THE FUTURE OF DUCHENNE TREATMENT
EMERGING THERAPIES

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Cure Duchenne™

WHAT IS DUCHENNE MUSCULAR DYSTROPHY?

DUCHENNE IS A PROGRESSIVE, MUSCLE-WASTING DISEASE.

It results from a defective gene responsible for producing the key muscle protein, dystrophin. Without dystrophin, cells easily become damaged and die, resulting in heart and breathing failure.

300,000

CHILDREN & YOUNG ADULTS WORLDWIDE

1 in 3,500 – 5,000 males

DUCHENNE'S IMPACT ON THE BODY

- DYSTROPHIN ABNORMALITIES
- POSSIBLE LEARNING AND COGNITIVE DIFFICULTIES

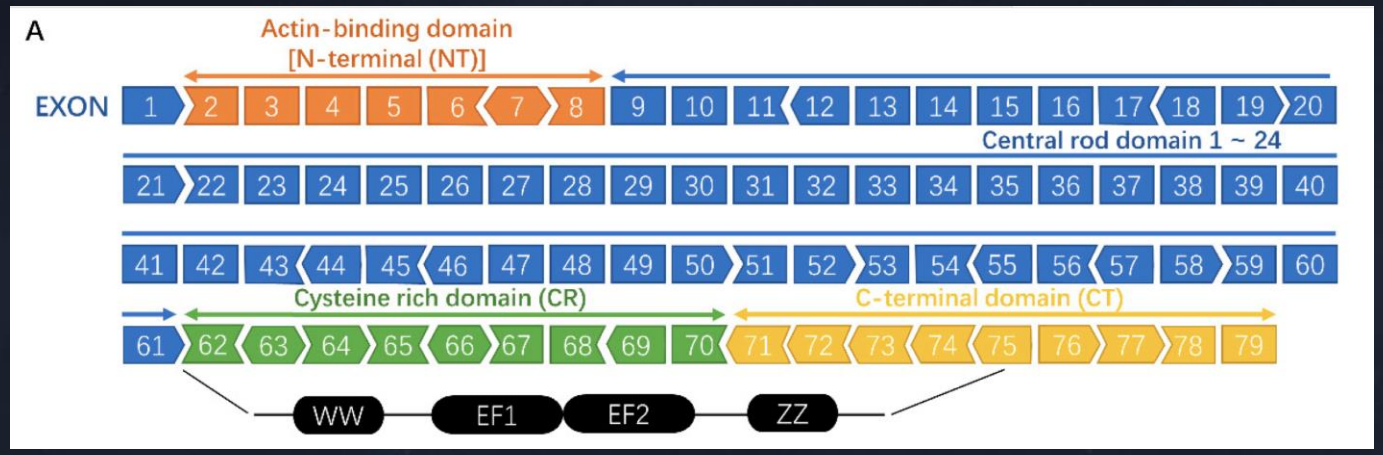
- DECREASED HEART FUNCTION
- CARDIOMYOPATHY
- LEADS TO HEART FAILURE

- WEAKENS DIAPHRAGM
- REQUIRES VENTILATOR
- LEADS TO PNEUMONIA

- LOSS OF MUSCLE MASS
- WEAKNESS
- INFLAMMATION
- FIBROSIS

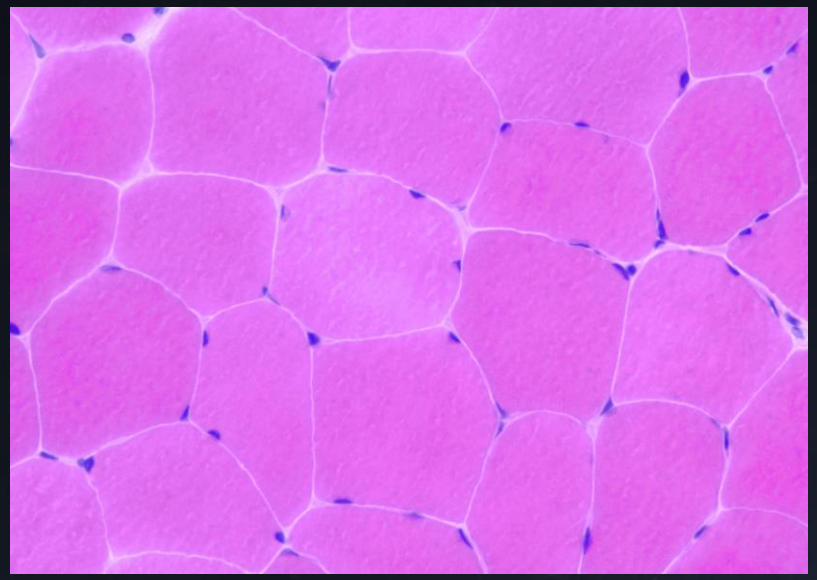
THE *DMD* GENE AND THE DYSTROPHIN PROTEIN

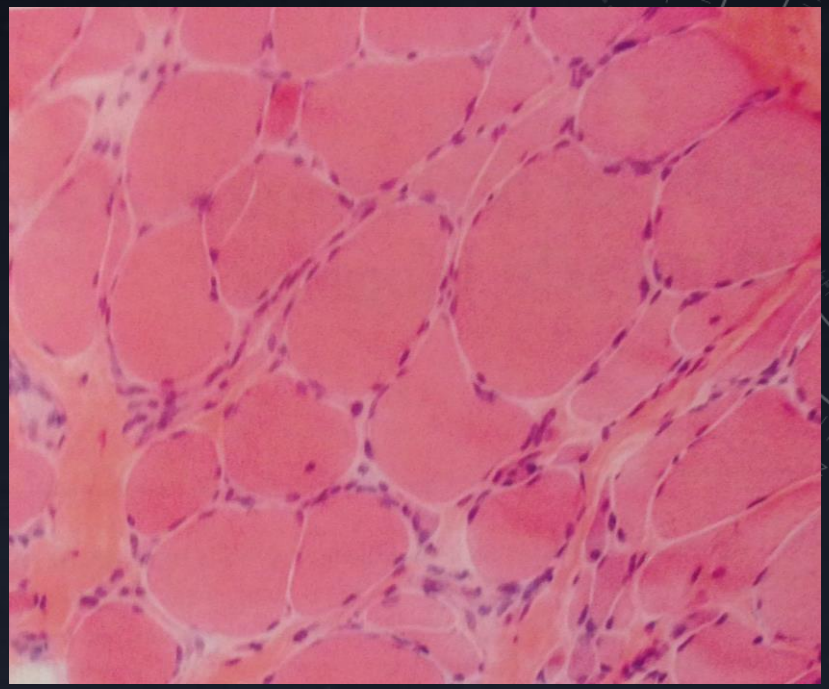
- Largest known human gene - 0.1% of the entire genetic code
- Master recipe or blueprint for the dystrophin protein
  - A vital shock absorber for muscle cells

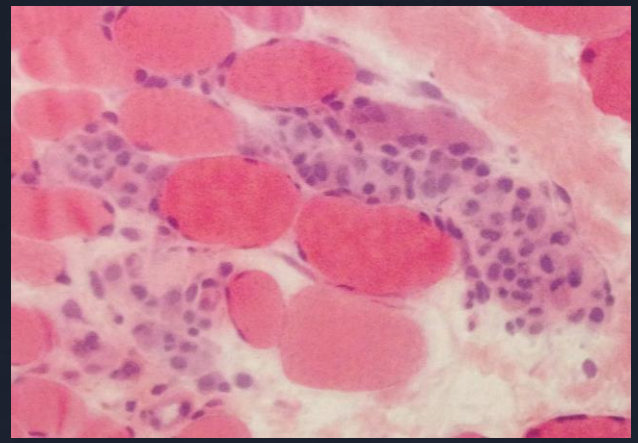


THE MISSING SHOCK ABSORBER

- Error/ ”variant” in the DMD gene
- Missing functional dystrophin protein
- Fragile muscle cells, easily damaged with everyday activity
- Toxic substances enter into the muscle cell causing cell death
- Body tries to repair the damage, but can’t keep up
- Muscles replaced by fat and scar tissue (fibrosis)
- Progressive muscle weakness







Normal muscle

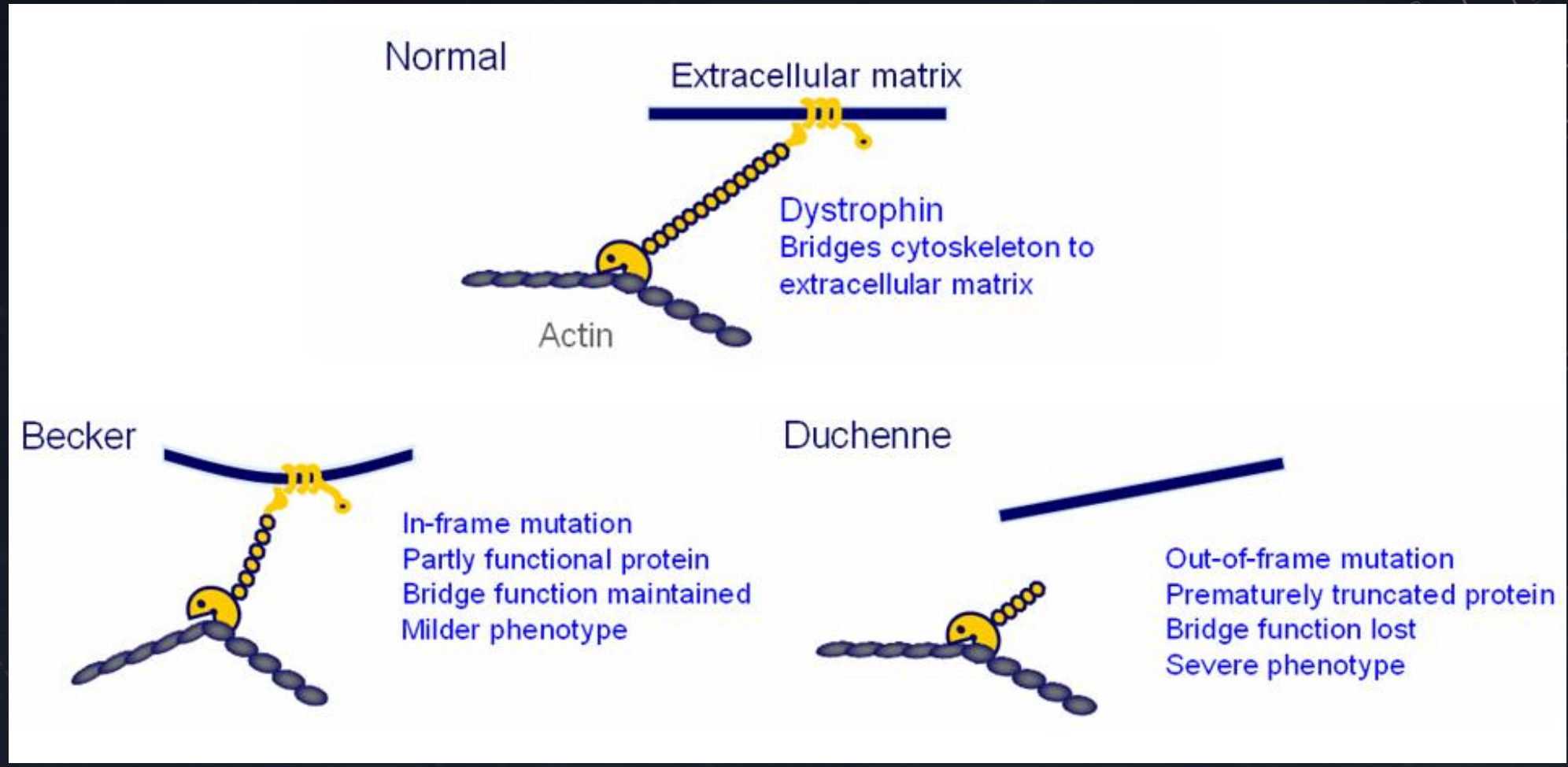
Fibrotic muscle

DMD MUTATIONS

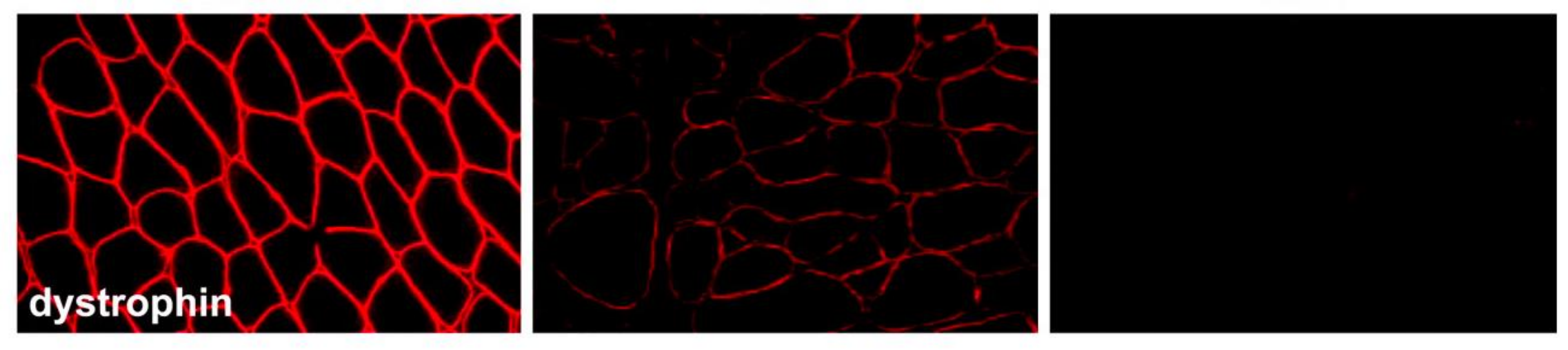
- Many different variants in the *DMD* gene
  - Deletion – missing a chunk of the *DMD* code
  - Duplication – extra segment of genetic code
  - Small spelling mistakes

- Out of frame mutations => Duchenne muscular dystrophy
- In frame mutations => Becker muscular dystrophy

“IN FRAME” AND “OUT OF FRAME” MUTATIONS



BECKER VS DUCHENNE MUSCULAR DYSTROPHY



Normal Becker Duchenne

CURRENT STANDARD OF CARE FOR DMD

- Multidisciplinary care

CURRENT STANDARD OF CARE FOR DMD

- CORNERSTONE: Corticosteroids (prednisolone or deflazacort)
  - Benefits: Slows muscle decline, delays breathing/heart issues and scoliosis
  - Downsides: Side effects
    - Weight gain
    - Short stature
    - Low bone density
    - Can affect mood and behaviour
    - Cataracts

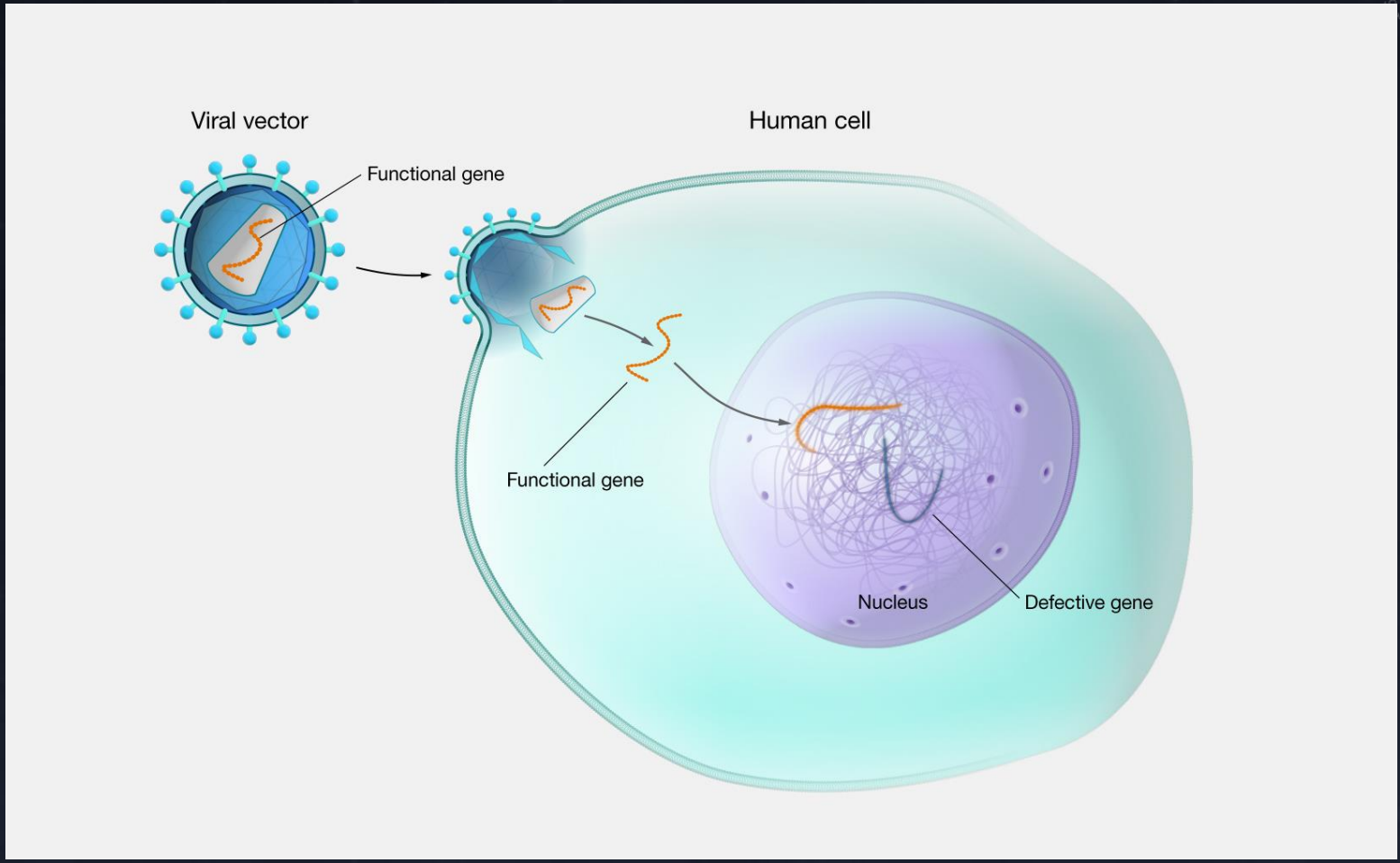
CURRENT STANDARD OF CARE FOR DMD

- Creatine monohydrate supplementation
  - Benefits: improved muscle strength
  - Downsides: cost $ / can be unpalatable

A NEW ERA IN DUCHENNE THERAPIES

- New therapies aim to intervene in the disease process.
- We will discuss five main types of emerging therapies:
  - Gene Therapy
  - Ataluren
  - Exon Skipping
  - "Smarter" Steroids (Vamorolone)
  - New Pathways (Givinostat)

GENE THERAPY



https://www.genome.gov/genetics-glossary/Gene-Therapy

GENE THERAPY

- Adeno-associated virus vectors (AAV)
  - Non-pathogenic, naturally occurring virus
- Infect a broad range of human cells
- Cause a mild immune reaction
- Don’t integrate into human genetic material
  - Reduces the risk of later cancer risk

GENE THERAPY FOR DMD

- Aim to introduce a functioning gene into muscle cells
- Needs to target skeletal muscles, including the diaphragm, and heart muscle
- Packaging challenges
  - The DMD gene is huge – it doesn't fit within a viral vector
  - Need to develop a "micro-dystrophin"
    - Based on dystrophin proteins found in adults with very mild Becker MD

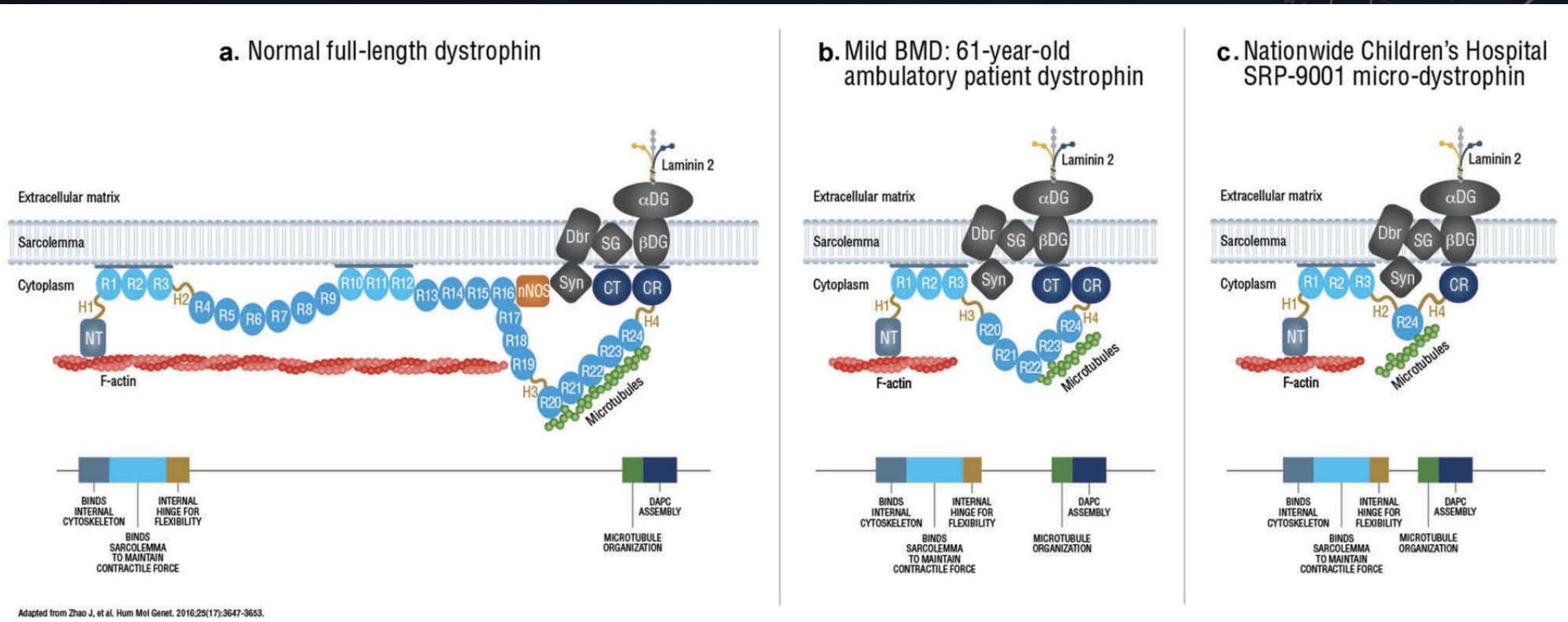


Figure 2. Dystrophin protein. Adapted from [47] with permission from Oxford university press.

GENE THERAPY

- Precluding factors
  - Pre-existing antibodies preclude a child from treatment
    - Up to 40% in older boys
  - Exons 1-17 variants – higher risk of immune mediated muscle inflammation
- One-time treatment
  - Antibodies to viral vector preclude participation in future gene therapy trials.
- Five products in trials
  - Sarepta (Elevidys (SRP9001)), Genethon, Solid Biosciences, REGENXBIO, Nationwide Children's Hospital
  - Discontinued: Pfizer (Fordadistrogene movaparvovec)

ELEVIDYS (DELANDISTROGENE MOXEPARVOVEC)

- FDA accelerated approval granted 2023
- Boys >4y with a confirmed mutation in DMD gene
  - Excludes mutations in exon 8/9
- Initial approval based on muscle biopsy data
  - Robust muscle dystrophin levels
  - But uncertain what level of dystrophin in muscle biopsy correlates with functional gains
- Trials looking at functional outcomes needed

ELEVIDYS

- EMBARK Phase III study
- 63 ambulatory 4-7y boys
- 2y follow up data:
  - Northstar ambulatory assessment:
    - 2.63 point improvement compared with baseline, controls -.25 pt decline
  - Time to rise (TTR):
    - 0.65s decline from baseline, controls 2.71s decline
  - 10m walk run test:
    - 0.04s improvement from baseline, controls 1.32s decline
  - Better results for subgroup with TTR 3.6-5s at baseline

Phase III EMBARK: 2-year results (intent-to-treat population)

At 2 years, delandistrogene moxeparvovec demonstrated significant and clinically meaningful functional improvements vs external controls[1]

Population (intent-to-treat):

- Ambulatory boys; aged 4–7 years*
- *DMD* mutations in exons 18–79, excluding exon 45

Dose:[2]

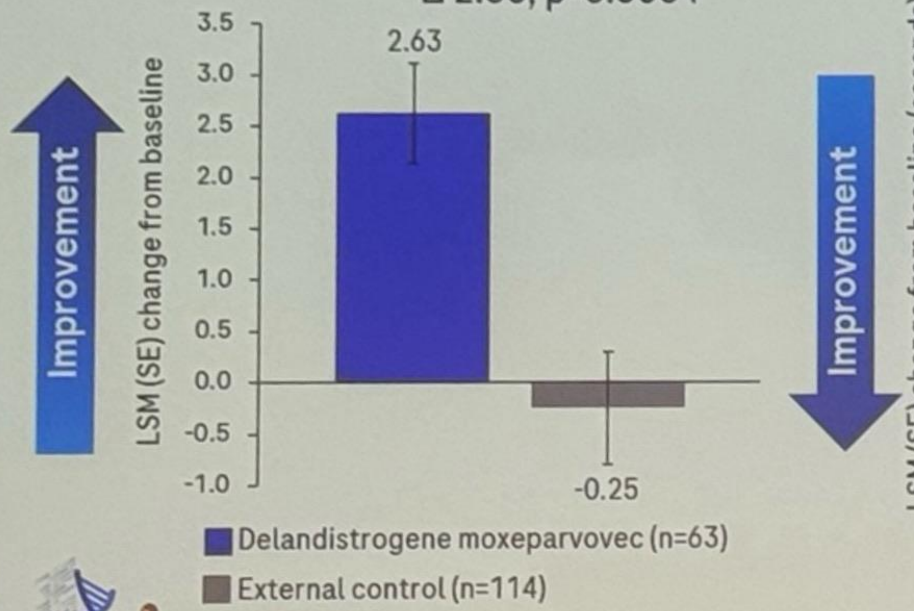
- 1.33×10^{14} vg/kg

N=63

2 years

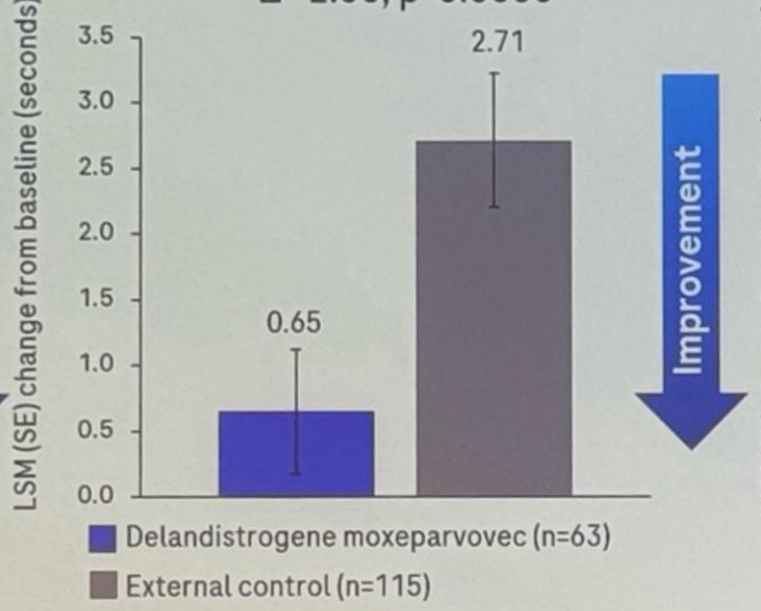
NSAA

Δ 2.88; p=0.0001



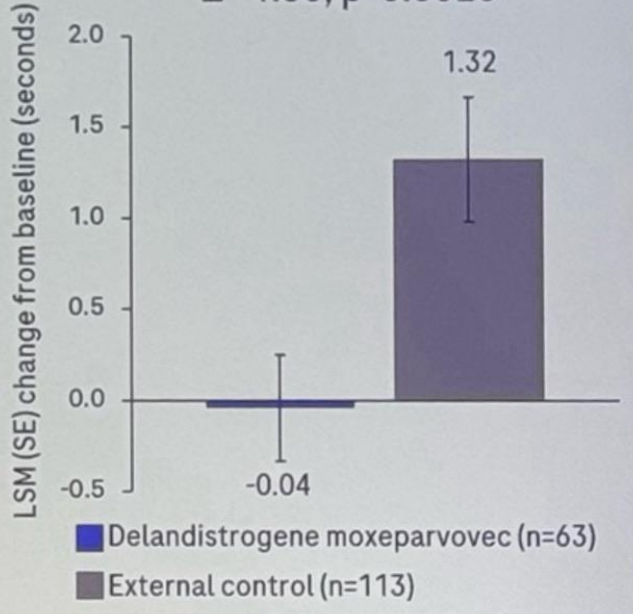
TTR

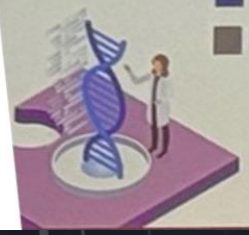
Δ −2.06; p=0.0033



10MWR

Δ −1.36; p=0.0028





All p-values reported are nominal and have not been adjusted for multiple comparisons.
*With baseline TTR <5.0 seconds.
10MWR, 10-metre Walk/Run; DMD, Duchenne muscular dystrophy; ITT, intent to treat; LSM, least-squares mean; NSAA, North Star Ambulatory Assessment; SE, standard error; TTR, Time to Rise; vg, vector genome.
1. Mendell JR, et al. Presented at MDA 2025 (Poster P169); 2. Mendell JR, et al. *Nat Med* 2025;31:332–41.

ELEVIDYS

- Phase I/II studies pooled analysis
- Ambulatory 4-7y boys, n=50
- 3y analysis
  - Northstar Ambulatory Assessment:
    - 2.55 point decline compared with baseline, controls 5.55 pt decline
  - Time to rise:
    - 2.79s decline from baseline, controls 4.59s decline
  - 10MWR:
    - 1.42s decline from baseline, controls 1.82s decline

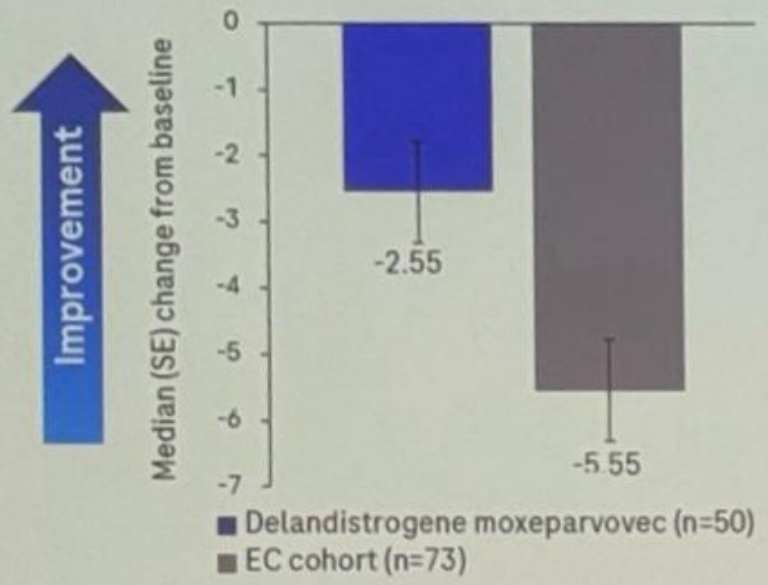
Phase I/II pooled analysis: 3-year results

In a pooled analysis, at 3 years, patients treated with delandistrogene moxeparvovec demonstrated functional benefit vs external controls[1]

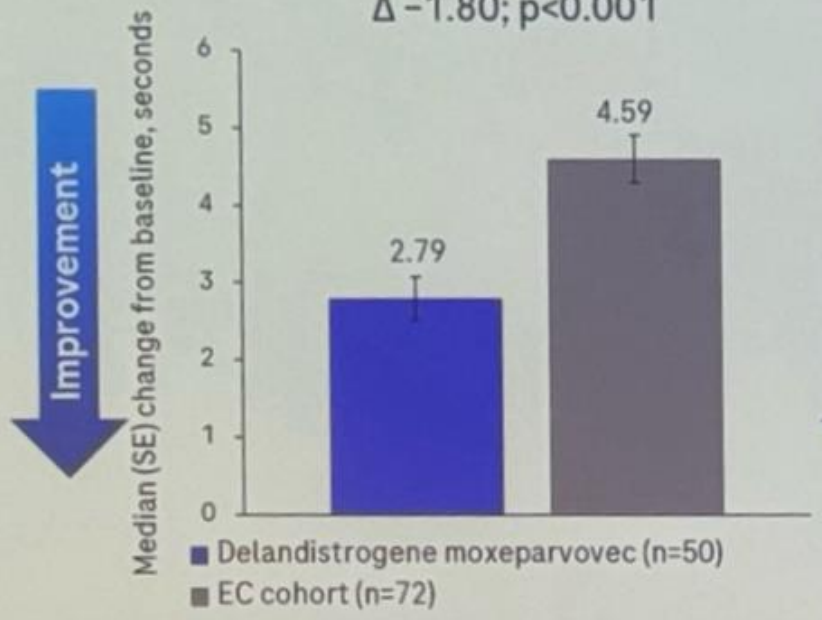
Population: Ambulatory boys; aged 4–7 years across Study 101, Study 102 and ENDEAVOR (Cohort 1) with baseline and Year 3 assessment values

N=50 | 3 years

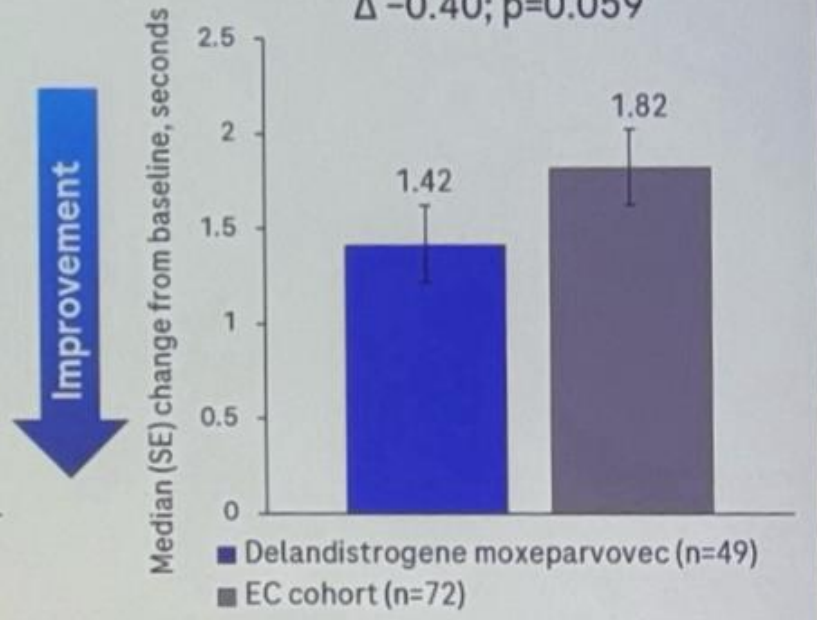
NSAA
Δ 3.00; p<0.001



TTR
Δ −1.80; p<0.001



10MWR
Δ −0.40; p=0.059



The functional improvements observed in the 3-year pooled analysis were consistent with the 5-year results observed in 4 patients who were treated in Study 101[2]

10MWR, 10-metre Walk/Run; EC, external control; NSAA, North Star Ambulatory Assessment; SE, standard error; TTR, Time to Rise.
1. Mendell JR, et al. Presented at MDA 2025 (Poster P167); 2. Mendell JR, et al. Presented at WMS 2024 (Poster 425P).

ELEVIDYS

- No evidence for effect on cardiac or respiratory function
- Cost USD 3.2 million

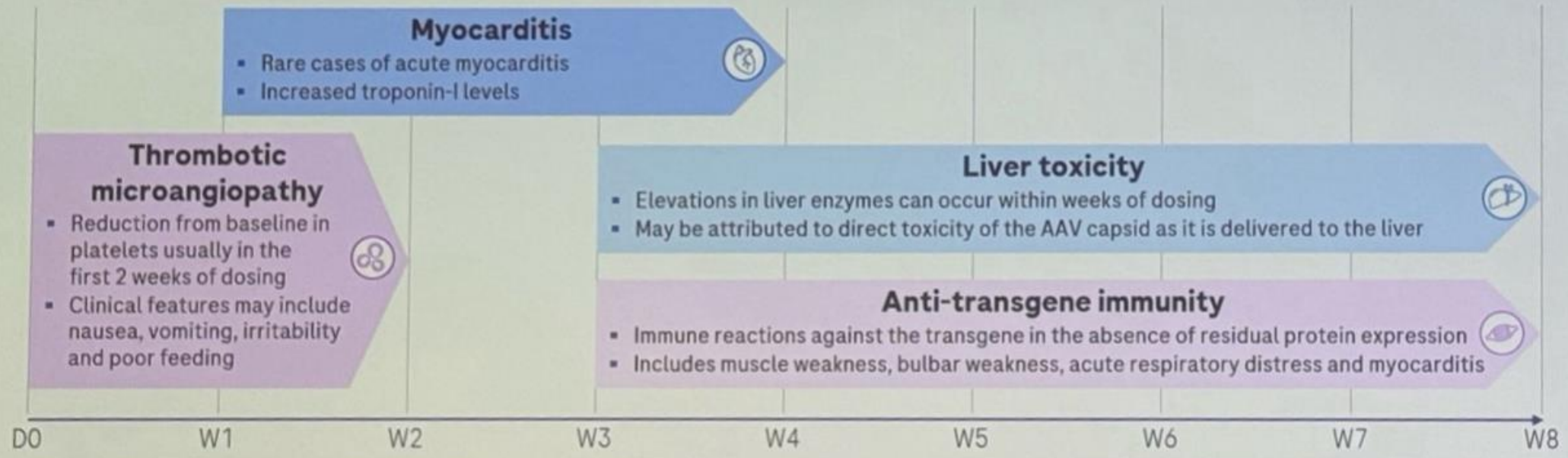
ELEVIDYS SIDE EFFECTS

- 207 + 678 patients dosed May 2025
- High dose needed, especially in older boys, can cause a strong immune response
  - Vomiting, nausea
  - Liver toxicity, including fatal liver failure n=3
  - Low platelet cell count with bleeding risk
  - Heart inflammation (myocarditis)
  - Muscle inflammation/breakdown (myositis/rhabdomyolysis)
- Treatment with steroids (1mg/kg, 3mo course) to reduce risk of side effects.
- Some mutations associated with higher risk of immune reactions excluded from treatment

AAV-based gene therapies are associated with potential immune-related safety risks that require close monitoring

Roche

Improved recognition, prevention and treatment of AEs related to AAV-based gene therapy is needed



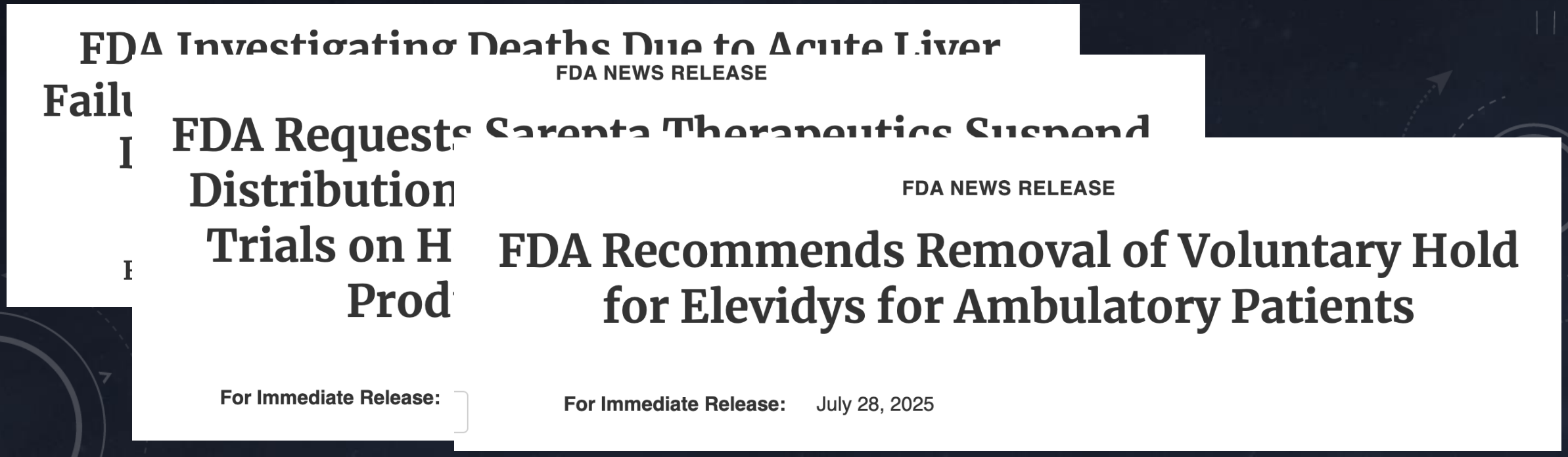
Monitoring (safety events are usually first observed in the above timeframe, but may happen earlier or later)

- Laboratory parameters, including full blood count, liver enzymes, troponin-I, in the days to weeks following gene therapy
- Cardiac MRI and ECHO

AAV, adeno-associated virus; AE, adverse event; ECHO, echocardiogram; MRI, magnetic resonance imaging.
Servais L, et al. *Neuromuscul Disord* 2023;33:884-96.

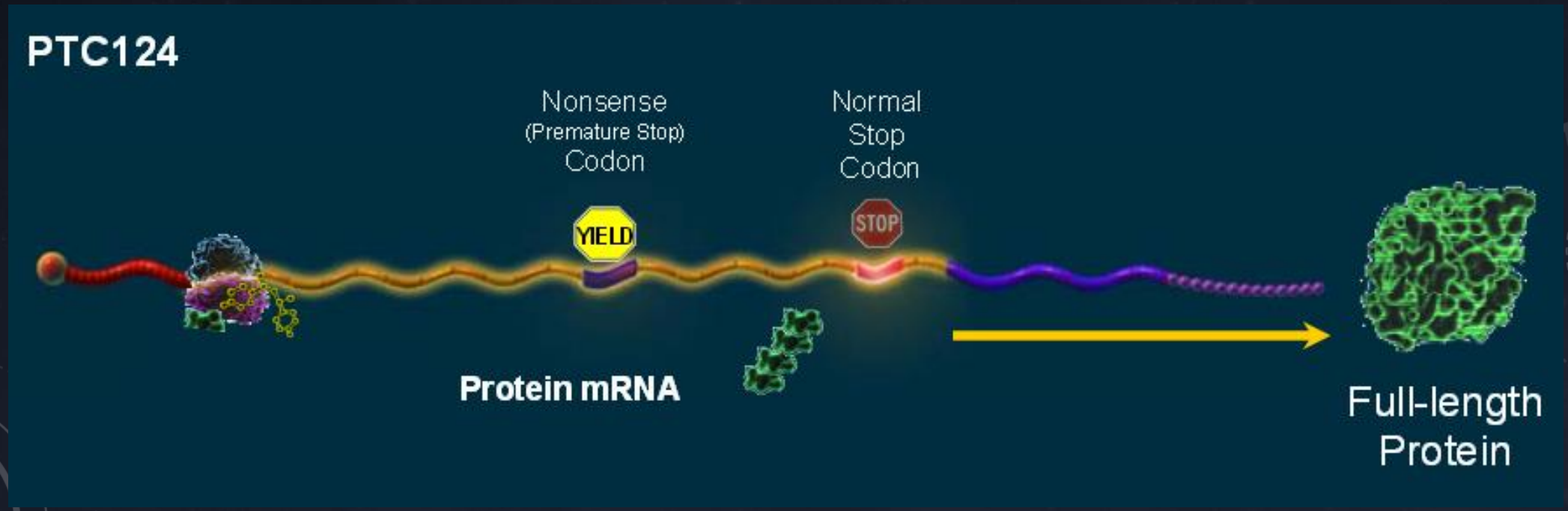
LIVER FAILURE RELATED DEATHS

- 3 deaths related to liver failure
- All trials in non-ambulatory patients on hold
- Across all gene therapy trials - 0.3% risk of fatality
- May be a role for stronger immune suppressing therapies



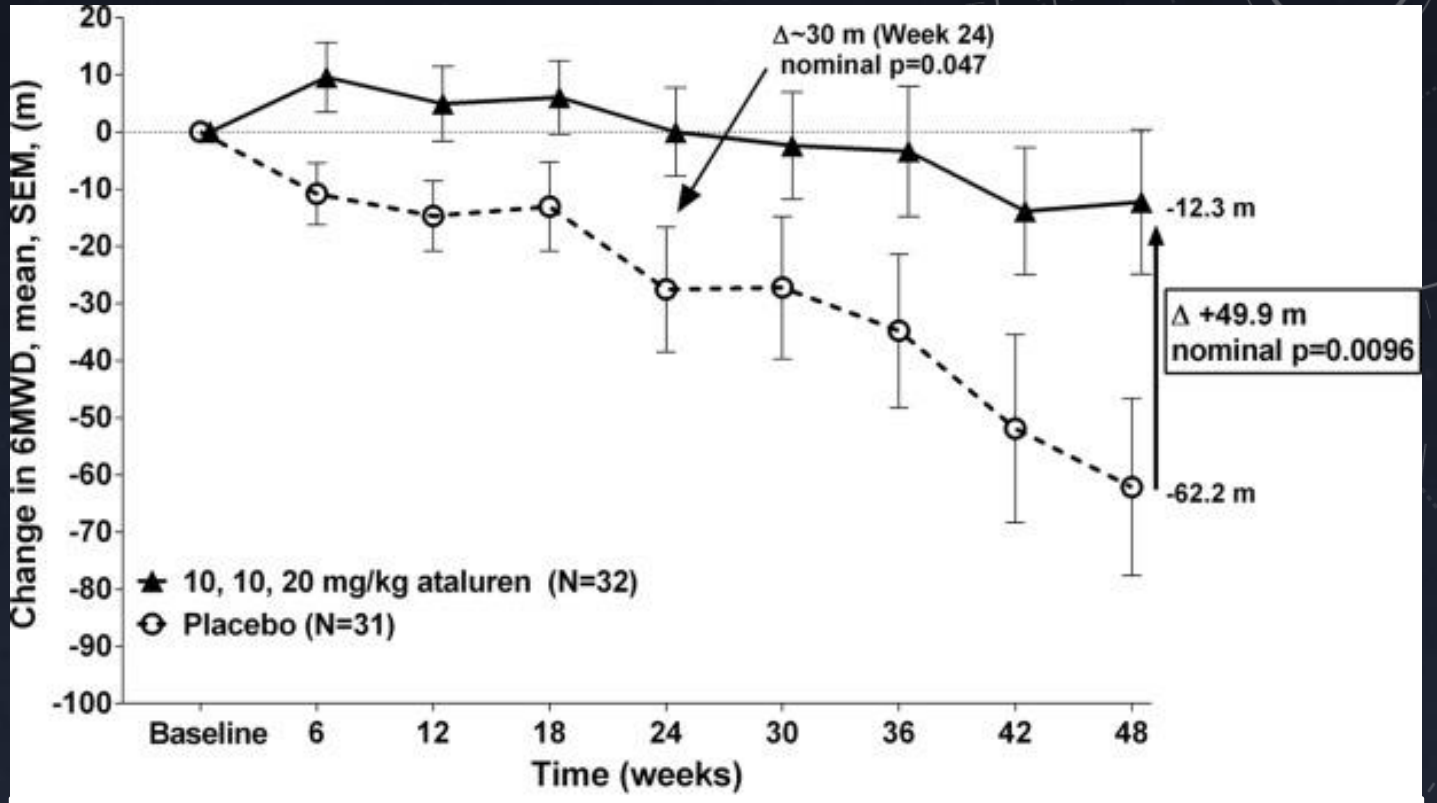
PTC124 (ATALUREN)

- Promotes the read through of premature stop codons (10-15% DMD)
- Developed in 2007
- Initial promising results in mouse studies



PHASE 2B

- 174 patients randomized
- Primary outcome - change in 6 minute walk distance over 48 weeks
- Terminated when it failed to demonstrate improvement in 6MWD
- Reinstated after subgroup analysis – stratified by 6 minute walk distance



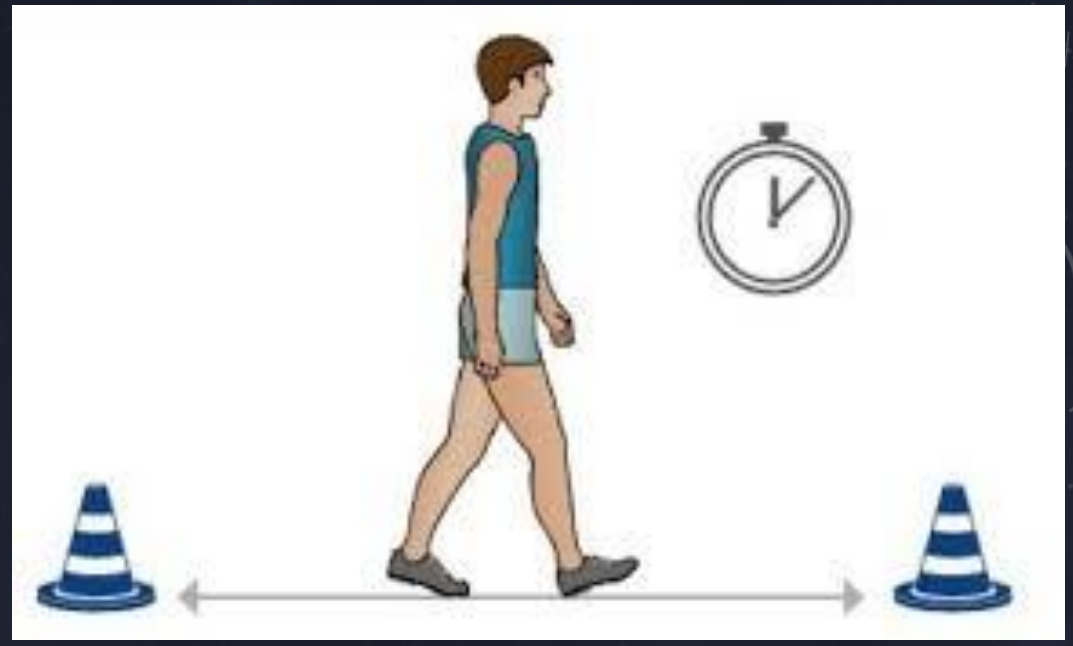
”Ambulatory decline phase”
7-16y, baseline 6MWD >150m and ≤80% predicted, taking corticosteroids.

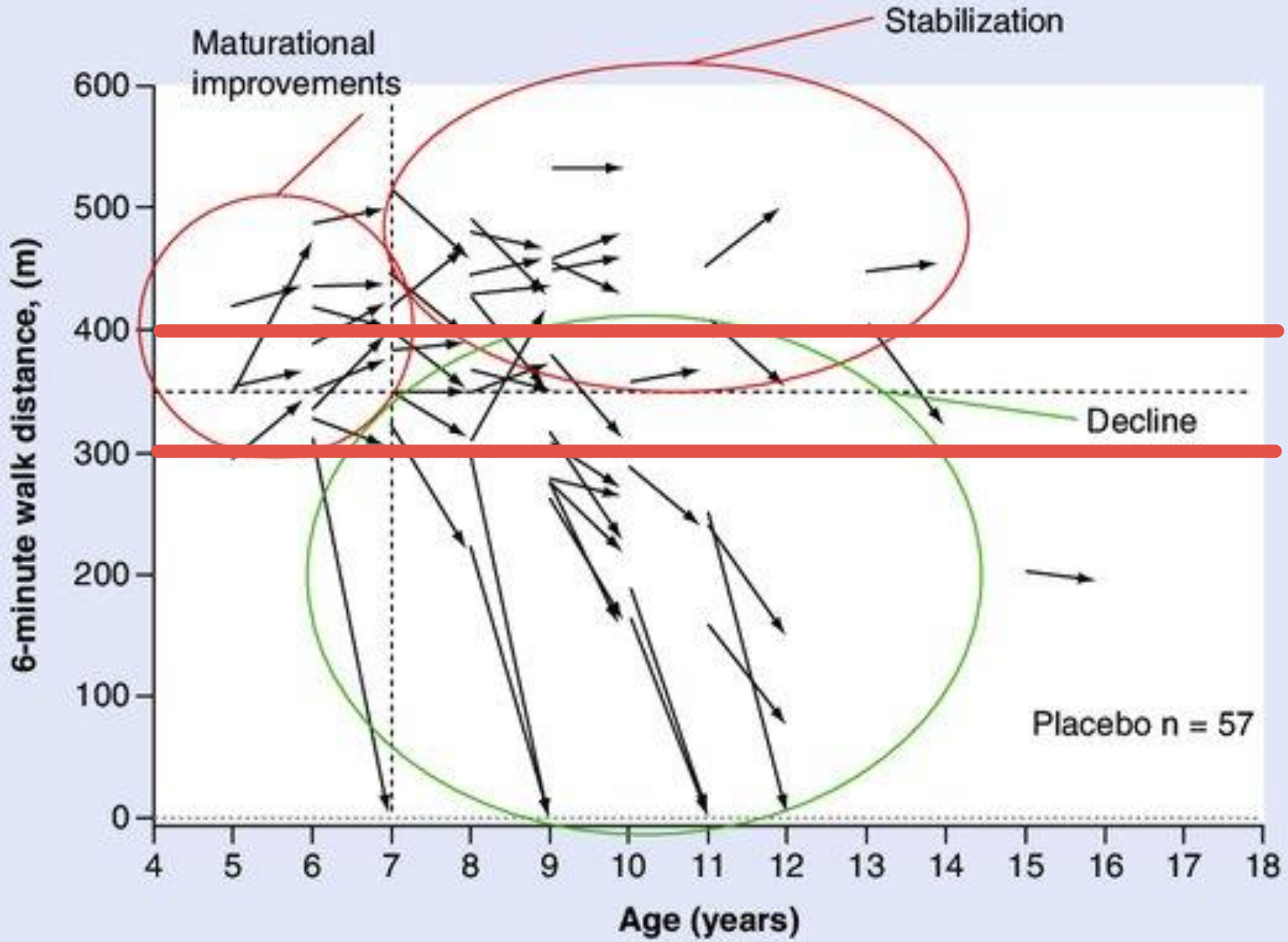
PTC124 (ATALUREN)

- 2014 – Approved by European Commission July
- 2017 – First of multiple declines by FDA – inconclusive efficacy
- Phase III (ACT-DMD) (2013-2015)
  - 230 boys ≥7 and ≤16 years
  - Receiving corticosteroids ≥6mo
  - Baseline 6MWD ≥150m and ≤80% predicted for age and height
  - ITT – no significant improvement
  - Subgroup analysis ≥300 - <400m
- Remains unapproved by FDA
- ~NZD 500 000 per year for a 30kg child

OUTCOME MEASURE SELECTION

- The first large scale randomized control trials in DMD
- Endpoints need to be appropriate to the treatment under investigation
- Natural history studies provide valuable data when planning trial outcomes and duration
- Extensive work on outcome measure validation
  - 6 minute walk test (6MWT)
  - Time function tests
    - 10m walk/run test
    - 4- stair climb
  - North Star ambulatory assessment (NSAA)
    - Specifically developed for DMD patients
    - Assesses a wider range of physical capability





McDonald CM, Henricson EK, Abresch RT, et al. The 6-minute walk test and other endpoints in Duchenne muscular dystrophy: longitudinal natural history observations over 48 weeks from a multicenter study. Muscle Nerve. 2013;48:343–56.

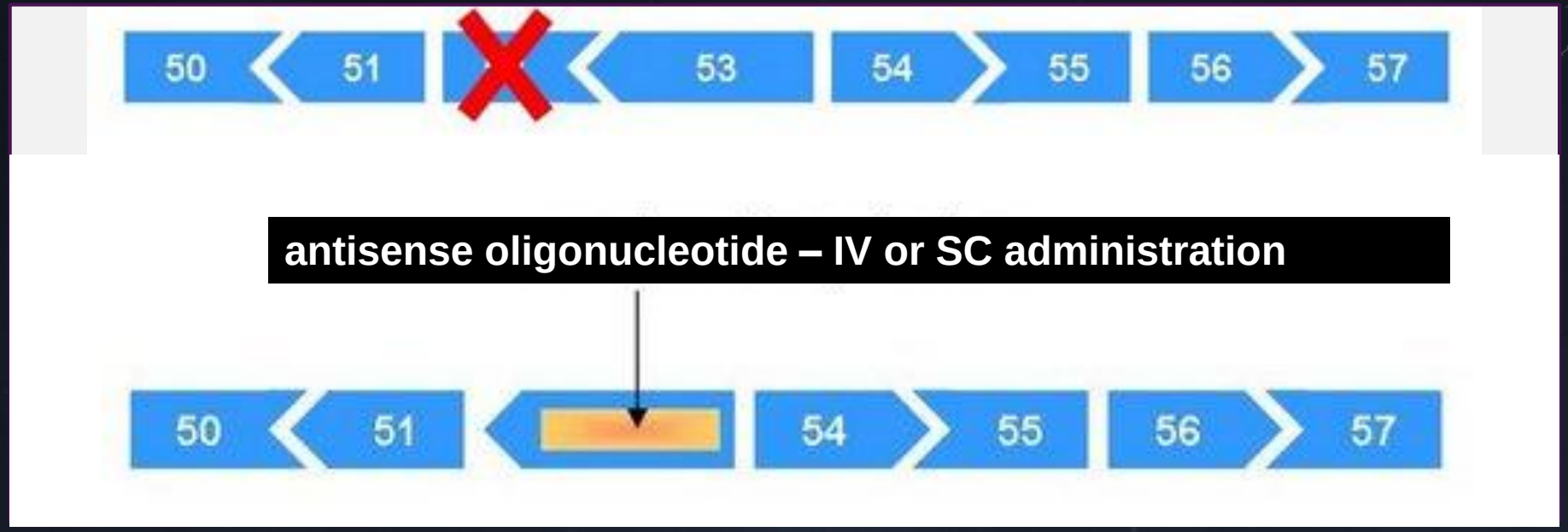
6MWD AS AN OUTCOME MEASURE

- 300-400m may be the optimal subgroup to show a treatment effect in a 1y clinical trial.
- Effort and fatigue dependent
  - Long trial assessment days
  - Travel to trial centre

EXON SKIPPING THERAPIES

- DMD gene has 79 exons – think of them as train cars
- In Duchenne a missing exon is like a missing train car, causing the connectors to not match up.
- Exon skipping uses a patch to cover one exon, allowing the train cars on either side to link up again, restoring the connection
- Results in a shorter, but functional, dystrophin protein.
  - Converts DMD into milder Becker MD

EXON SKIPPING THERAPIES



EXON SKIPPING THERAPY

- Mutation specific therapy – potential to benefit ~30% of patients
  - Exon 51 skipping - ~14% of patients
  - Exon 53 skipping - ~10% of patients
  - Exon 45 skipping - ~9% of patients
- Clinical studies started in 2006
- 4 drugs with FDA accelerated approval
  - Based on dystrophin levels in muscle biopsy NOT functional data
  - Additional research needed to determine long-term clinical outcomes.

EXON 51 SKIPPING

- Drisapersen and suvodirsen – discontinued 2013 – uncertain efficacy, and unacceptable injection site reactions
  - Phase III trial 186 patients - Primary outcome improvement in 6MWD not met

- Eteplirsen
  - Phase 1 and 2a studies
    - Western blot - increase in dystrophin levels in biopsies
  - Sept 2016 – FDA granted accelerated approval
  - Phase 3 trial ongoing – *Mission*
    - Final patients recruited - 150 total
    - Multinational collaboration – 51 sites

EXON SKIPPING THERAPY

Name	Target	FDA approval	EMA approval	Company
Eteplirsen (Exondys)	DMD exon 51	2016	Declined	Sarepta
Golodirsen (Vyondys)	DMD exon 53	2019	Declined	Sarepta
Casimersen	DMD eon 45	2021	Declined	Sarepta
Viltolarsen (Viltepso)	Exon 53	2020	Declined	NS Pharma

Plus others in clinical trials:
Exon 44 (NS Pharma), Exon 51 (Dyne), Exon 51 (Wade), Exon 44 (Avidity), Exon 2 dup (Nationwide children's hospital), Exon 51 (Biomarin)

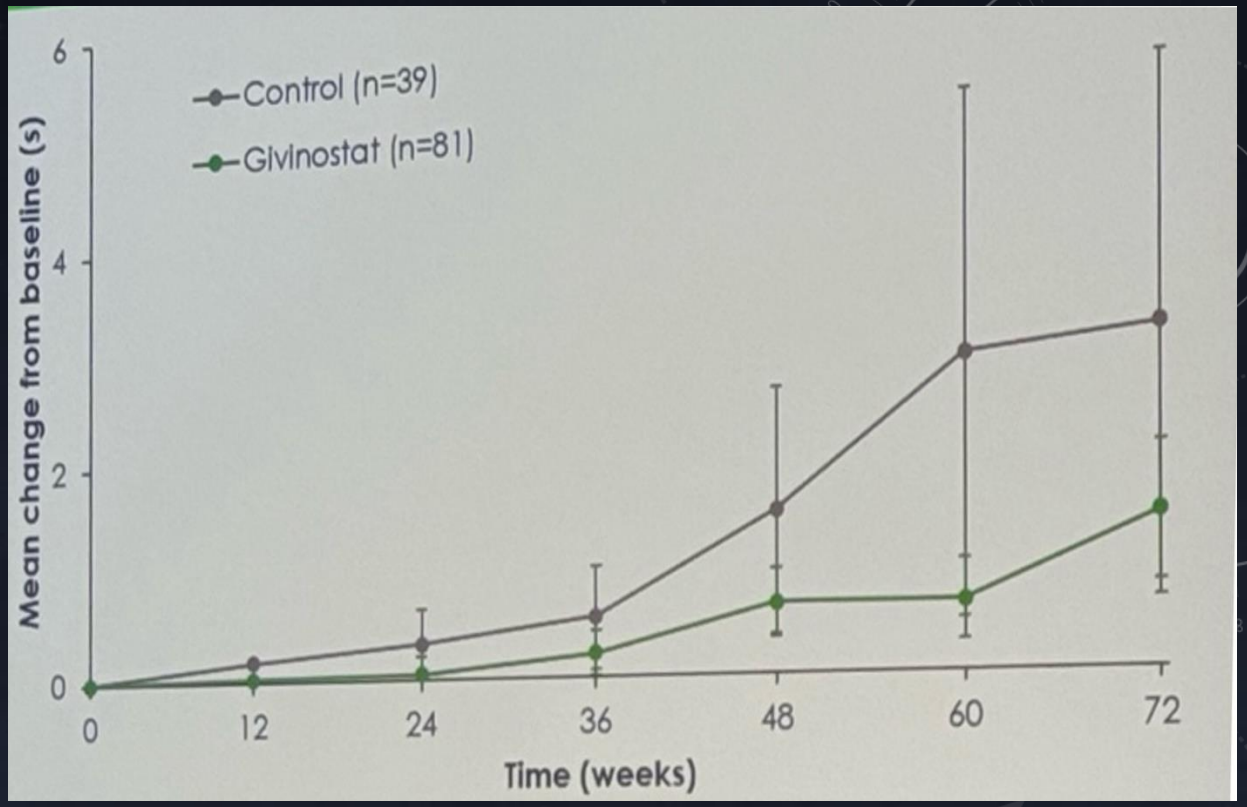
EXON SKIPPING

- More studies needed on long term functional outcomes
- Effect on heart muscle uncertain
- Potentially slow decline /convert to milder Becker MD
- Weekly intravenous infusion
  - Significant burden on families.

A NEW APPROACH – GIVINOSTAT (DUVYZAT)

- Can be used independent of DMD mutation
- Histone deacetylase (HDAC) inhibitor
  - HDAC overactivity -> reduced muscle repair -> increased fibrosis
- Givinostat allows the body's own repair systems to work better
- FDA approved March 2024, EC conditional approval June 2025, not yet available in UK except via Early Access Programme
- Cost per bottle ~USD 37,000 = NZD 1.16 million per year for a 30kg child

GIVINOSTAT (DUVYZAT)



- Phase 3 study – EPIDYS
  - 72 weeks treatment
  - 179 ambulant boys 6-17yrs
  - Northstar ambulatory assessment – 1.9 points higher @18mo
  - Trend towards slower decline in time to climb 4 stairs
    - Declined 1.25 vs 3.30s
  - Reduced fat infiltration on muscle MRI

GIVINOSTAT (DUVYZAT)

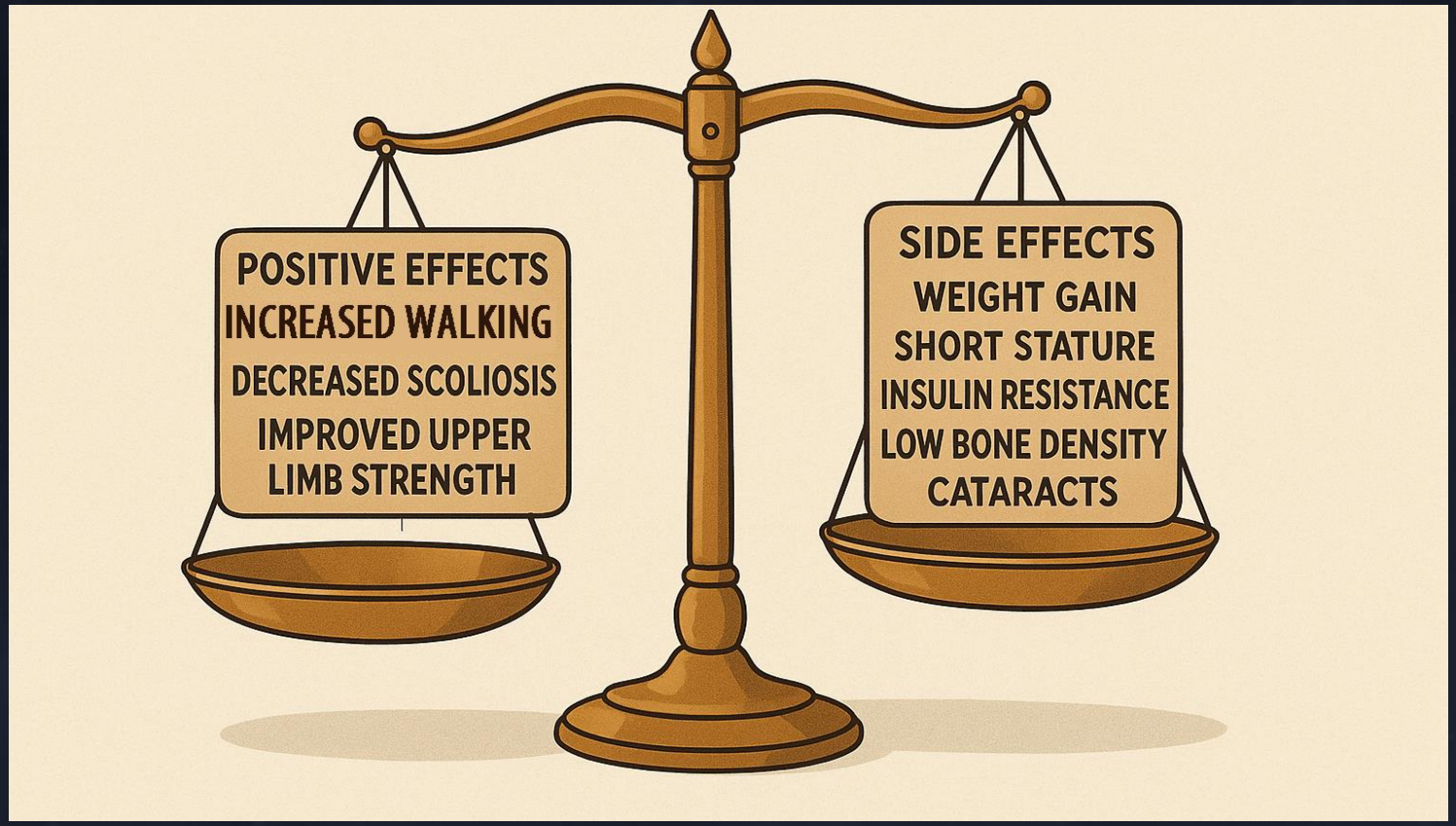
- Side effects
  - Gastro intestinal side effects common
  - Abdominal pain, diarrhoea and vomiting - usually improve with time
  - Low platelet counts in 20%
    - Increased risk of bleeding
    - May require dose reduction, but most can continue treatment.
  - Increased triglycerides (3-4% severe)

GIVINOSTAT (DUVYZAT)

- Project Hercules – set up by DMD UK
- Predictive modelling using the EPIDYS phase 3 trial and OLE study-51 to simulate the long term impact of givinostat
  - 3.2 life years gained
  - 4.4y longer in ambulatory health state (2.7y in early ambulatory, 1.7y late ambulatory)
  - Estimates loss of ambulation at 18.75 vs 14.75y
  - Loss of hand to mouth function 26.42y vs 19.42
  - Longer survival 34.24y vs 26.25y

VAMOLORONE (AGAMREE)

- Aiming to develop a steroid, with anti-inflammatory effect, but less side effects



VAMOLORONE (AGAMREE)

- Efficacy:
  - Equivalent efficacy to glucocorticoids
  - TTSTAND velocity - no significant difference between vamorolone and steroids
  - TTRW velocity – increased TTRW velocity compared with steroids (0.14s faster)
  - TTCLIMB velocity – no significant difference

Elhalag et al, Efficacy of vamorolone in treatment of Duchenne muscular dystrophy. A meta-analysis. Frontiers in Neurology, 2023

VAMOLORONE (AGAMREE)

- Adverse effects:
  - Height - less effect than corticosteroids - tendency towards ”catch up growth”
  - Weight - no statistically significant difference compared with glucocorticoids
  - Favorable bone biomarker profile - increased osteocalcin levels – might correlate with reduced impact on bone density
  - Adrenal suppression – similar with vamorolone therapy
  - Behaviour – limited data, effect uncertain, may have less side effects
  - Insulin resistance – trend towards less effect

VAMOLORONE (AGAMREE)

- EC approved Dec 2023 (4+ years), FDA approved Feb 2024 (2+ years)
- ~$10 000 per 100ml 40mg/ml - ~NZD 166, 000 per year @ 30kg
  - vs prednisolone NZD 350 per year

- Biocelect is the pharmaceutical company who have partnered with Santhera to market in Australia and New Zealand
  - Delayed any decision making regarding registration in Australia and NZ until late 2025

MEDICINE ACCESS IN NEW ZEALAND

- MedSafe / Pharmac
- Part 1 – The Long Road to Access: Understanding Drug Development, Approval and Funding pathways

WHERE TO FROM HERE

- Accurate population data - Join Punaha Io, the New Zealand Neurogenetic Disease Registry
  - *neurogenetics@adhb.govt.nz*
- Add your voice - stories matter in access decisions
- Political awareness and advocacy around medicines access