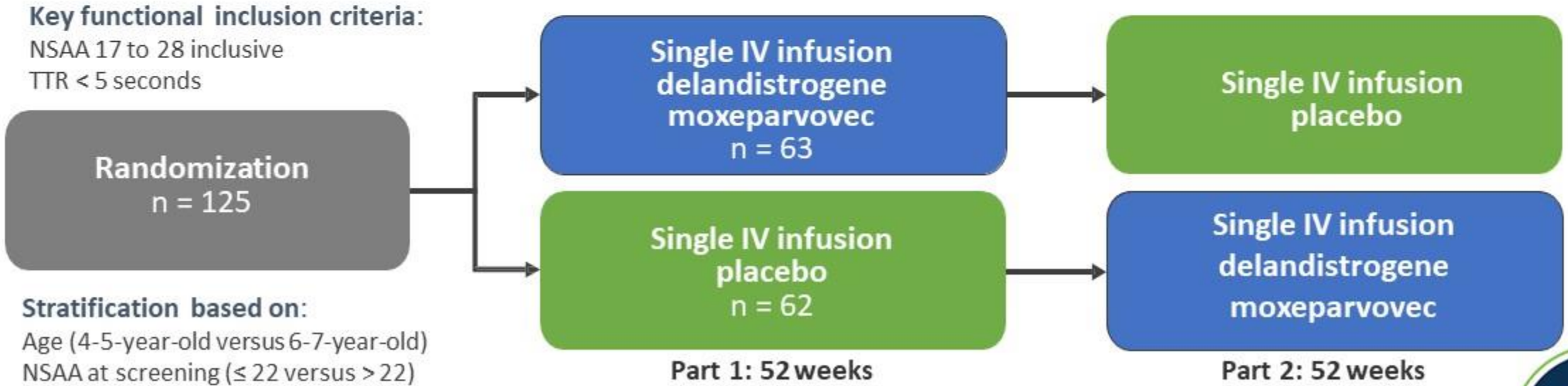


- 17 items assess motor function
- Each item scored
  - —0 = unable to perform
  - —1 = performed with difficulty
  - —2 = able to perform

Mayhew A, et al. *Dev Med Child Neurol*. 2011;53:535-42; Muntoni F, et al. *PLoS One*. 2019;14:e0221097.

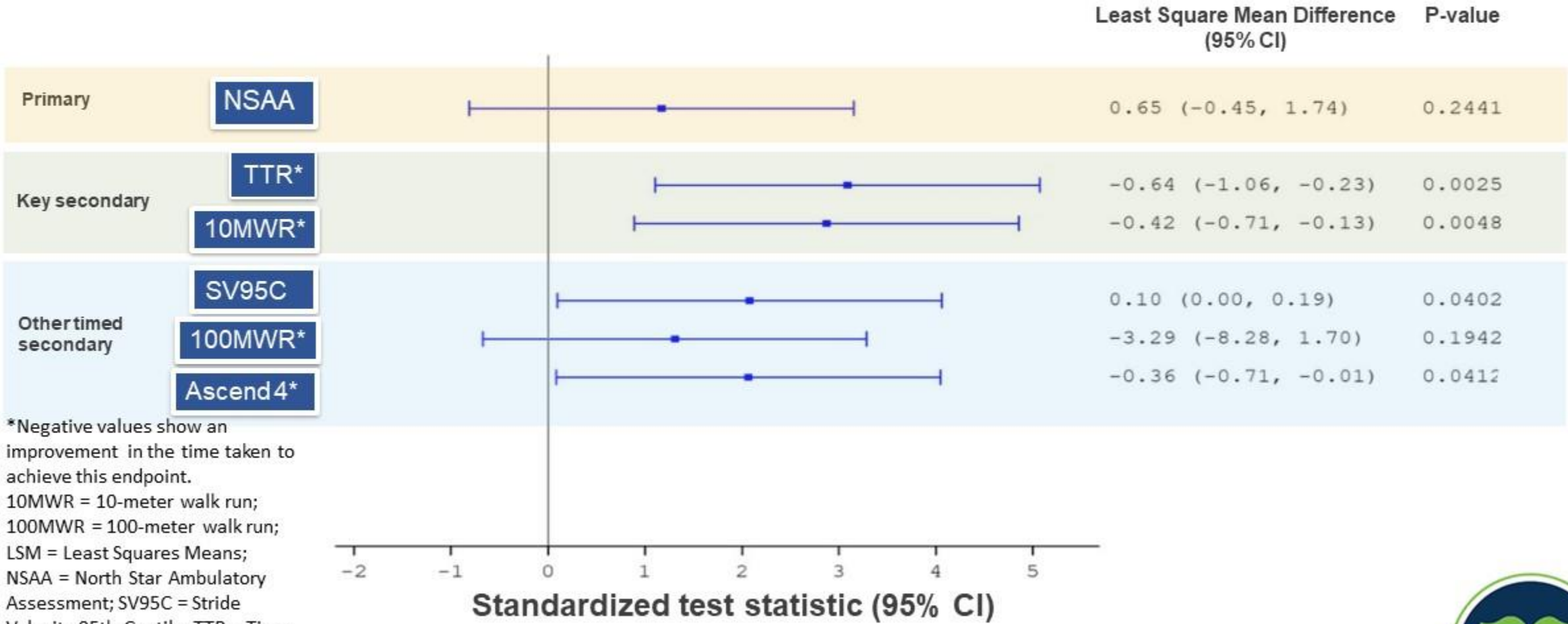
EMBARK: Phase 3 Results of Delandistrogene Moxeparvovec Across Age Groups

An ongoing Phase 3 multinational double-blind, randomized, placebo-controlled study evaluating the safety and efficacy of delandistrogene moxeparvovec compared to placebo in boys with DMD aged 4-7 years old



Data on file. Sarepta Therapeutics.

EMBARK; Phase 3 Results of Delandistrogene Moxeparvovec Across Age Groups



*Negative values show an improvement in the time taken to achieve this endpoint.
10MWR = 10-meter walk run;
100MWR = 100-meter walk run;
LSM = Least Squares Means;
NSAA = North Star Ambulatory Assessment; SV95C = Stride Velocity 95th Centile; TTR = Time to Rise

Data on file. Sarepta Therapeutics.

Fordadistrogene Movaparvovec: Phase 1b Study

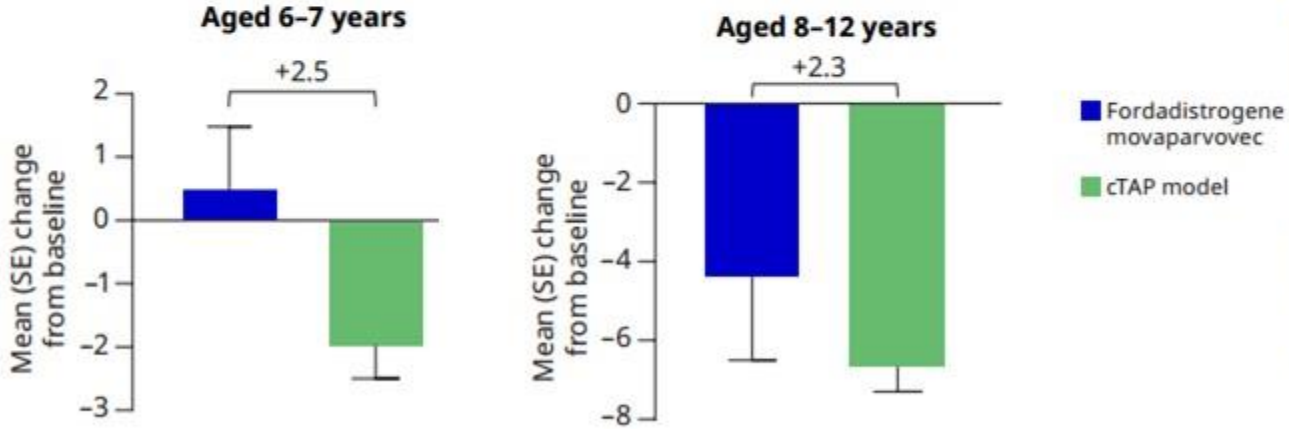
Boys aged 6-12* (N = 16)
*Stratified by age 6-7 years old & 8-12 years old

Single dose fordadistrogene movaparvovec

1 year (primary completion)
4 years of follow-up

Outcome Measures:
- Safety
- Microdystrophin expression

Mean change in NSAA at 2 years by age group vs predicted controls



Time relative to baseline	Fordadistrogene movaparvovec		cTAP Model		Difference		
	Mean	SE	Mean	SE	Mean	SE	P value
Year 1	0.75	0.99	–2.31	0.30	3.06	1.03	0.0031
Year 2	–2.56	1.46	–4.93	0.48	2.37	1.53	0.1223

cTAP = Collaborative Trajectory Analysis Project; NSAA = North Star Ambulatory Assessment; SE = standard error
Shieh P, et al. Poster #35. Poster presented at: World Muscle Society; October 3-6, 2023; Charleston, SC.

RGX-202: Phase 1/2 Study

Single dose RGX-202
$1x10^{14}$ GC/kg

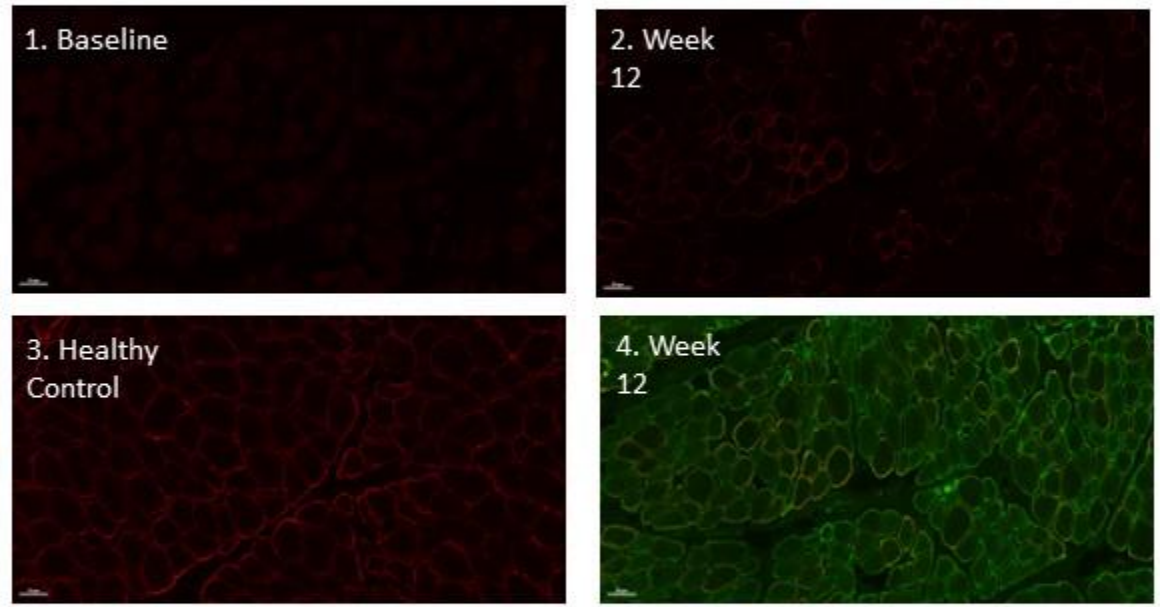
Boys (N = 5)

Outcome Measures:
- Safety
- RGX-202 microdystrophin expression

Serum Creatine Kinase

Patient	Age at Dosing (years)	Weight at Dosing (kg)	Western blot RGX-202 Microdystrophin (% Normal Control)	CK Levels, week 10 (% reduction from baseline)
1	4.4	17.8	38.8	-43
2	10.5	28.3	11.1	-44
3	6.6	26.8	83.4	-93

RGX-202 Microdystrophin Expression at 12 Weeks



RGX-202 has been well tolerated in 5 participants up to 3 weeks to 9 months post-administration

Avg = average; CK = creatine kinase

Veerapandiyan A, et al. Late Breaking Poster #19. Poster presented at: World Muscle Society; October 3-6, 2023; Charleston, SC.

Risks of Gene Transfer Therapy for DMD

Hepatic	Gastrointestinal	Hematologic	Cardiologic	Musculoskeletal	Other
• Acute liver injury/immune hepatitis/transaminitis (elevated transaminases) — Mitigated via modulation in corticosteroid administration	• Vomiting • Nausea • Anorexia	• Activation of sC5b9 complement • SIRS • Thrombocytopenia	• Myocarditis • Elevated troponin • Hypotension	• Immune-mediated myositis • Rhabdomyolysis	• Pyrexia 7/9 • Fatigue • Headache • Dehydration AKI resolved in 3 weeks • 1 death paused study in Aug 2021

AKI = acute kidney injury; SIRS = systemic inflammatory response syndrome

Cellular, Tissue, and Gene Therapies Advisory Committee May 12, 2023 Meeting Briefing Document- FDA; IGNITE DMD Phase I/II Study of SGT-001 Microdystrophin Gene Therapy for DMD: 2-Year Outcomes Update, MDA 2022; PF-06939926 (musculardystrophynews.com) Last Updated March 7, 2022.

Comparison of FDA-approved Therapies

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 exons 8/9) • Significant microdystrophin protein production on biopsy • Improved functional outcomes • Single administration	• Only FDA approved currently for 4-5-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

Combining different therapies for Duchenne muscular dystrophy (DMD) holds the potential to improve patient outcomes and reduce the overall disease burden by targeting multiple pathways associated with the disease spectrum

Heydemann A, Siemionow M. *Biomedicines*. 2023;11(3):830.

Summary of Therapies for DMD

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

Case Discussion

Dr. Crystal Proud

6-year-old Alex

Alex is a 6-year-old male, who was diagnosed with DMD and underwent gene therapy treatment at age 5.

After gene transfer therapy, Alex improved in his ability to rise from a seated position on the floor, and his walking was much faster.

However, he still fatigues after a long day of activity and has some difficulty going up and down stairs.

His parents would like to optimize his long-term outcome; they ask the neuromuscular team what other interventions may be beneficial?

Case Discussion

Considerations for Goals of Treatment as Applicable to Each Phase of DMD

Phase	Motor	Respiratory	Cardiac
Ambulatory Phase (Early/Late)	Prevention of loss (or prolonged time before loss) of ambulation Maintenance of standing (weight bearing)	Avoidance of need (or prolonged time before need) for nocturnal NIV or assisted cough	Prevention of (or prolonged time before) reduction of cardiac function and cardiac fibrosis
Early Non-ambulatory	Preservation of arm function (hands over head, hand to mouth)	Avoidance of need (or prolonged time before need) for nocturnal NIV or assisted cough	Prevention of (or prolonged time before) reduction of cardiac function and cardiac fibrosis
Late Non-ambulatory	Preservation of hand function (propelling chair independently, utilizing computer/remote)	Avoidance of (or prolonged time before need) for diurnal NIV or invasive ventilation	Maintenance of cardiac function, avoidance of progressive cardiac fibrosis

NIV, noninvasive ventilation

Provided by The France Foundation

Evolutions in the Management of

DUCHENNE MUSCULAR DYSTROPHY:

Treatment Implications for the Present and Future

MONDAY, MARCH 4, 2024

7:00–8:00 AM • Hilton Orlando

ORLANDO, FLORIDA