

Introduction on DMD and current therapies

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&
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Multistakeholder workshop on Real-World Data collection in Duchenne muscular dystrophy

25 September 2026, 09:00 – 17:30 (CET/CEST)

In-person at the EMA building, Amsterdam (2C) + virtual enabled



Francesco Muntoni: disclosures

Duchenne

Clinical trials

- CI of 4 antisense oligonucleotides clinical trials with Sarepta.
- PI of Sarepta and Roche AAVrh74 microdystrophin trial
- CI of Genethon AAV8 microdystrophin trial
- PI of Solid Bioscience microdystrophin trial

Spinal Muscular Atrophy

- PI of Biogen antisense oligonucleotide nusinersen Phase III study
- PI of Novartis AAV9 phase II and III trials in SMA I
- PI of Roche risdiplam Jewellfish study

Myotubular Myopathy

- PI of AAV8 MTM1 gene natural history and gene therapy trial

- **Other financial disclosures**

- Member of Dyne Therapeutics and Solid Bioscience SAB
- Ad-hoc SAB or symposia participation for Astellas, Novartis, Biogen, Roche, PTC, Rocket Pharma, Satellos, Sarepta Therapeutics, Biomarin

Topic discussed

- What is dystrophin – the protein deficient in people with DMD
- Why there is progressive muscle damage: role of dystrophin in muscle
- DMD progression and trajectories
- Different treatment modalities give rise to very different treatment responses
- Cardiorespiratory involvement in DMD
- Brain dystrophin deficiency is responsible for the central nervous system manifestations in DMD

What is DMD

Progressive muscle weakness

Most common muscular dystrophy of childhood

Incidence 1:4-5000 male births

Delayed motor milestones 50% cases

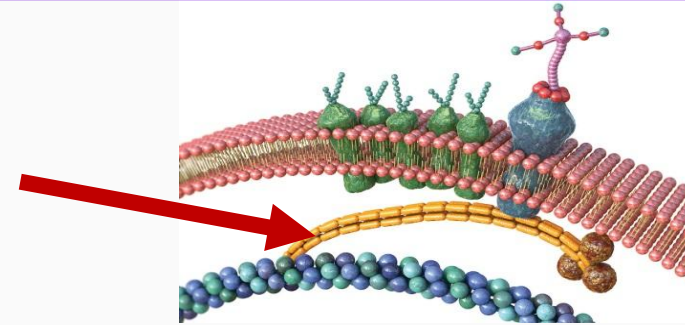
Never able to run

Max function: ~ 6 yrs

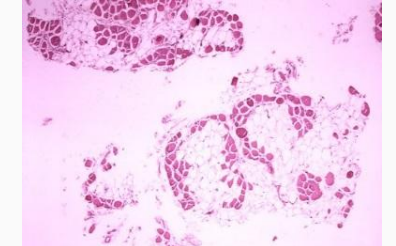
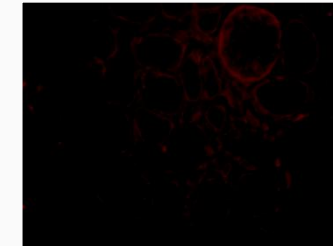
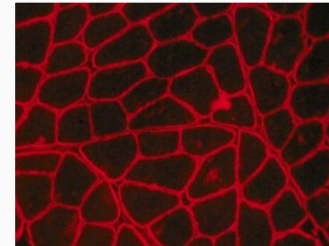
Mean age at loss of ambulation: 9.5yrs

Scoliosis in teen age yrs

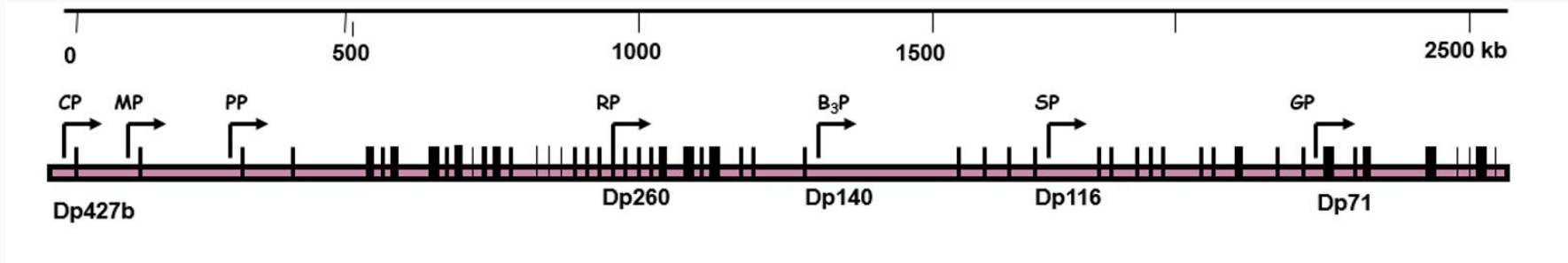
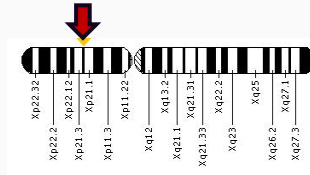
Cardiorespiratory insufficiency late teens



- Lack of sarcolemmal protein dystrophin
- Protects muscle from contraction induced injury
- Absent dystrophin → progressive muscle destruction
- Muscle is replaced by connective tissue and fat

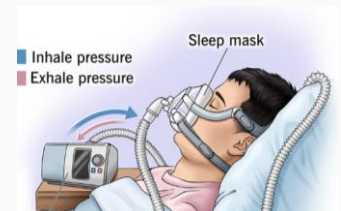
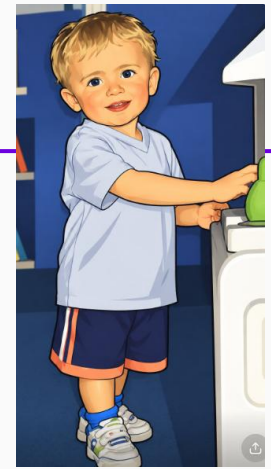


Genomic organisation of *DMD* gene, the largest in the human

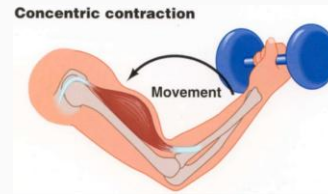


Clinical presentation

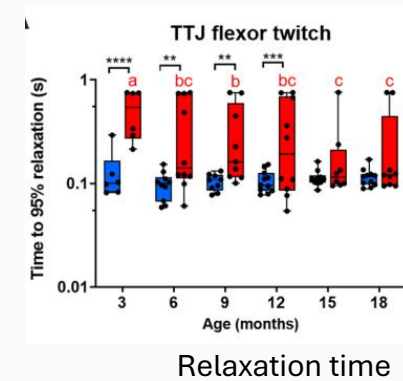
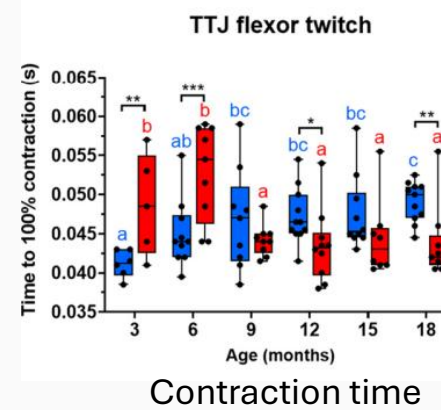
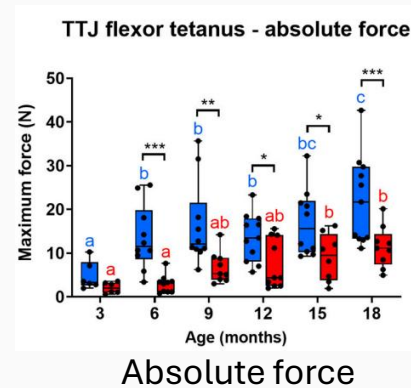
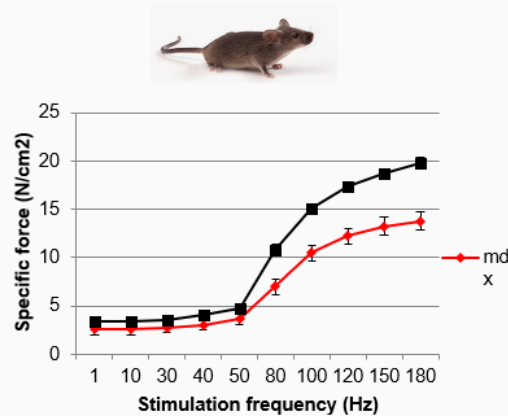
- Subtle initial symptoms in the first 12-24 months of life
- 50% present with delayed speech and delay of acquisition of early motor milestones
- In the first few years children appear to “improve” although the gap with normally developing kids widens
- Mean diagnostic delay: ~ 2 years
- With current standards of care, corticosteroids are initiated shortly after the diagnosis (~ 5 years)
- Mean age at loss of ambulation changed in my professional life between 9.5 and 13-14 years of age, largely due to steroids
- Dystrophin deficiency impacts on cardiorespiratory function
- Dilated cardiomyopathy and respiratory insufficiency, 2-3 decade of life
- Mean age of survival late 20s, slowly improving



What causes weakness in DMD muscles

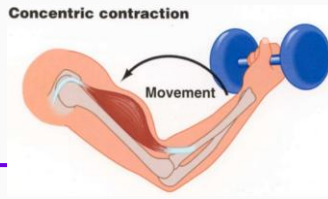


1. Reduced force generation in dystrophin deficient muscle



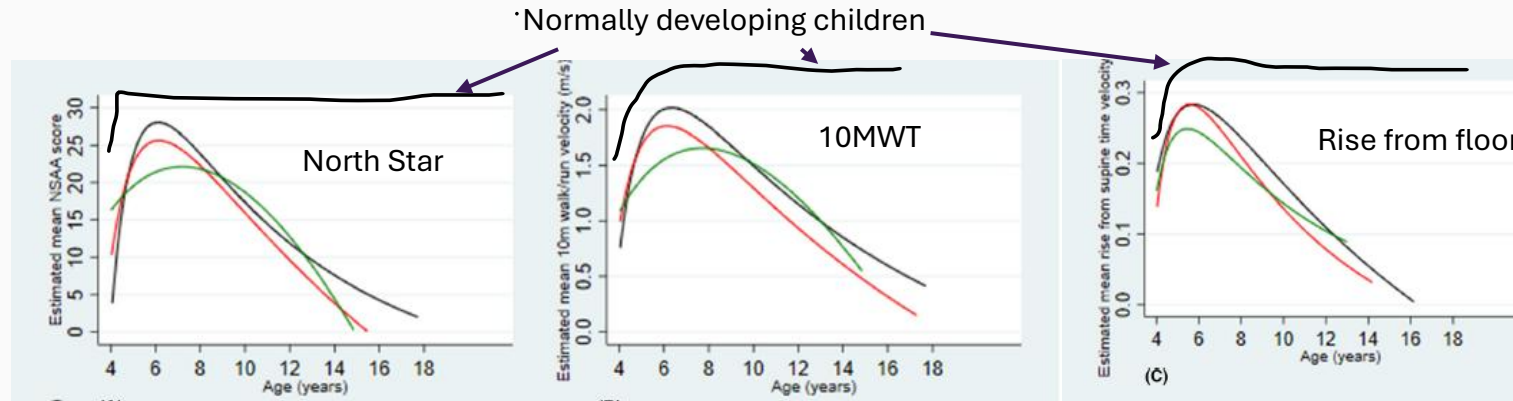
Riddel et al,
DM&M, 2023

What causes weakness in people with DMD

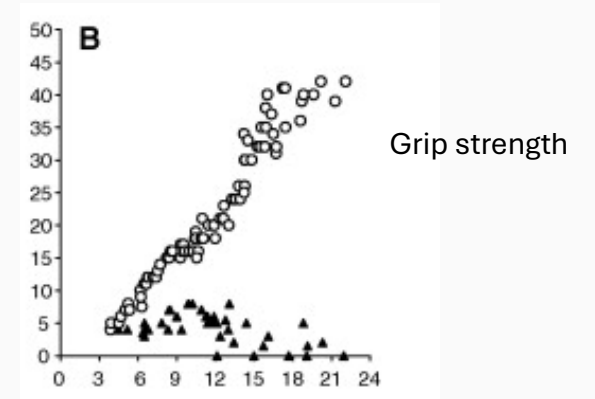


Consequences in the DMD boys of the reduced force generation

DMD



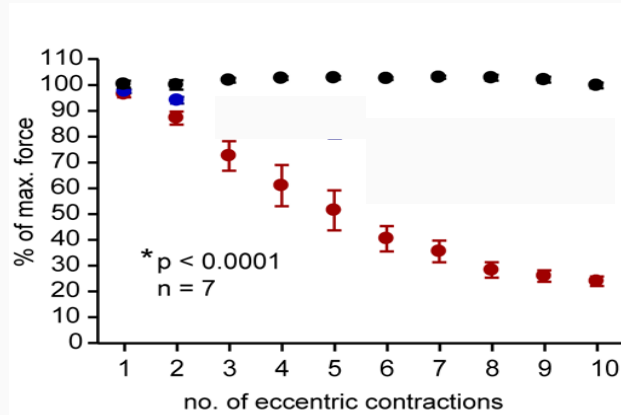
Chesshyre et al, JCSM, 2022



Mattar et al, NMD, 2008

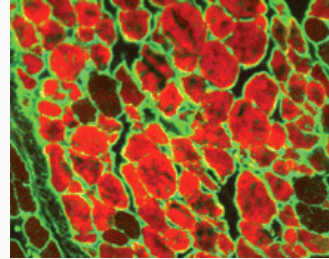
In the early stages of the disease, before major muscle damage occurs, reduced function is due to reduced muscle power, compounded in some kids by neurodevelopmental delay

What causes **progression of weakness** in people with DMD

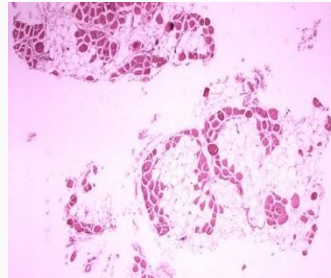
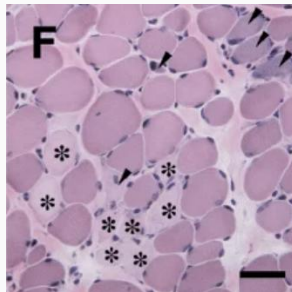
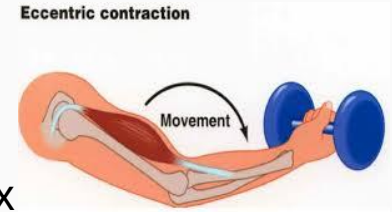


Sharp & Wells, 2011

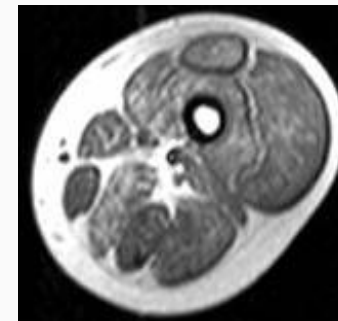
mdx EB uptake



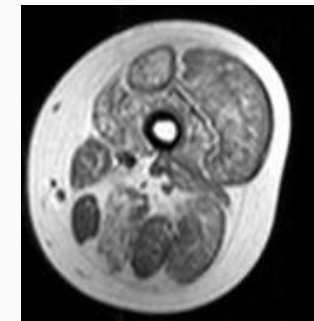
Lack of dystrophin induces massive influx of calcium especially during eccentric exercise, followed by muscle degeneration



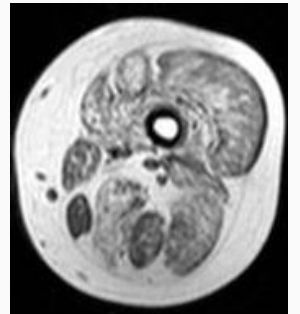
9.5 years



10.3 years

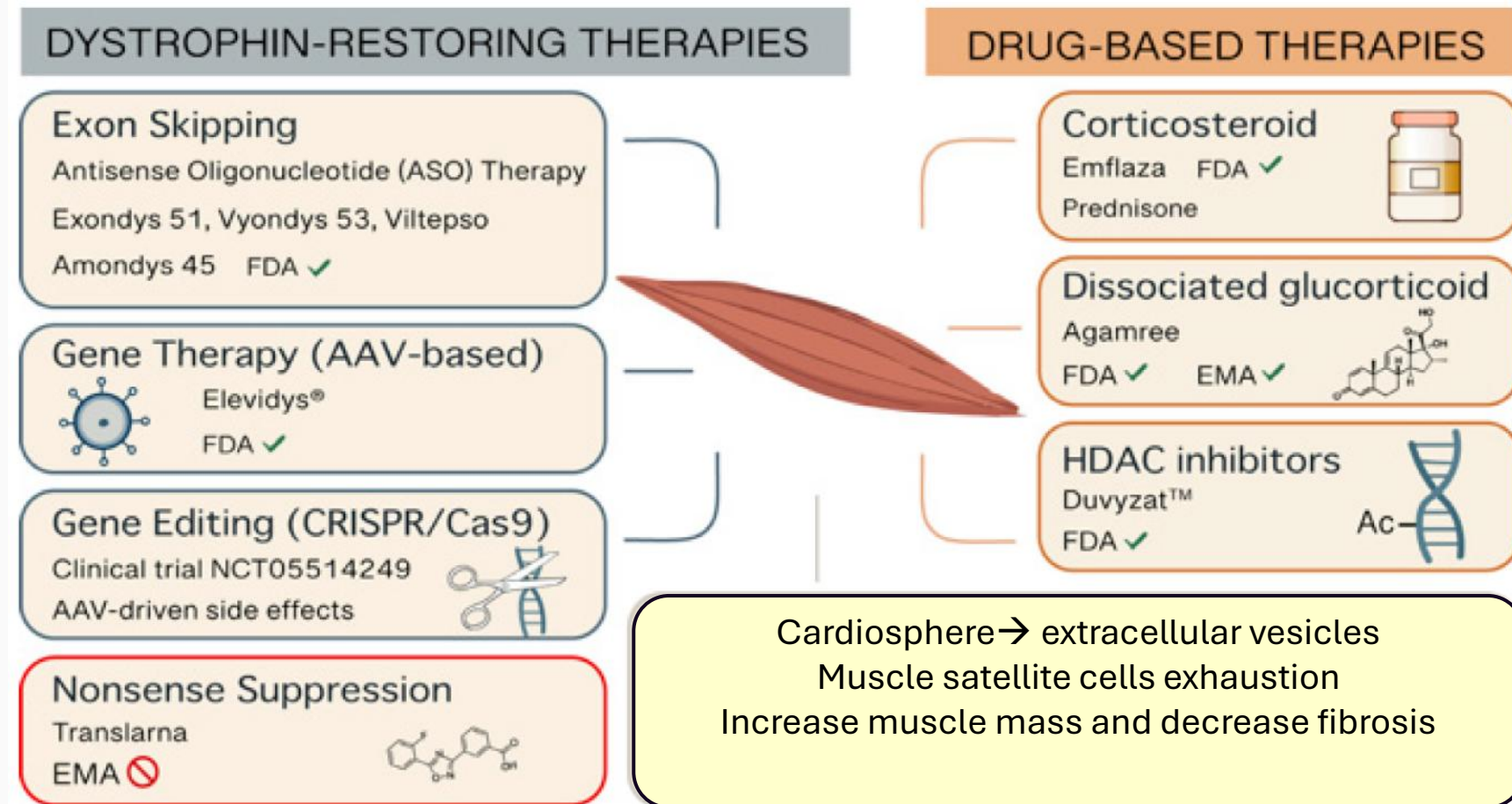


11 years



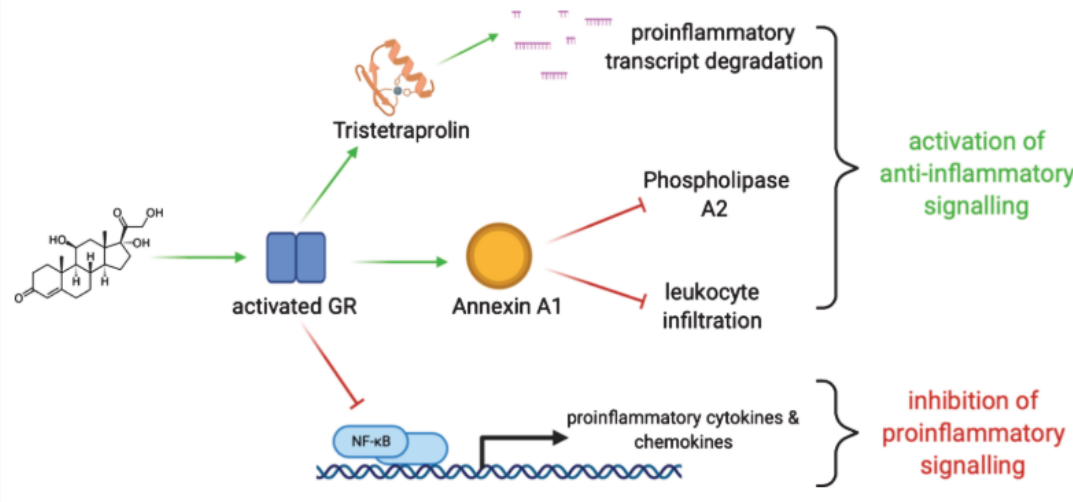
The progressive weakness observed from ~ 5 onwards is due to the loss of muscle mass, replaced by fibro-adipose tissue

Which therapeutic targets are currently being explored



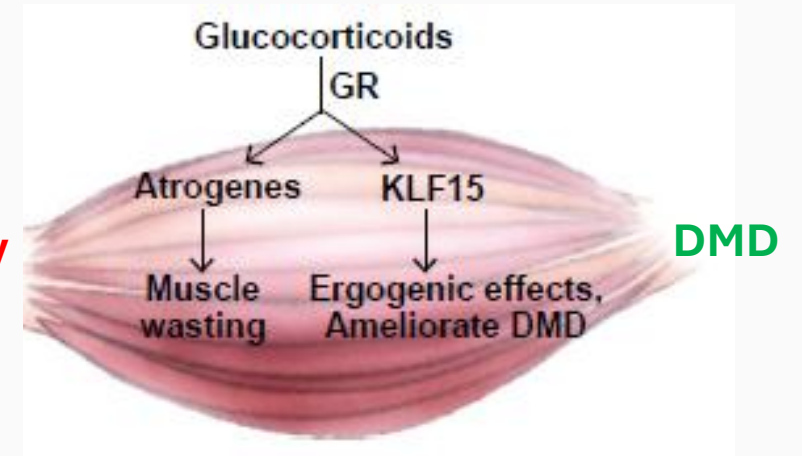
Corticosteroids and derivatives: the oldest on the scene

Multiple anti-inflammatory effects



Boost of muscle metabolic activity

Healthy

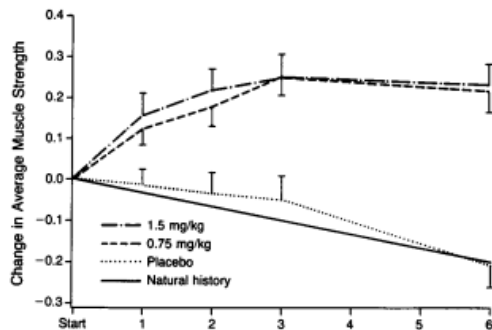


DMD

Quattorcelli et al, JND 2021

1592 THE NEW ENGLAND JOURNAL OF MEDICINE June 15, 1989

RANDOMIZED, DOUBLE-BLIND SIX-MONTH TRIAL OF PREDNISONE IN DUCHENNE'S MUSCULAR DYSTROPHY



It is of particular interest that urinary creatinine excretion was significantly increased in the prednisone-treated patients as compared with those given placebo ($P < 0.0001$). Although changes in serum lev-

Due to the multiple effects of corticosteroids, the rapid increase in muscle power makes possible to consider short study design

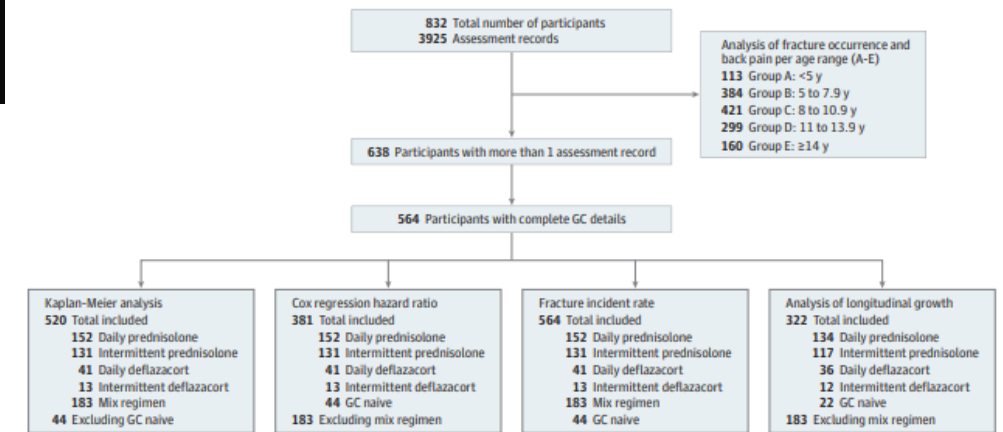
Classical corticosteroids associated with severe long-term side effects

1. Increased weight gain
2. Cushingoid appearance
3. Bone health with fractures and loss of height – **up to 30 cm**
4. Adrenal suppression
5. Delayed puberty
6. Worsening of behavioural problems
7. Body image induced interpersonal relationship difficulties

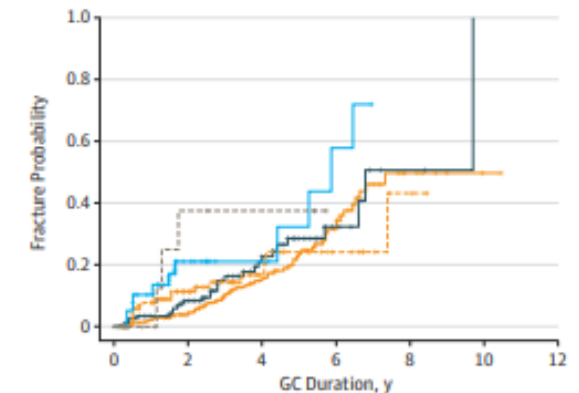
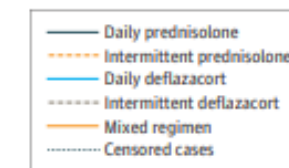


JAMA Neurology | Original Investigation

Fractures and Linear Growth in a Nationwide Cohort of Boys With Duchenne Muscular Dystrophy With and Without Glucocorticoid Treatment
Results From the UK NorthStar Database



B Different GC regimens



The unequivocal beneficial effect of chronic corticosteroids in DMD is associated with very severe and often permanent side effects

Exon skipping strategies

DMD mutations

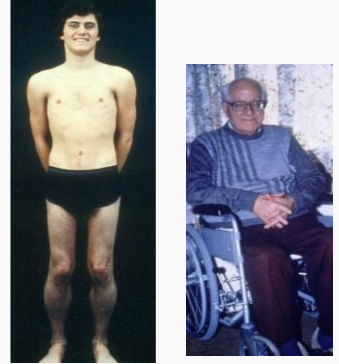
- 65% out-of-frame DMD deletions
- 10% out-of-frame duplications
- 10-15%% nonsense mutations
- Remaining: small mutations



Skip specific exons adjacent to the deletion

In-frame deletions → Becker MD

Extremely large gene, mRNA 11.5 Kb



- Milder allelic variant
- Majority of patients ambulant until late adult life
- Cardiomyopathy common
- Main age of survival middle 60s



Targeting exon 51: eteplirsen¹

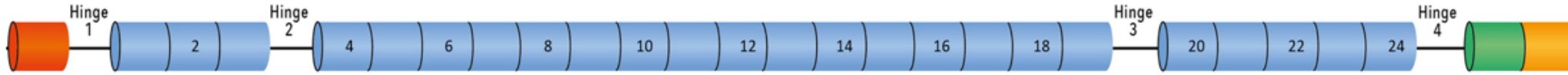
Targeting exon 53: golodirsen⁴



Planning clinical trials based on dystrophin biology

- Major improvement of muscle power not expected
- Very low levels of dystrophin (in the 1-5%) reduce inflammation and muscle pathology but with limited protection from ongoing muscle damage
- Levels of 20-30% protect muscle from damage, and higher levels necessary to improve force generation

AAV gene therapy strategies: finding the most efficacious transgene and viral vector



Wild-type dystrophin¹



Gene therapy	AAV vector	Promoter	Known micro-dystrophin transgene sequence																			
<u>Delandistrogene</u> <u>moxeparvovec</u> ² (Sarepta/Roche)	AAVrh74	MHCK7	ABD	H1	R1	R2	R3	H2											R24	H4	CR	
SGT-003 ^{2,3} (Solid Biosciences)	AAV9	CK8	ABD	H1	R1	R16 R17										R23	R24	H4	CR			
<u>Fordadistrogene</u> <u>movaparvovec</u> ^{*,2} (Pfizer)	AAV9	Muscle-specific promoter	ABD	H1	R1	R2	H3										R22	R23	R24	H4	CR	
GNT0004 ² (Genethon)	AAV2/8	Spc5.12	ABD	H1	R1	R2	R3	H2											R24	H4	CR	
RGX-202 ⁴ (REGENXBIO)	AAV8	Spc5.12	ABD	H1	R1	R2	R3	H3										R24	H4	CR	CT	

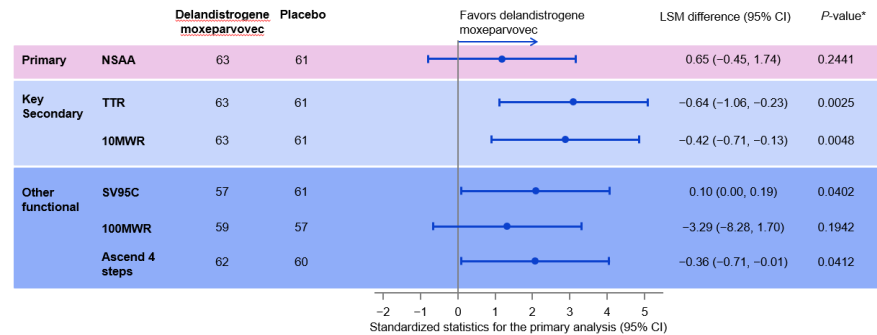
AAV micro-dystrophin ~ 1/3 of full length

AAV gene therapy strategies

AAV gene therapy for Duchenne muscular dystrophy: the EMBARK phase 3 randomized trial

Nature Medicine

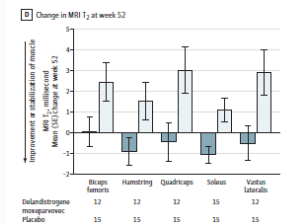
Jerry R. Mendell^{1,2,1718}, Francesco Muntoni^{3,18}, Craig M. McDonald⁴, Eugenio M. Mercuri⁵, Emma Ciafaloni⁶, Hirofumi Komaki⁷, Carmen Leon-Astudillo⁸, Andrés Nascimento⁹, Crystal Proud¹⁰, Ulrike Schara-Schmidt¹¹, Aravindhan Veerapandian¹², Craig M. Zaidman¹³, Maitea Guridi¹⁴, Alexander P. Murphy¹⁵, Carol Reid¹⁵, Christoph Wandel¹⁴, Damon R. Asher¹⁶, Eddie Darton¹⁶, Stefanie Mason¹⁶, Rachael A. Potter¹⁶, Teji Singh¹⁶, Wenfei Zhang¹⁶, Paulo Fontoura¹⁴, Jacob S. Elkins¹⁶ & Louise R. Rodino-Klapac¹⁶



JAMA Neurology | Original Investigation | JAMA Neurology Published online May 12, 2025

Quantitative Muscle Magnetic Resonance Outcomes in Patients With Duchenne Muscular Dystrophy

An Exploratory Analysis From the EMBARK Randomized Clinical Trial



Quantifying Variability in Motor Function in Duchenne Muscular Dystrophy: UK Centiles for the NorthStar Ambulatory Assessment, 10 m Walk Run Velocity and Rise from Floor Velocity in GC Treated Boys

Journal of Neuromuscular Diseases 11 (2024) 153–166

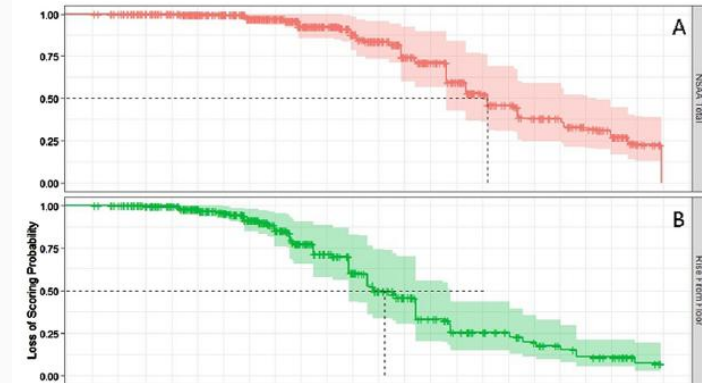
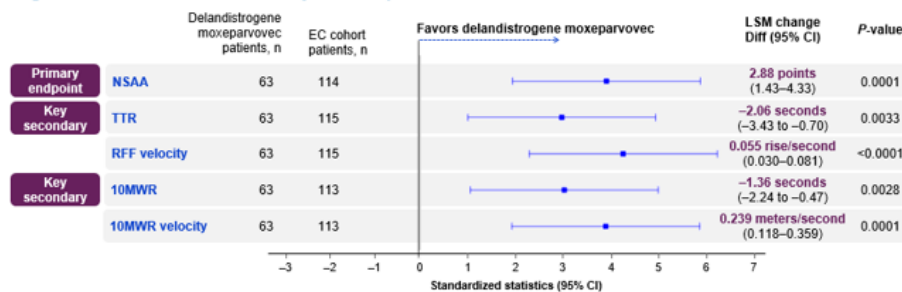


Figure 2. Functional outcomes at 2 years compared with the EC cohort



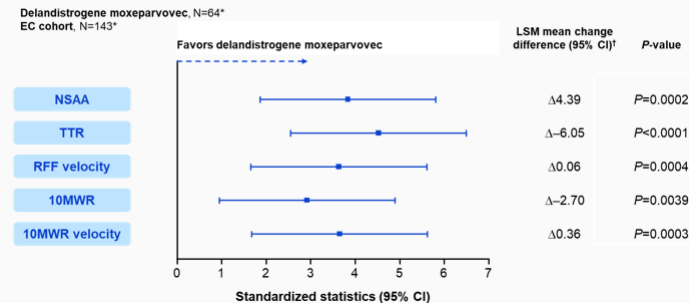
Two-Year Outcomes Following Delandistrogene Moxeparvovec Treatment in Ambulatory Patients with Duchenne M

EMBARK Trial | Neurol Ther (2026) 15:545–559

A lot of work to identify data driven criteria for propensity matching with external controls

Potential for residual bias on the use of external controls needs urgent clarification

EMBARK 3-Year Results



Long-Term Delandistrogene Moxeparvovec in Duchenne Muscular Dystrophy: EMBARK Trial 3-Year Results

Submitted for publication



Are randomised placebo controlled AAV GT trials perfect?

Safety and efficacy of ffordadistrogene movaparvovec in ambulatory participants with Duchenne muscular dystrophy (CIFFREO): a phase 3, double-blind, randomised, placebo-controlled study [thelancet.com/neurology](https://www.thelancet.com/neurology) Vol 25 March 2026

Francesco Muntoni, Andres Nascimento, Jinhong Shin, Michela Guglieri, Georg M Stettner, Aravindhan Veerapandian, Silvina Gallo, Heliang Shi, Balaram Gundapaneni, Srividya Neelakantan, Kasia Lobello, Qi Shen, Daniel I Levy, Eugenio Mercuri, on behalf of the CIFFREO Study Group*

	Fordadistrogene movaparvovec (n=79*)	Placebo (n=35*)
Total participants with adverse events	78 (99%)	27 (77%)
Vomiting	60 (76%)	5 (14%)
Pyrexia	49 (62%)	3 (9%)
Decreased appetite	26 (33%)	1 (3%)
Nausea	23 (29%)	3 (9%)
Liver glutamate dehydrogenase increased	19 (24%)	0
Nasopharyngitis	19 (24%)	6 (17%)
Abdominal pain	17 (22%)	3 (9%)
Thrombocytopenia	15 (19%)	0
Headache	14 (18%)	4 (11%)
Diarrhoea	10 (13%)	4 (11%)
Platelet count decreased	10 (13%)	0

AAV gene therapy for Duchenne muscular dystrophy: the EMBARK phase 3 randomized trial Nature Medicine

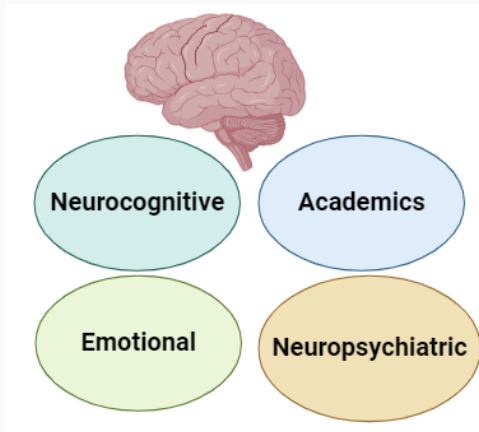
Jerry R. Mendell^{1,2,7,18}, Francesco Muntoni^{3,18}, Craig M. McDonald⁴, Eugenio M. Mercuri⁵, Emma Ciafaloni⁶, Hirofumi Komaki⁷, Carmen Leon-Astudillo⁸, Andrés Nascimento⁹, Crystal Proud¹⁰, Ulrike Schara-Schmidt¹¹, Aravindhan Veerapandian¹², Craig M. Zaidman¹³, Maitea Guridi¹⁴, Alexander P. Murphy¹⁵, Carol Reid¹⁵, Christoph Wandet¹⁴, Damon R. Asher¹⁶, Eddie Darton¹⁶, Stefanie Mason¹⁶, Rachael A. Potter¹⁶, Teji Singh¹⁶, Wenfei Zhang¹⁶, Paulo Fontoura¹⁴, Jacob S. Elkins¹⁶ & Louise R. Rodino-Klapac¹⁶

Patients with any TR-SAE, n (%)	7 (11.1)	0
Number of TR-SAEs, n	10	0
Patients with an AE leading to study discontinuation, n (%)	0	0
Number of deaths, n (%)	0	0
TR-TEAEs occurring in >10% of patients, n (%)		
Vomiting	34 (54.0)	0
Nausea	20 (31.7)	5 (8.1)
Decreased appetite	17 (27.0)	1 (1.6)
GLDH increased ^a	15 (23.8)	2 (3.2)
Pyrexia	10 (15.9)	0
Abdominal pain upper	8 (12.7)	1 (1.6)

Clear unblinding in 60-80% of treated patients.
Why is this considered a perfect study paradigm?
What is the regulatory position when facing this
“RCT blinding misconception”

Consider the brain as a therapeutic target

Lack of brain dystrophin cause a “non-progressive synaptopathy”



This result in intellectual disability of neurobehavioural complications in 30-50% of patients, limiting their full participation to life

Duchenne muscular dystrophy: recent insights in brain related comorbidities

Cyrille Vaillend^{1,7}, Yoshitsugu Aoki^{2,7}, Eugenio Mercuri^{3,7}, Jos Hendriksen^{4,8}, Konstantina Totorou⁵, Aurélie Goyenvalle^{6,8} & Francesco Muntoni⁵

Nature Communications | (2025)16:1298



Impact of distinct dystrophin gene mutations on behavioral phenotypes of Duchenne muscular dystrophy

Amel Saoudi^{1,2}, Manuela D Mitsogiannis^{3,4}, Faouzi Zarrouki¹, Claire Fergus⁴, Erwina Stojek³, Silvia Talavera³, Dervla Moore-Frederick³, Vincent P Kelly⁴, Aurélie Goyenvalle², Federica Montanaro⁵, Francesco Muntoni⁵, Jack A Prenderville³, Ewa Sokolowska^{3,6}, Cyrille Vaillend^{1,8}

► Author information ► Article notes ► Copyright and License information

PMCID: PMC11698058 PMID: 39718030

Emotional behavior and brain anatomy of the mdx52 mouse model of Duchenne muscular dystrophy

Amel Saoudi¹, Faouzi Zarrouki¹, Catherine Sebré³, Charlotte Izabelle¹, Aurélie Goyenvalle², Cyrille Vaillend¹

The behavioural consequences of dystrophinopathy

Minou A T Verhaeg¹, Elizabeth M van der Pijl¹, Davy van de Vijver¹, Christa L Tanganyika-de Winter¹, Tiberiu L Stan¹, Angel van Uffelen¹, Luciano Censoni², Maaike van Putten¹

Hyperactivity, compulsive-like behaviours, and impaired flexibility in mouse models of Duchenne muscular dystrophy

Faouzi Zarrouki¹, Léa Ceschi², Rubén Miranda³, Amel Saoudi¹, Cyrille Vaillend⁴

The brain phenotype in mdx mice is reversible with exon skipping and AAV gene therapy strategies

Take home message

- Natural history of DMD is complicated by different variables, temporarily dissociated between them
- Dystrophin restoration therapies address to different extent the root cause of the disease but long trials necessary.
- Do not think that a drug that “works slowly” over time is worst compared to a “fast acting” one
- However prolonged trials are financially unsustainable, and prolonged placebo studies ethically challenging
- Placebo studies are “gold-standard”, but they were not designed for therapies in which we can unblind in weeks more than half of the patients
- Role of well curated, independent from sponsors, registries to prospectively enrich RCT, and assess long term safety and efficacy of novel therapies

UCL / GOSH acknowledgements

The Novo
Nordisk Prize

Dubowitz Neuromuscular Centre



Genetic Therapy Accelerator Centre



20
Years
Powering
life-changing
research



Great Ormond Street Hospital
NIHR GOSH Clinical Research Facility ...

MRC
Medical
Research
Council
Centre for
Neuromuscular Diseases

Great Ormond Street
Hospital for Children
NHS
NHS Trust

NHS
National Institute for
Health Research

MUSCULAR DYSTROPHY CANADA
DYSTROPHIE MUSCULAIRE CANADA
MUSCLE.CA

Muscular
Dystrophy
Campaign
NorthStar
Clinical Network

LifeArc
action medical research
for children

UKRI
UK Research
and Innovation

Duchenne
Parent
Project
aps

AFM
Association Française contre les Myopathies

UCL 200