Gene Therapies in Neuromuscular Disorders: Changing the Future of Patient Care

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September 20, 2024

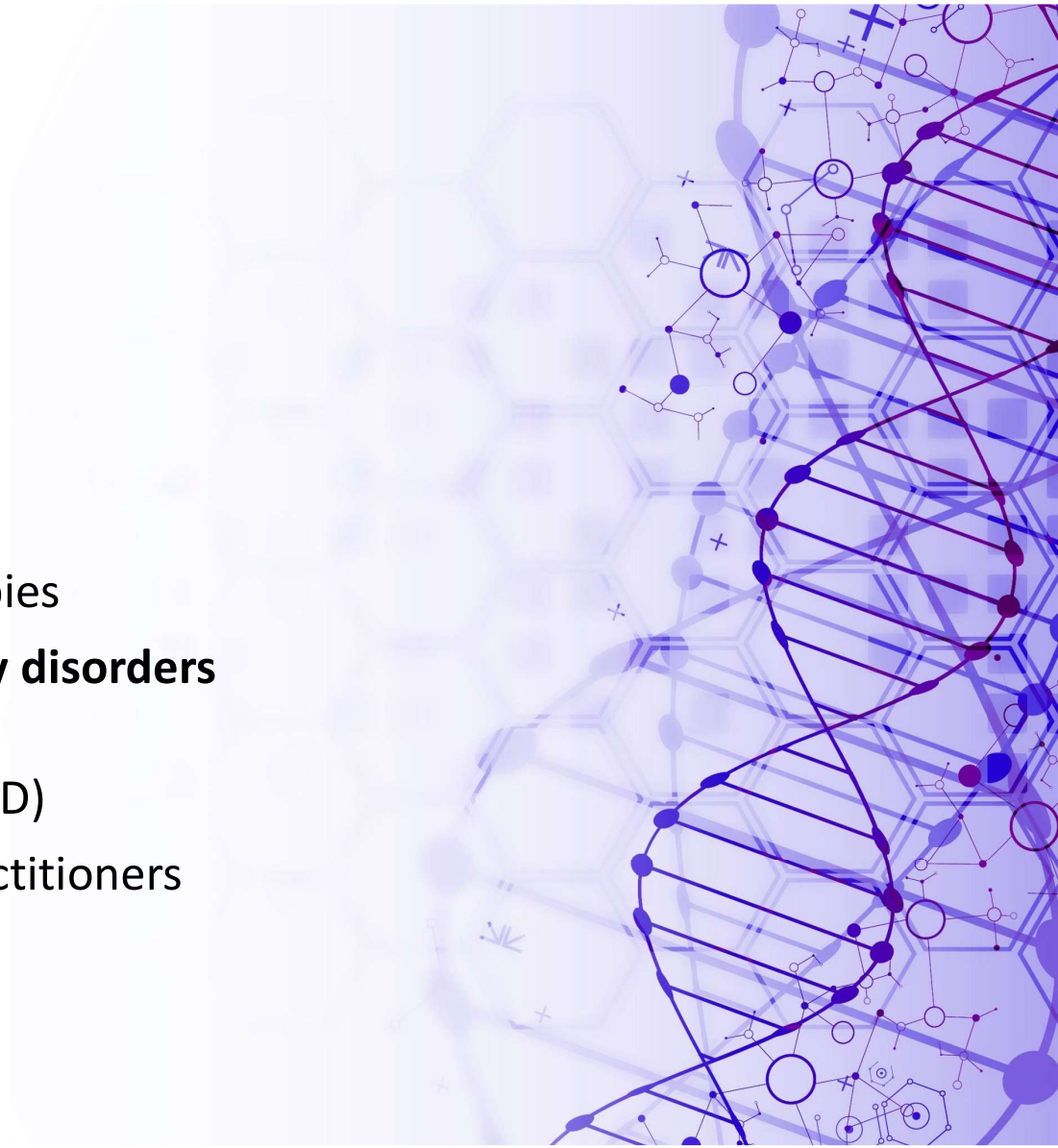
Conflict of Interest

I have served on the following advisory boards:

- Sarepta
- Biogen
- Scholar Rock
- ITF therapeutics
- Catalyst

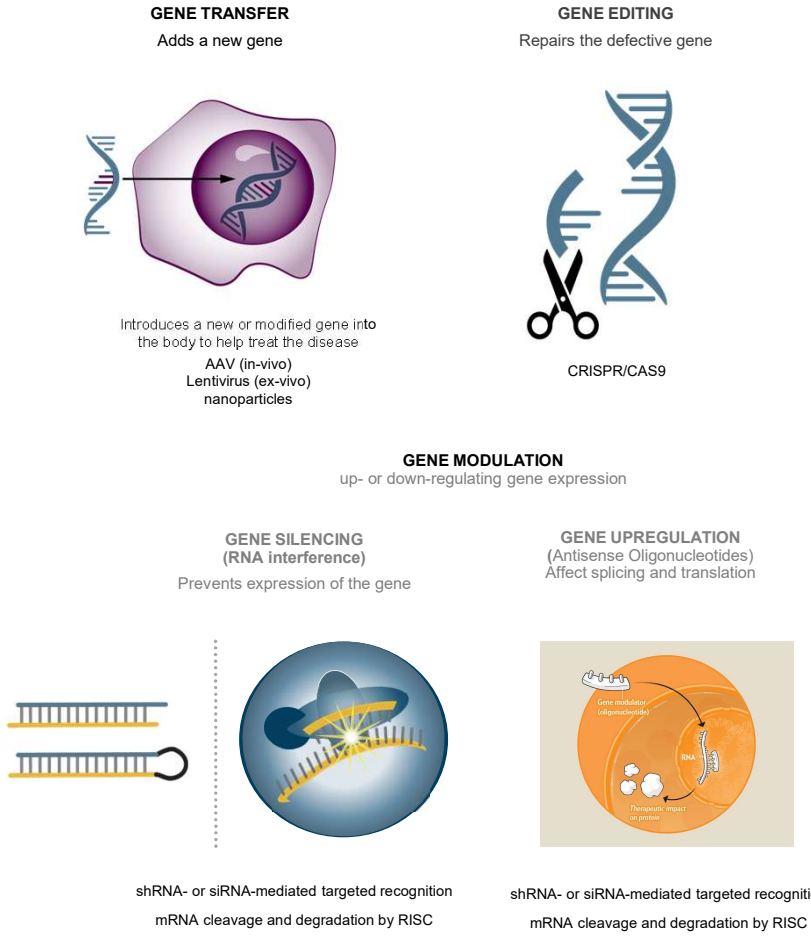
Outline

- Introduction to gene therapies
- Overview of FDA-approved gene therapies
- **Neuromuscular gene therapies and key disorders**
  - Spinal Muscular Atrophy (SMA)
  - Duchenne Muscular Dystrophy (DMD)
- Practical considerations for general practitioners
- Future directions



What are Gene Therapies?

- Strategy to treat or prevent disease by modifying a patient's genetic material
- Targets root cause- mutated or missing gene
- Not necessarily a cure



FDA Approved Gene Transfer Therapies

Ophthalmology

- Retinal Dystrophy (Biallelic RPE65 mutation)

  Voretigene neparvovec (Luxturna, 2017)- AAV2 delivers RPE65 gene via subretinal injection

Neurology

- Cerebral Adrenoleukodystrophy (boys)

  Elivaldogene autotemcel (Skysona, 2022)- Lentiviral ABCD1 gene in stem cells

Urology

- Bladde cancer

  Nadofaragene firadenovec-vncg (Adstiladrin, 2022) – AAV5 delivers the interferon-alpha-2b (IFNα2b) gene

Hematology

- β-thalassemia requiring transfusions:

  Betibeglogene autotemcel (Zynteglo, 2022)- Lentiviral (Ex-vivo) β-globin gene in stem cells
- Sickle Cell Disease and β-thalassemia

  Exagamglogene autotemcel (Casgevy, 2023)- CRISPR-Cas9 edits BCL11A enhancer
- Sickle Cell Disease

  Lovotibeglogene autotemcel (Lyfgenia, 2023)- Lentiviral anti-sickling β-globin
- Hemophilia B

  Etranacogene dezaparvovec-drlb (Hemgenix, 2022)- AAV5 delivers B-domain-deleted human factor VIII
- Hemophilia A

  Valoctocogene roxaparvovec-rvox (Roctavian, 2023) – AAV5 delivers a DNA sequence encoding the Padua variant of human Factor IX

FDA Approved Gene Therapies- Neuromuscular

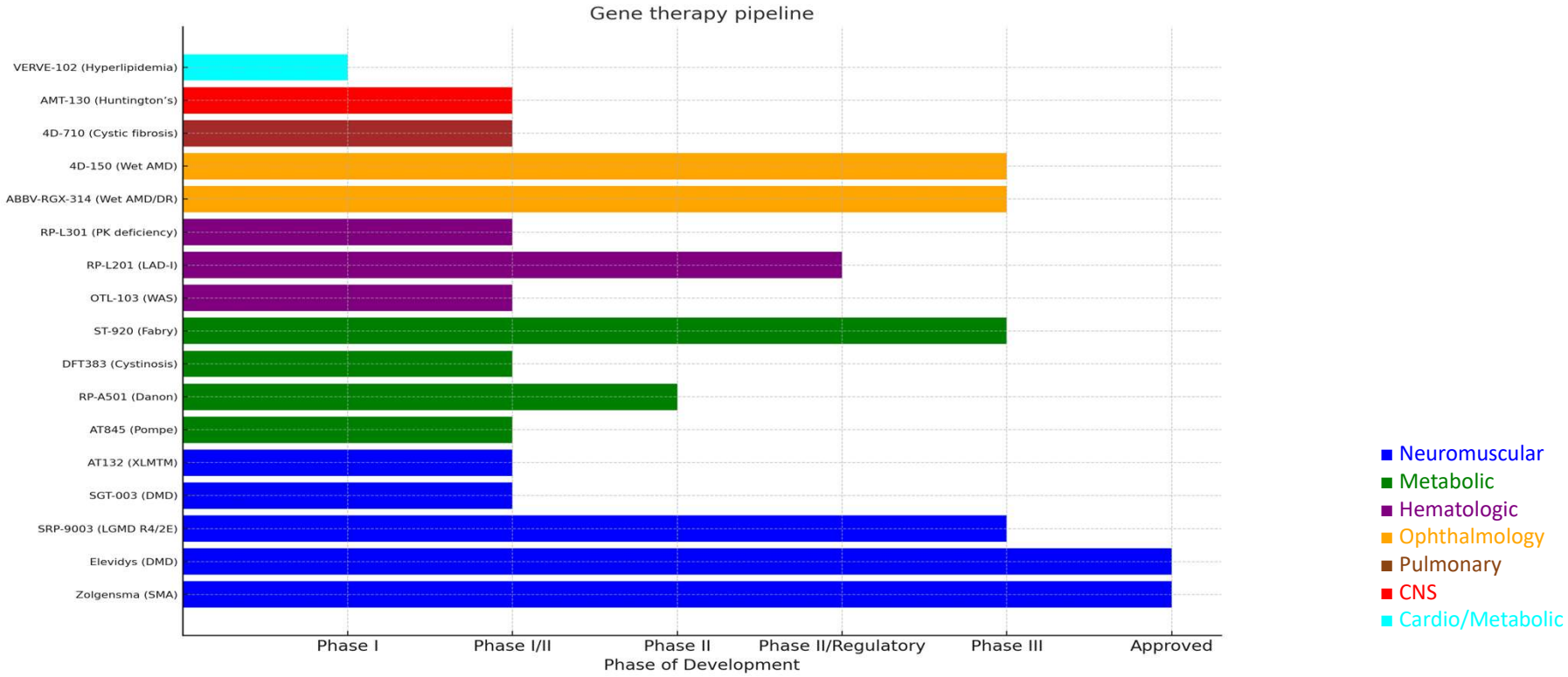
Spinal Muscular Atrophy (SMA)

- Onasemnogene abeparvovec (Zolgensma, 2019)- AAV9 vector delivers SMN1 gene
- Spinraza (Nusinersen, 2016) - Intrathecal SMN2 splicing modulation
- Risdiplam (Evrisdy, 2020)- Oral SMN2 splicing modulation

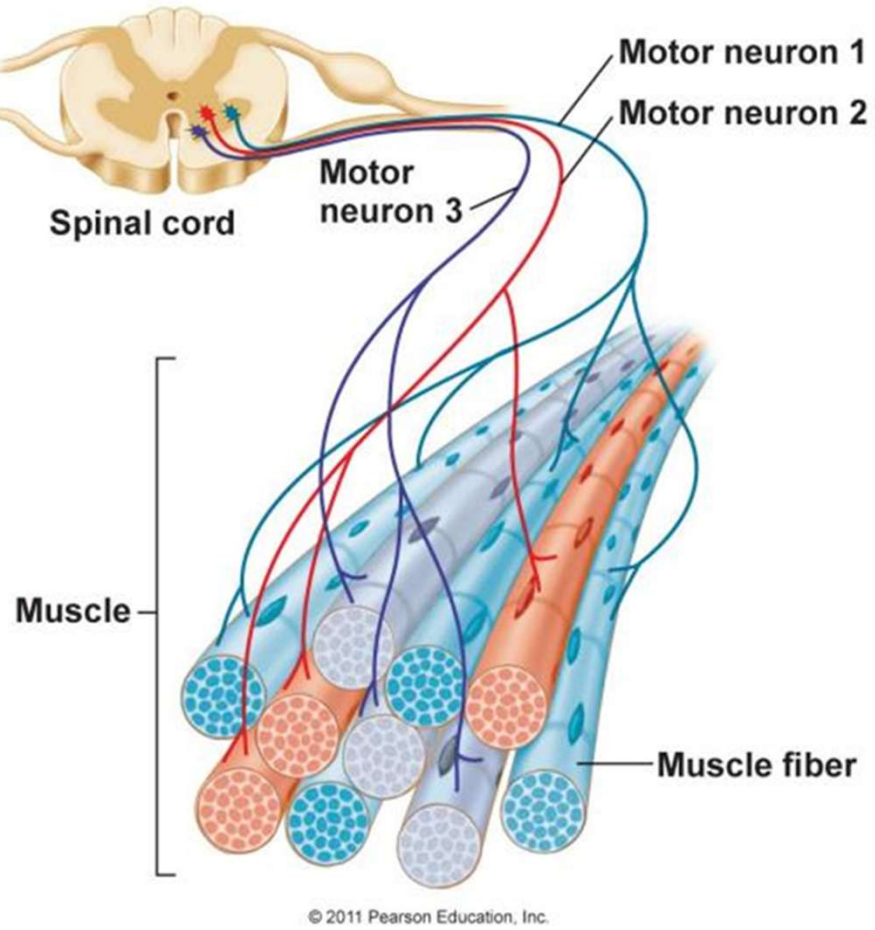
Duchenne Muscular Dystrophy (DMD)

- Delandistrogene moxeparvovec (Elevidys, 2023–24)- AAVrh74 vector delivers micro-dystrophin
- Exon skipping drugs

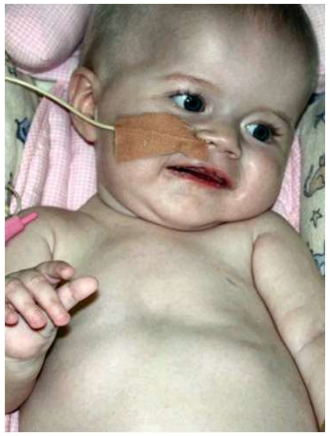
Gene Therapy Pipeline

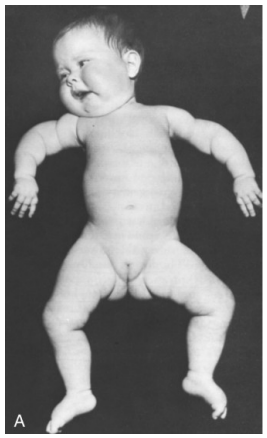


Key Neuromuscular Disorders



Spinal Muscular Atrophy (SMA)





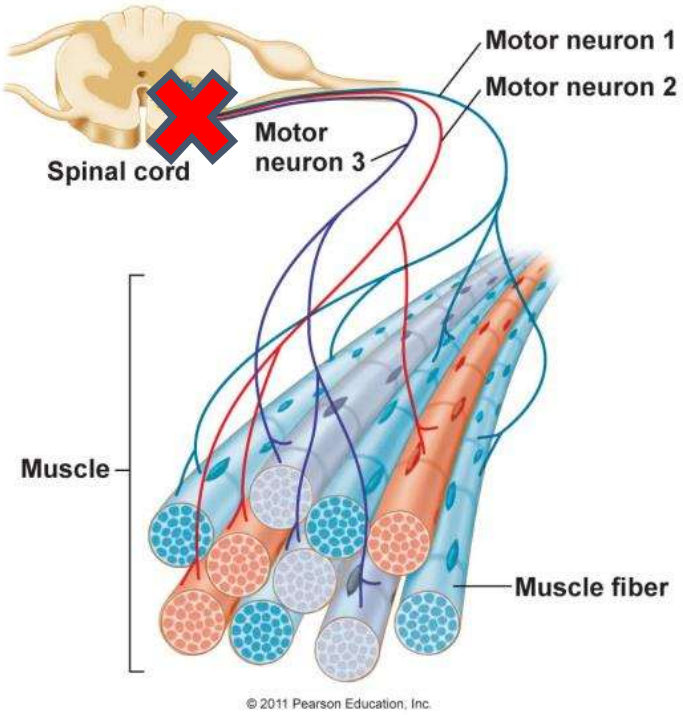
- 1-2 in 6,000 - 10,000 live births
- Key symptom: proximal weakness & muscle atrophy
- Spectrum of disease
  - Classification based on maximum motor milestone achieved
- 60% type I SMA (Werdnig-Hoffman disease)

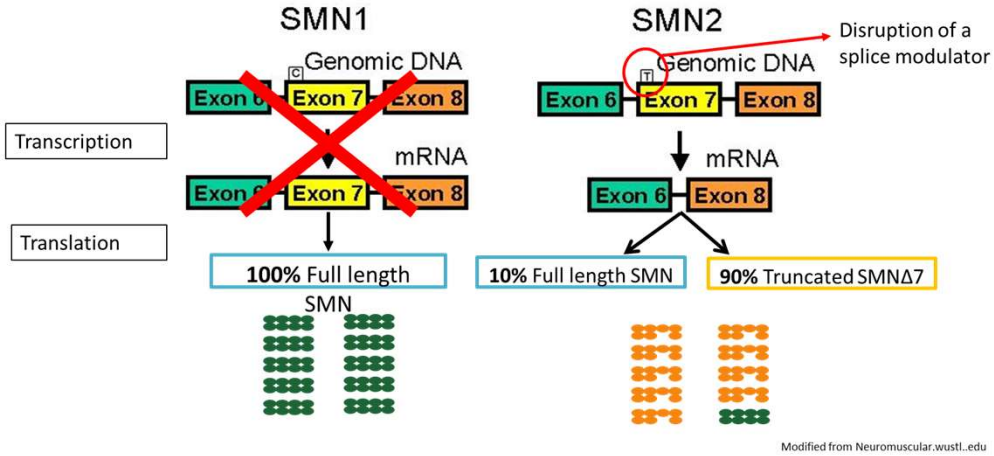
Table 1. Classification of Spinal Muscular Atrophy 5q13

Type	Onset	Maximum Function Achieved	Life Expectancy
0	Prenatal	Needs respirator support at birth	Fatal at birth without respirator support
1	<6 mo	Sits with support only	<2 y
2	6-18 mo	Sits independently when placed	10-40 y
3	>18 mo	Walks independently ε25 steps	Indefinite
4	>5 y	Walks normally	Indefinite

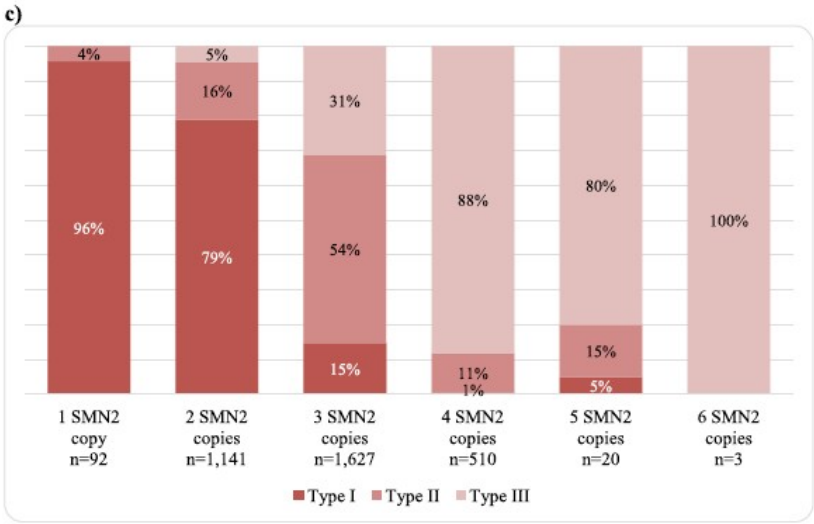
Russman, 2007

SMA: Genetic Pathophysiology





More copies of SMN2 = less severe phenotype



M. Calucho et al./Neuromuscular Disorders 28 (2018) 208–215

SMA Diagnosis

- Newborn Screen – now implemented in all states
  - WA in 2020
- Confirmatory testing with SMN1 and SMN2 copies
- Usually, normal basic labs including CK

** Early detection = early treatment = prevention of motor nerve loss**

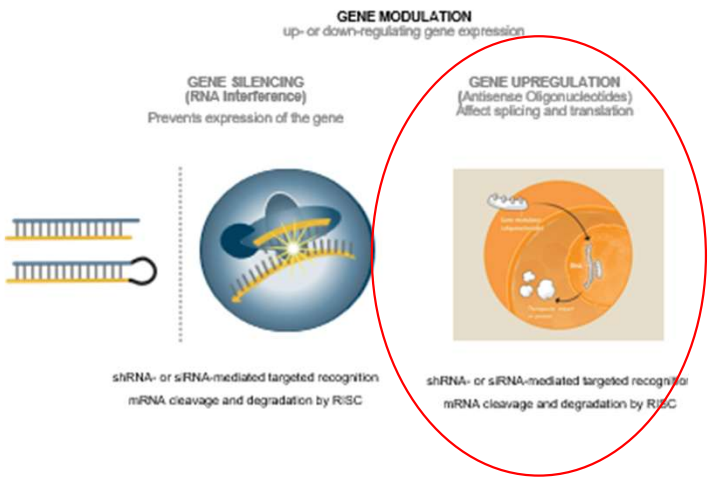
SMA: Disease Modifying Therapies

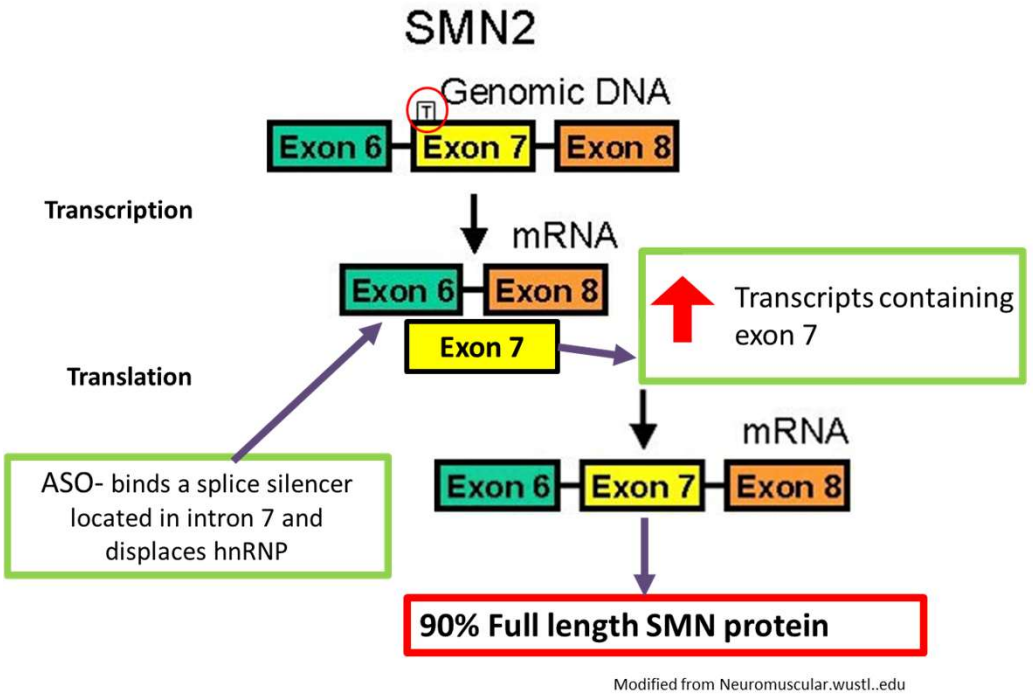
Nusinersen (ASO)

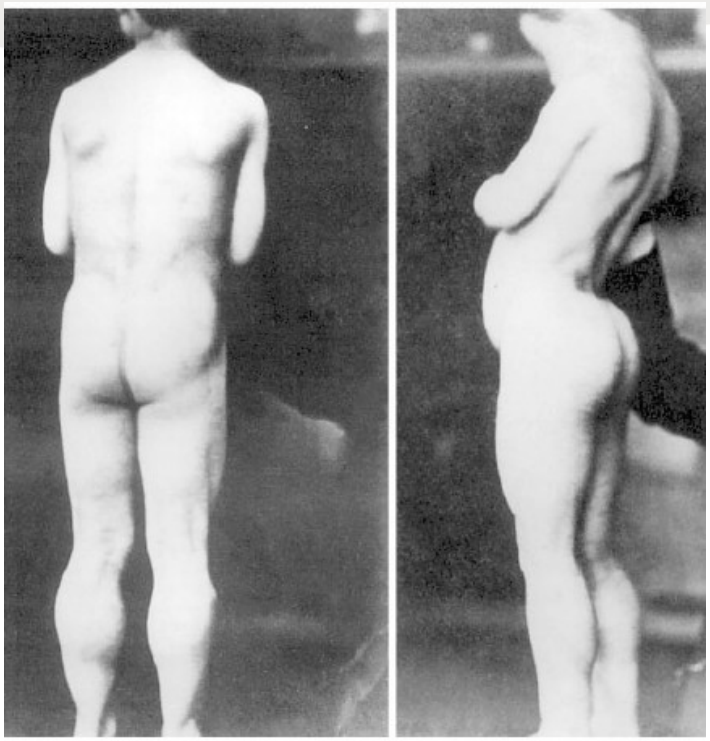
- Intrathecal - Q4 months

Risdiplam

- Oral- daily dosing







Case 1, age 9. Photo by Duchenne. (excerpted from Tyler,K. 2003. Muscle & Nerve, 28: 402)

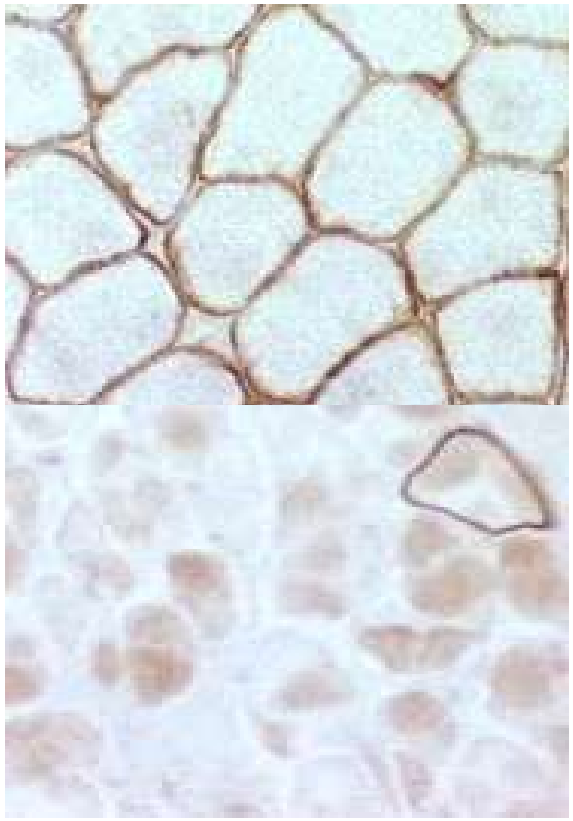
Duchenne Muscular Dystrophy (DMD)

Most common neuromuscular disease of childhood

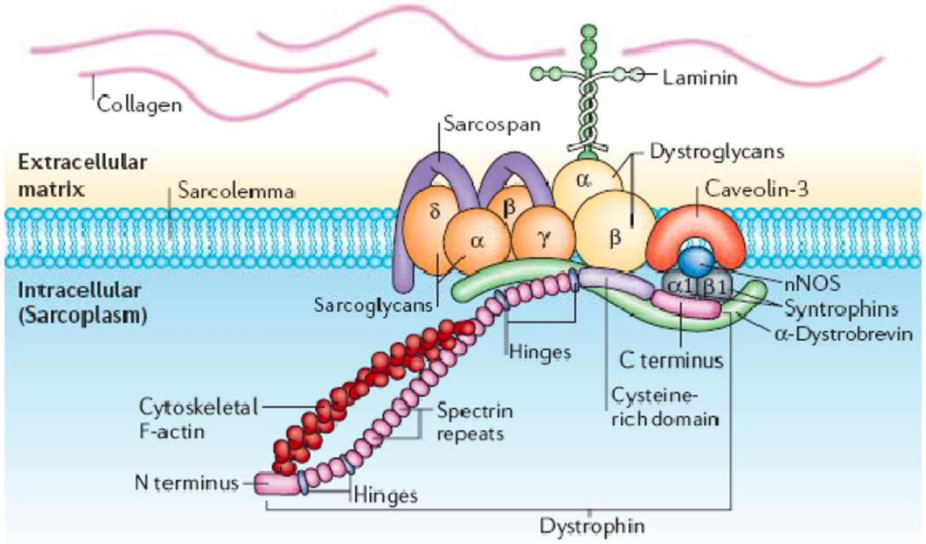
Affects 1 in 3500 – 5000 live male births

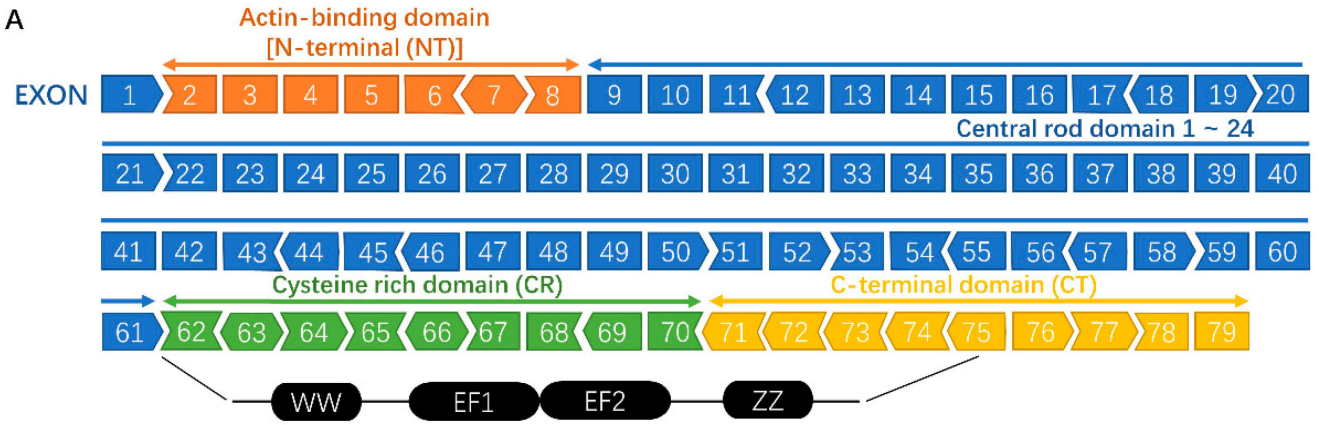
About 20,000 new cases each year (400-600 in the US)

Duchenne MD: Genetic Pathophysiology



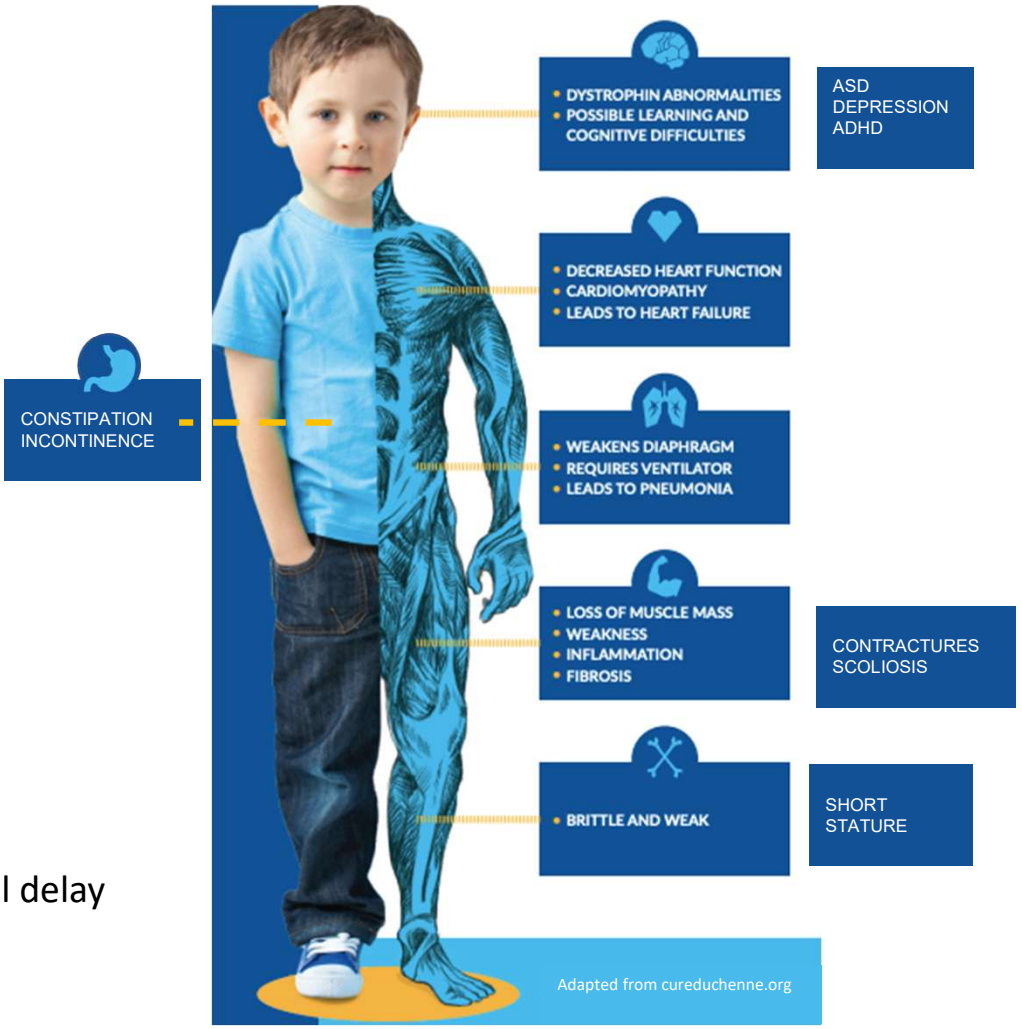
DMD
Encodes dystrophin
2.4 Mb
79 exons

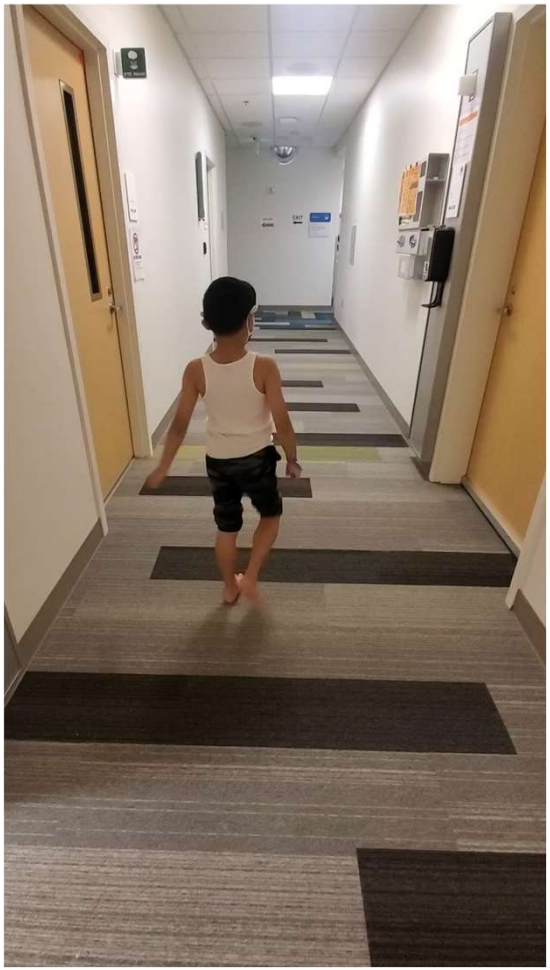




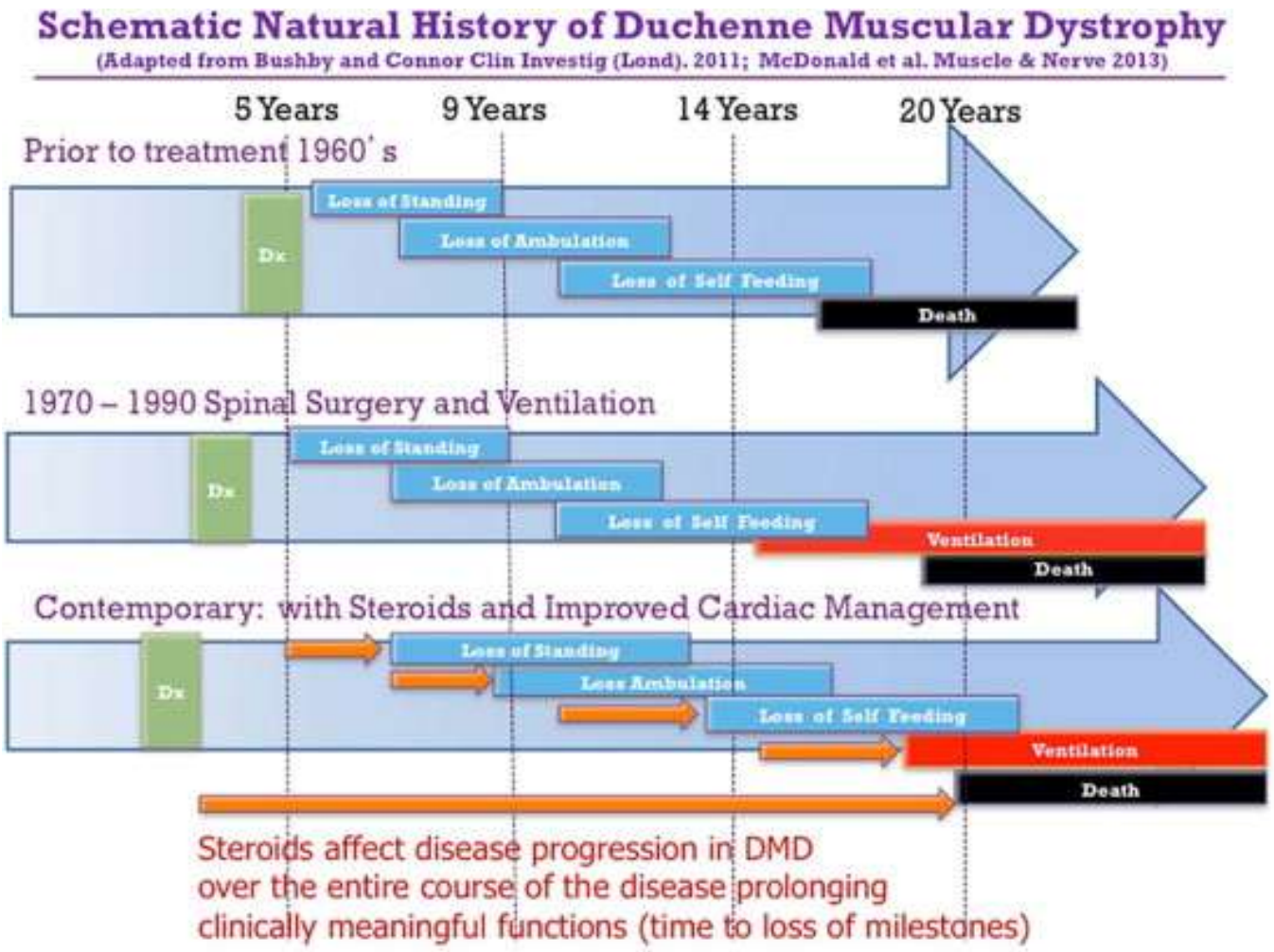
DMD – Clinical Presentation

- Gross motor delays
- Clinical weakness: onset at 2-3 yrs
  - Proximal > distal, LE > UE
- Waddling and hyperlordotic gait
- Slower than peers
- Frequent falling
- Difficulty jumping and climbing stairs
- Calf & other muscle hypertrophy
- Pain or cramping
- +/- mild cognitive impairment, global developmental delay
- **Average age at diagnosis: 5 yrs**



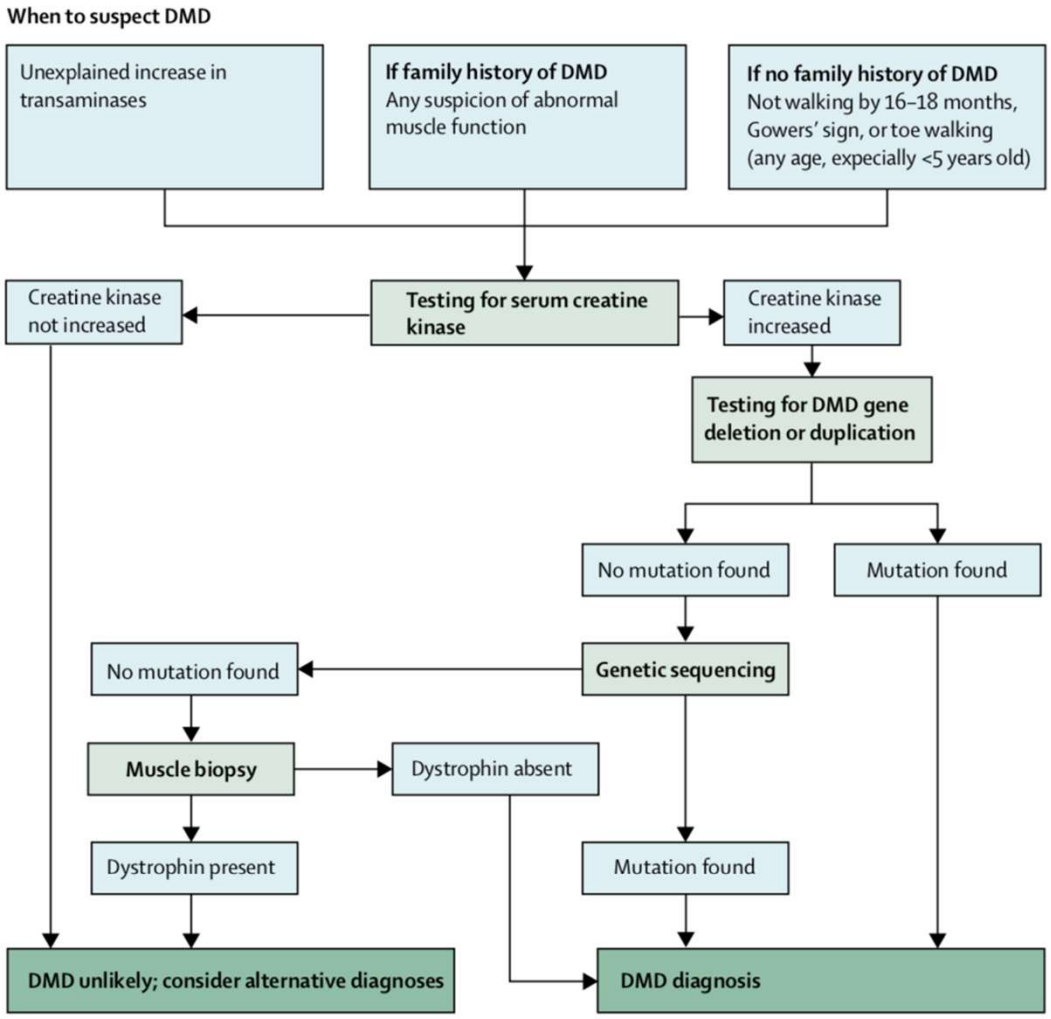


DMD Disease Progression



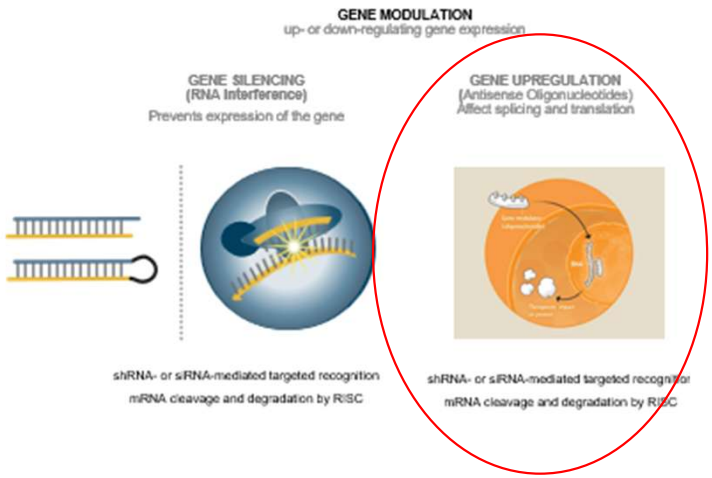
Diagnosis of DMD

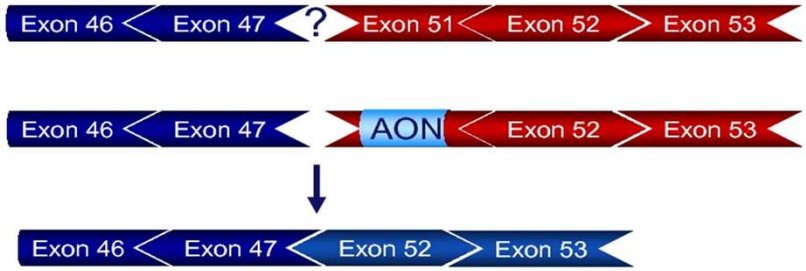
- Elevated CK >10K
- LFT's: high AST,ALT and LDH. Normal GGT
- Muscle biopsy (rare)
- Targeted genetic testing

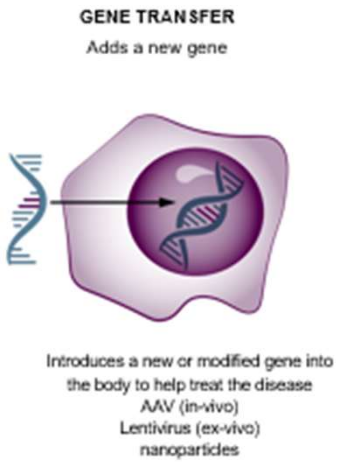


DMD: Existing Disease-Modifying Drug Therapies

- Exon-skipping drugs
  - ASO
  - Restore *DMD* reading frame→dystrophin expression



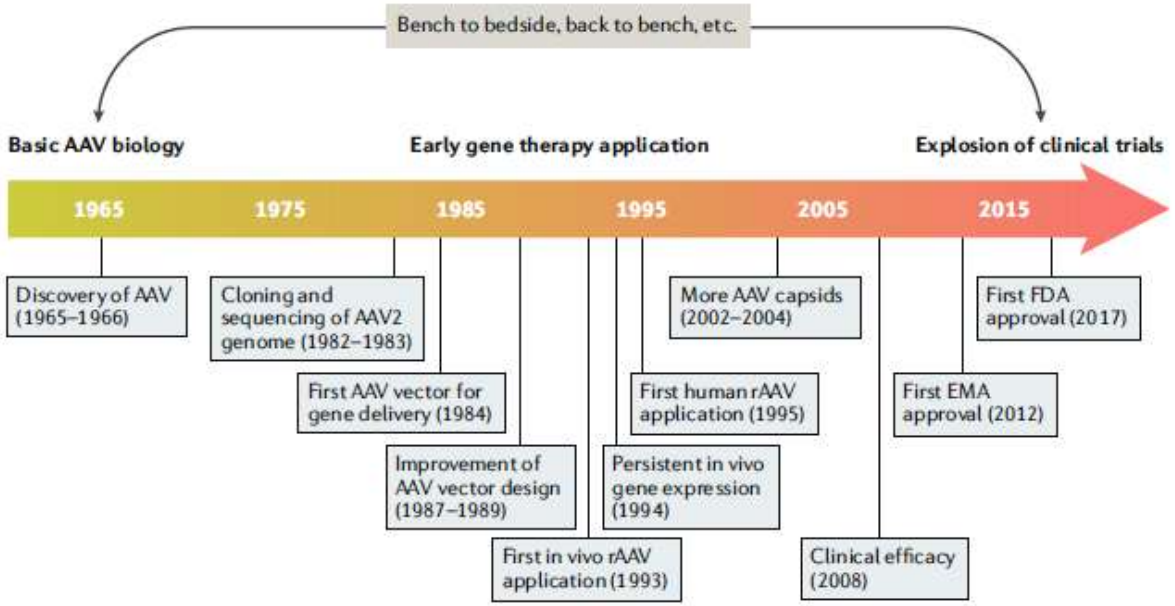




AAV Vector Gene Therapies for SMA and DMD

AAV

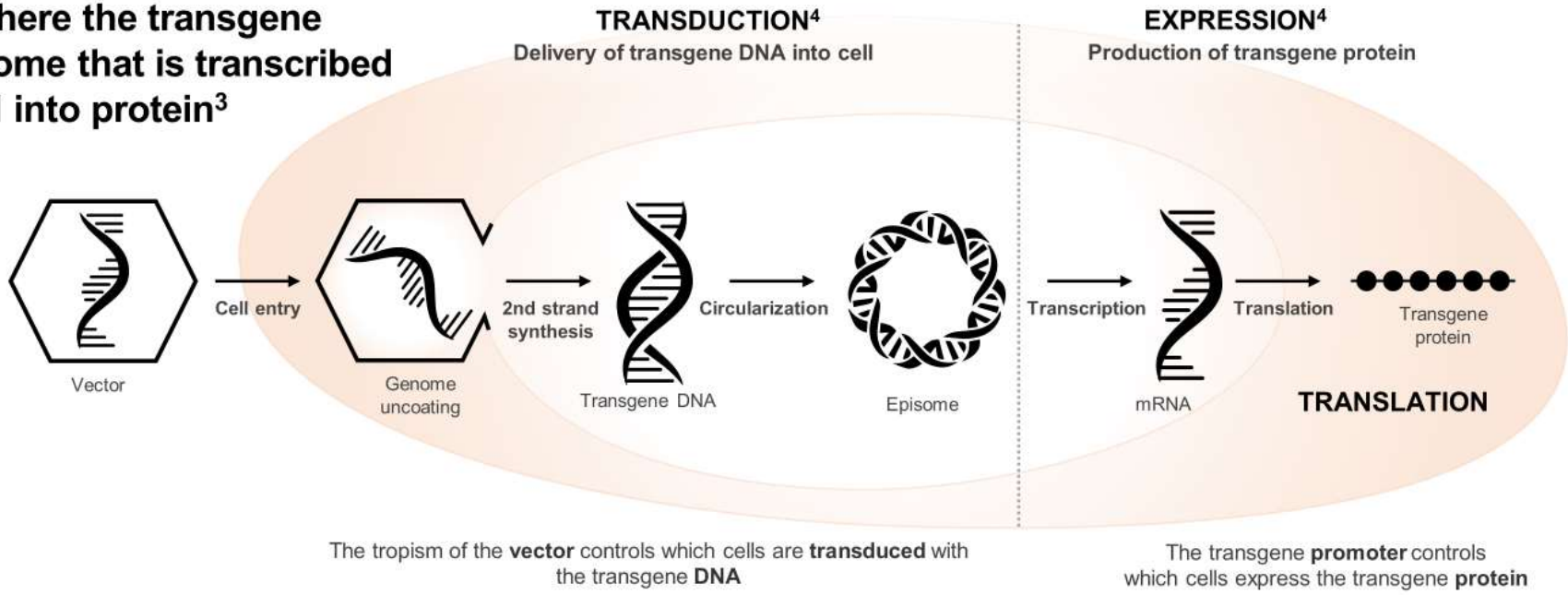
- Discovered 1965, contaminant of adenovirus preparation
- “Defective” parvovirus
- Doesn’t cause human illness
- 13 human serotypes, >100 primate serotypes
- Different tissue tropisms
- Maximum capacity ~4.7 kb (ssAAV)



Wang et al, 2019

AAV vectors stably transduce target cells, forming an extrachromosomal episome[1–3]

Therapeutic genes are delivered to target cells, where the transgene forms an episome that is transcribed and translated into protein[3]



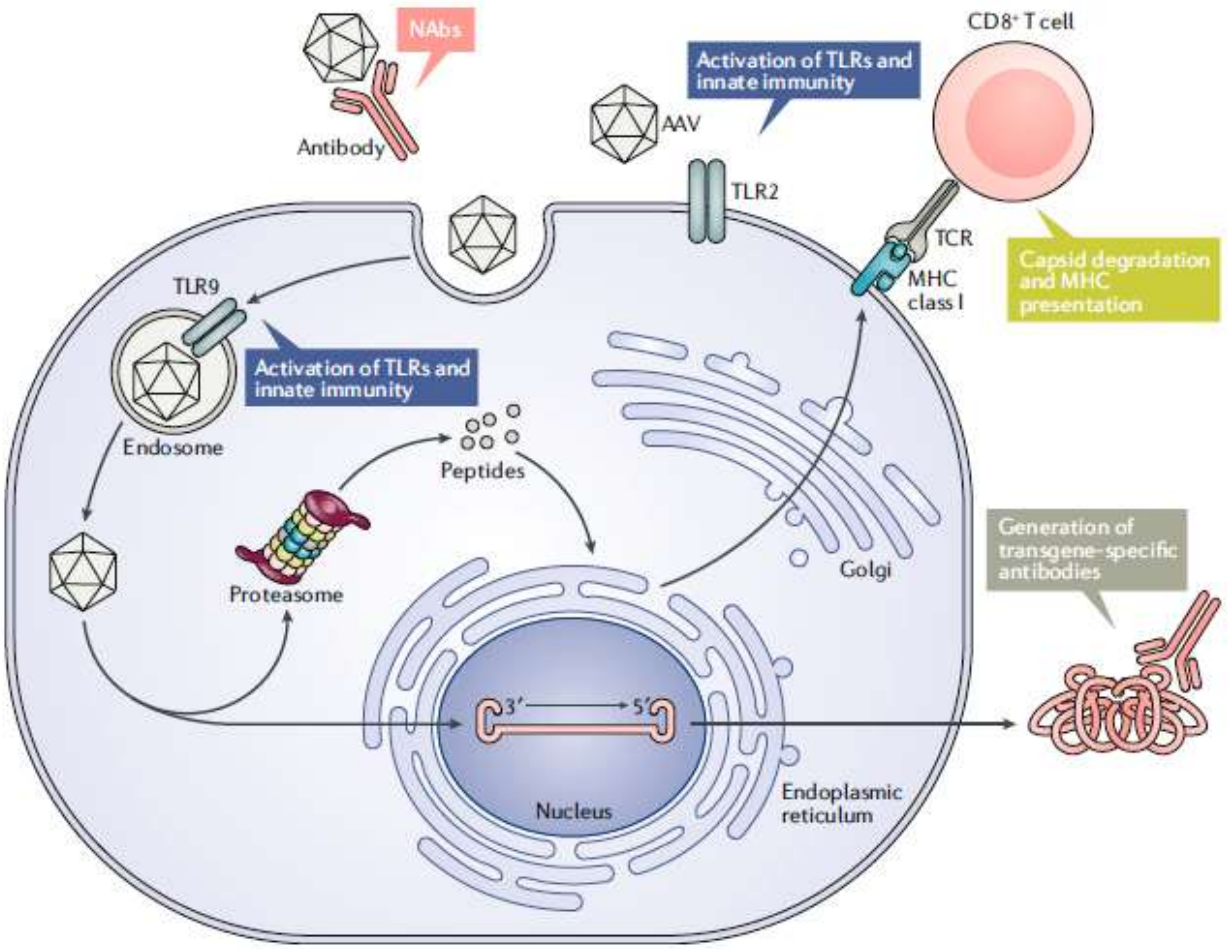
DNA; deoxyribonucleic acid; mRNA, messenger ribonucleic acid.

1. Asher DR, *et al. Expert Opin Biol Ther.* 2020;20(3):263-74. 2. Lee CS, *et al. Genes Dis.* 2017;4(2):43-63. 3. Muhuri M, *et al. Mol Ther.* 2022;30(4):1364-80. 4. *The Scientist* (2012). Targeting DNA. Available at: https://www.the-scientist.com/features/targeting-dna-40937. Last accessed: May 2022.

AAV Challenges

- Production cost
- Carrying capacity: ~5 kb
- Persistence: non-replicating episomes, low DNA integration
- Immunologic:
  - 40-80% have anti-AAV neutralizing Ab's
    - Cross-reactivity of Ab's to different AAV serotypes
  - Humoral immune response post-administration
  - Toll-like receptor (TLR) activation→pro-inflammatory cytokine production
  - Cytotoxic T-cell response to transduced cells (esp hepatic)
    - CD8+ cell suppression w/ steroids

Immune Response



Wang et al, 2019

Zolgensma (onasemnogene abeparvovec)

- Full-length SMN-encoding transgene
- AAV9 vector
- Historical controls w/ SMA type 1: never reach 40 points (black dashed line)
- All patients reached 20+ mos old w/o need for permanent ventilation
  - 8% in historical controls
- FDA approval May, 2019 for kids < 2y/0
- Over 4,000 kids have been infused

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 2, 2017 VOL. 377 NO. 18

Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy

J.R. Mendell, S. Al-Zaidy, R. Shell, W.D. Arnold, L.R. Rodino-Klapac, T.W. Prior, L. Lowes, L. Alfano, K. Berry, K. Church, J.T. Kissel, S. Nagendran, J. L'Italien, D.M. Sproule, C. Wells, J.A. Cardenas, M.D. Heitzer, A. Kaspar, S. Corcoran, L. Braun, S. Likhite, C. Miranda, K. Meyer, K.D. Foust, A.H.M. Burghes, and B.K. Kaspar

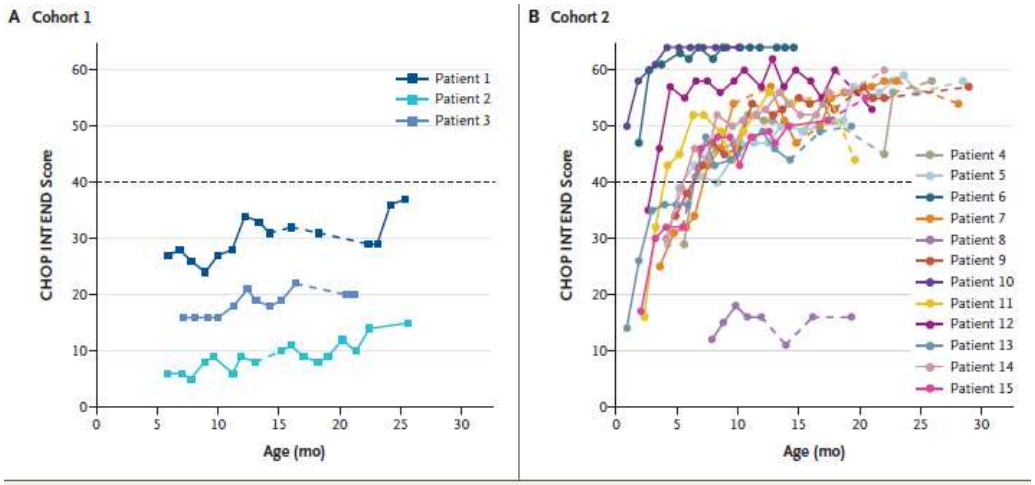
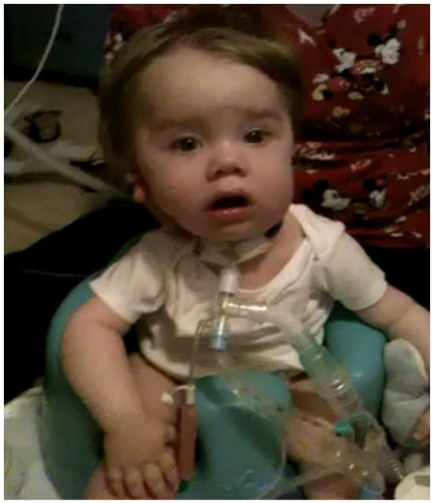
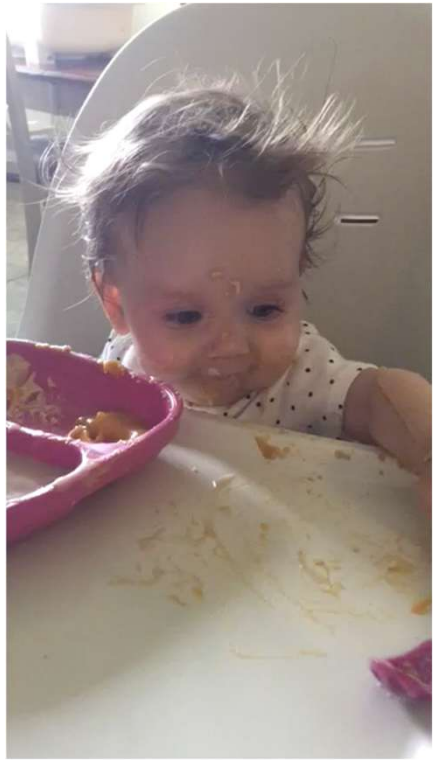


Figure 2. Motor Function after Gene Therapy.

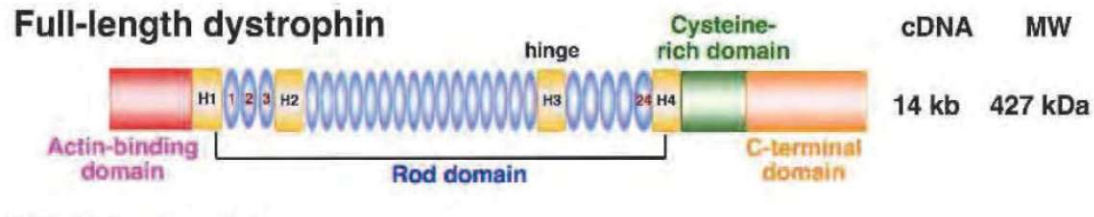
Siblings with SMA Type 1 (1 y/o)
2 SMN2 copies





DMD Gene Transfer Challenges

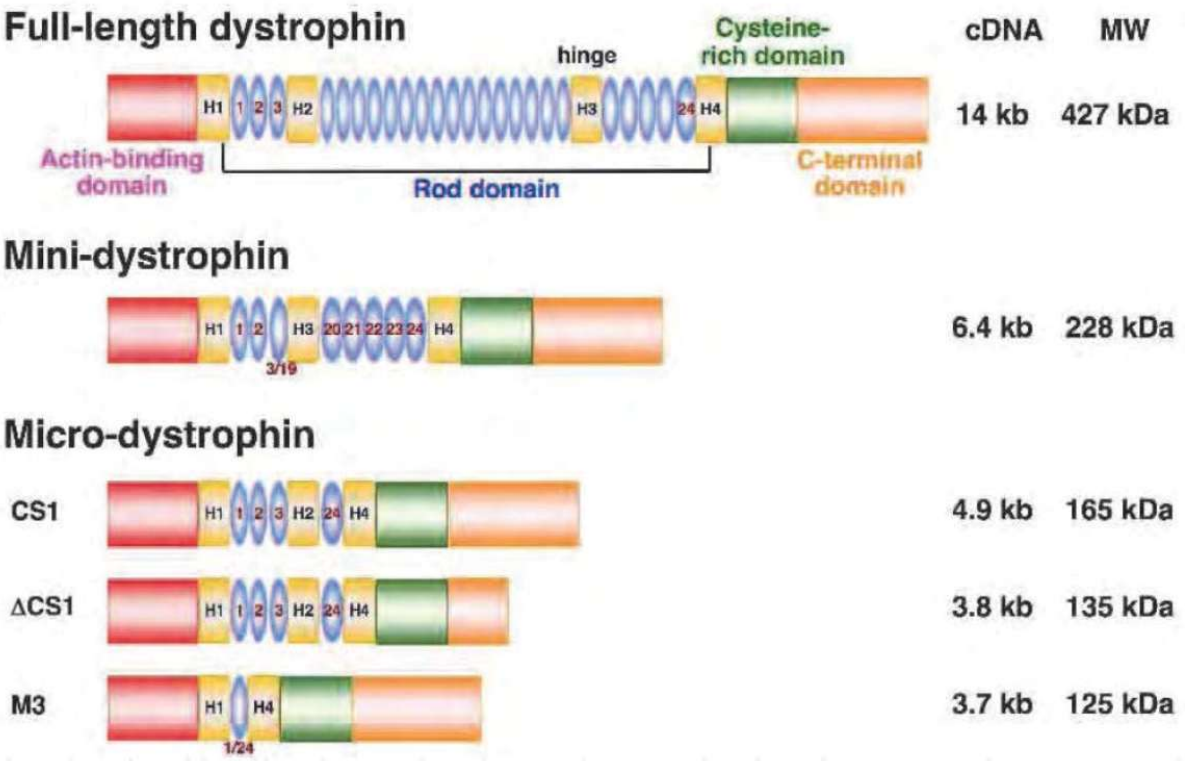
- *DMD* size
  - Full gene 2.4 Mb



- Mild Becker MD patients
  - England et al, 1990: 61 yo ambulatory man w/ deletion of exons 17-48 (in-frame, 46% of dystrophin coding region deleted)

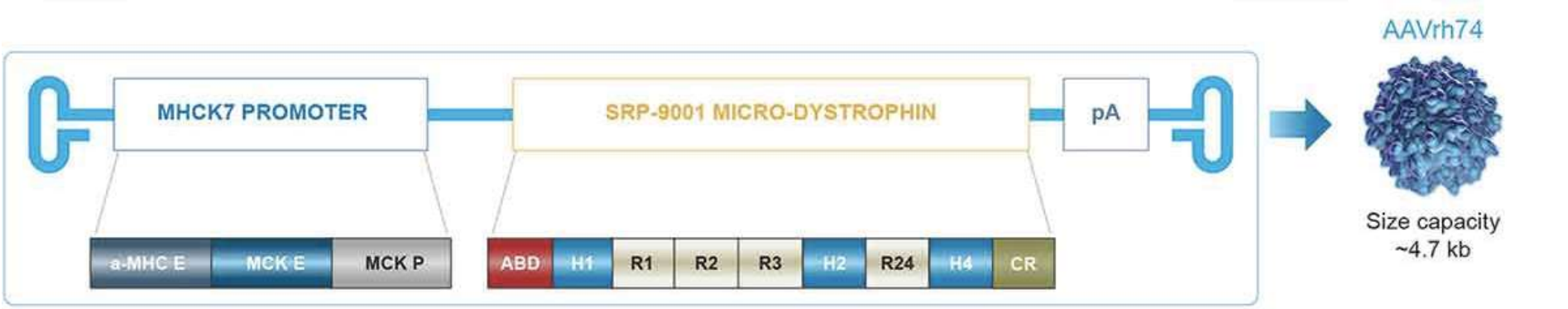
Mini- and Micro-Dystrophin Constructs

- Multiple companies developing
  - Pfizer, Sarepta, Solid, Regenxbio



Elevidys (delandistrogene moxeparvovec-rokl)

- Sarepta
- AAVrh74 vector
- Micro-dystrophin transgene



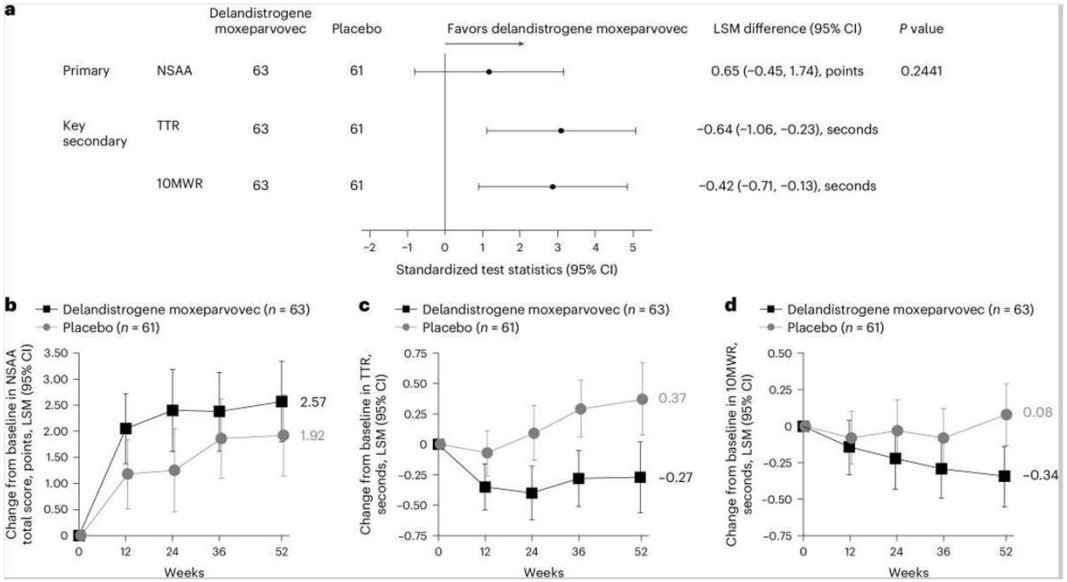
Promoter
- Drives expression in intended tissues
- Minimal off-target expression
- Minimal length to economize vector capacity

Transgene
- Produces a functioning version of the protein of interest
- Sequence optimized for best expression

Vector
- Must deliver the transgene to target cells with minimal immune response
- Favorable safety profile
- Appropriate tissue tropism
- Low pre-existing immunity

Elevidys (Delandistrogene moxeparvovec-rokl)

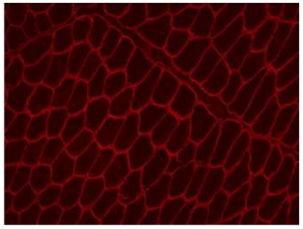
- Accelerated FDA approval June, 2023 for 4–5-year-old kids
  - Expression of micro-dystrophin in skeletal muscle
- Expansion to all kids >4y/o regardless of ambulatory status June 2024
  - Expression of micro-dystrophin in skeletal muscle
  - Improvement in motor outcomes was shown in patients ages 4-8
  - No clinical efficacy data in older patients
- 2 deaths prompted Sarepta to halt Elevidys use in non-ambulatory kids (June 2025
- Over 1,000 patients have been infused



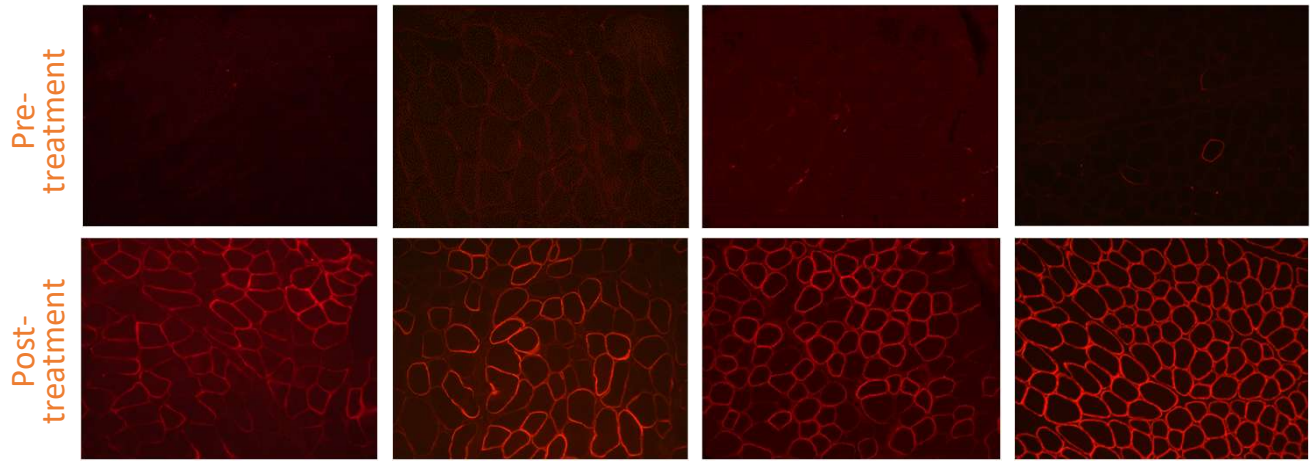
Mendell, J. R et all. (2025). AAV gene therapy for Duchenne muscular dystrophy: the EMBARK phase 3 randomized trial. Nature medicine, 31(1), 332–341. https://doi.org/10.1038/s41591-024-03304-z

SRP-9001-101: Micro-dystrophin expression in gastrocnemius muscle fiber Day 90

Normal control



Micro-dystrophin expression (IF)



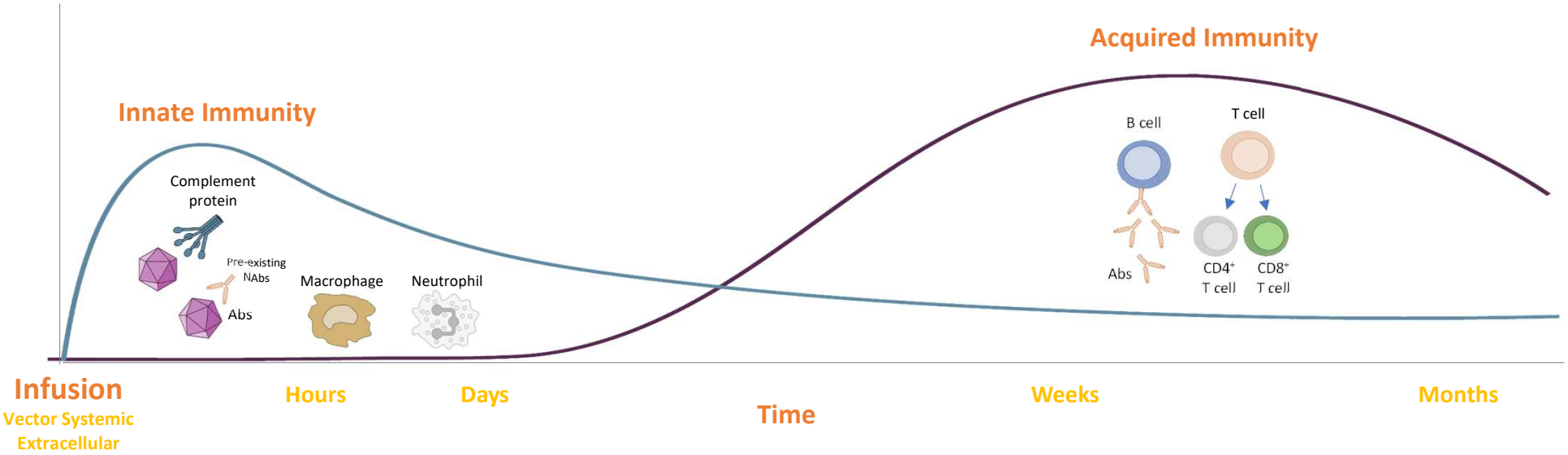
	Intensity	Percentage of dystrophin-positive fibers
Mean (n=4)	96.0%	81.2%

IF=immunofluorescence. ClinicalTrials.gov Identifier: NCT03375164

Mendell JR, *et al. JAMA Neurology*. Published online June 15, 2020. doi:10.1001/jamaneurol.2020.148

Zolgensma & Elevidys: Similar Risk Profiles

- Must NOT have pre-existing anti-vector antibodies
- Immunologic response



Serious Safety Events Reported for Systemic AAV Gene Transfer Therapies*

Liver

- Serious acute liver injury[1,4,6,7]

Gastrointestinal

- Severe vomiting [1,8]
- Dehydration[1,8]
- GI infection[2,5]
- GI bleed[6]

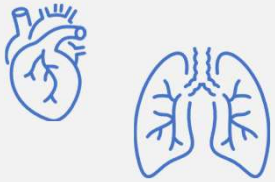
Muscle

- Myositis [1,4,6,7]
- Rhabdomyolysis [1,4,6,7]

Hematological

- Complement mediated HUS[3,8,11]
- Severe thrombocytopenia[1,3, 4, 11]

Cardiopulmonary



- Myocarditis
- Cardio-pulmonary insufficiency[3]
- Elevated troponins[4]

CNS

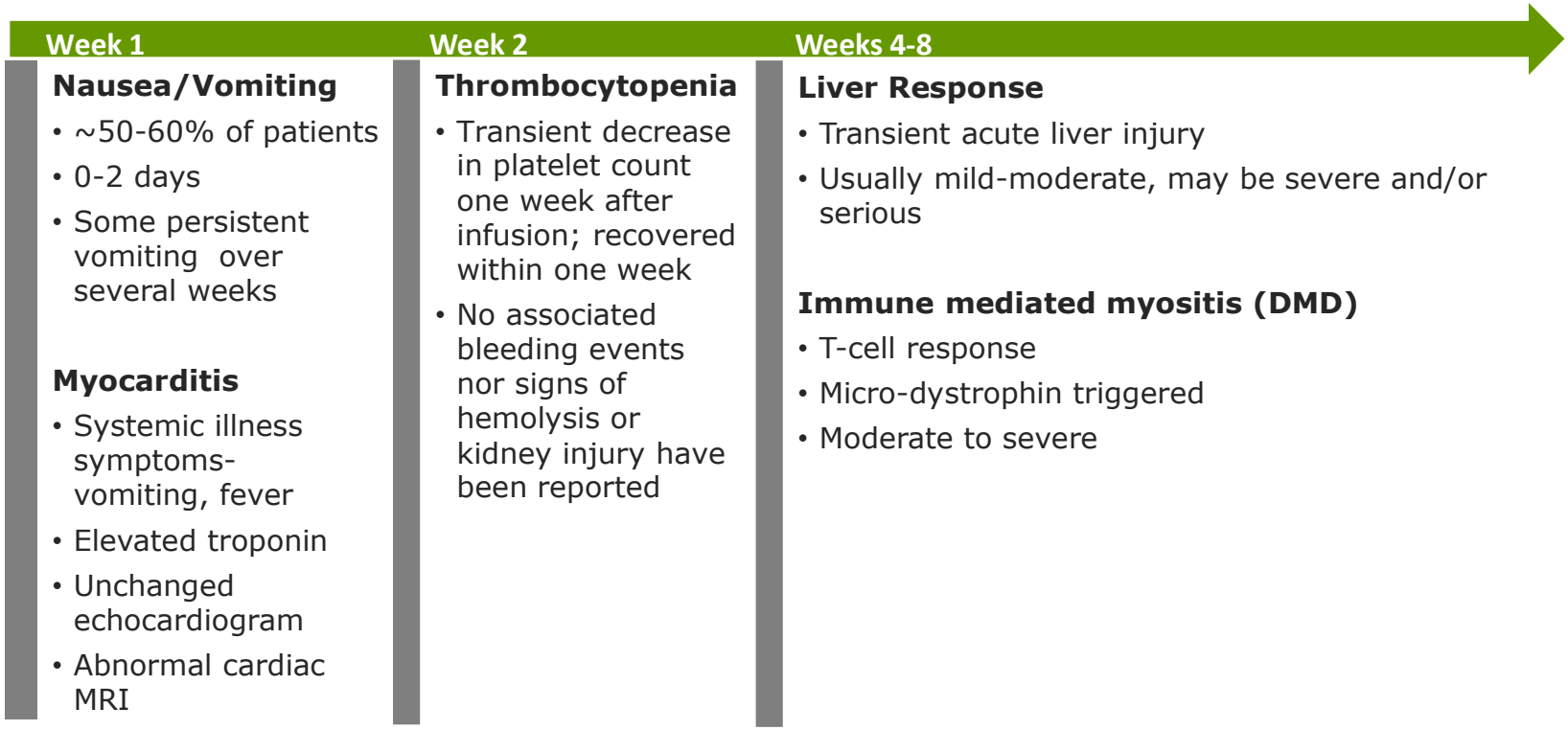
- Severe headache[9,10]

Other Events

- Death[6,8]
- Sepsis[6]
- Grade 2 pyrexia[9]
- Severe pain (back, extremities, etc)[9]

1. Sarepta Therapeutics (2020). Clinical Updates: Gene Therapy Programs. 2. Solid Biosciences (2019). 3. Solid Biosciences (2019). Solid Biosciences Provides SGT-001 Program 4. FDA (2022). ZOLGENSMA (onasemnogene abeparvovec-xioi) 5. Audentes Therapeutics (2018). First Dose Cohort of ASPIRO, a Phase 1/2 Clinical Trial of AT132 in Patients With X-Linked Myotubular Myopathy. 6. Audentes Therapeutics (2020). ASPIRO Clinical Trial Evaluating AT132 in Patients with X-linked Myotubular Myopathy. 7. Spark Therapeutics (2020). SPK-8011 from Phase 1/2 Clinical Trial in Hemophilia A at ISTH 2020 8. Pfizer (2019). Pfizer Presents Initial Clinical Data on Phase 1B Gene Therapy Study for Duchenne Muscular Dystrophy (DMD). 9. BioMarin (2018). BioMarin Provides 2 Years of Clinical Data in 6e13 vg/kg Dose from Ongoing Phase 1/2 Study in Valoctocogene Roxaparvovec Gene Therapy for Severe Hemophilia 10. Pfizer (2020). Pfizer and Sangamo Announce Updated Phase 1/2 Results Showing Sustained Factor VIII Activity Levels and No Bleeding Events rr Factor Usage In 3E13 vg/kg Cohort Following Giroctocogene Fitelparvovec (SB-525) Gene Therapy. 11. Pfizer (2020). Pfizer's New Phase 1B Results of Gene Therapy in Ambulatory Boys with Duchenne Muscular Dystrophy (DMD) Support Advancement into Pivotal Phase 3 Study.

Anticipated AE Timeline



Who Qualifies for Gene Transfer Therapy?

For SMA:

- Eligible: <2 years with confirmed SMA; ? if >4 SMN2 copies
- Excluded: AAV9 antibody–positive

For DMD

- Eligible: Ambulatory with confirmed DMD
- Excluded: Exon 8–9 deletions, cardiac EF <40, AAVrh71 antibody–positive, >70 kg, unclear phenotype (biopsy may help

Infusion and Monitoring

- Outpatient infusion:
- Family to be within short distance of SCH for the first days to weeks
- Lab monitoring:
  - AAV ab titers prior to infusion
  - Weekly or more frequent LFTs, Troponin, INR, and for the first 3 months
  - ECG and TTE or cardiac MRI for Elevidys
- Steroids to reduce the risk of immune-related complications:
  - start prior to infusion and continue for several months

Practical Considerations for General Practitioners

Spot the Signs Early!

- Watch for hypotonia, delayed milestones, or motor regression.
- Refer promptly for genetic testing—it makes a difference.

In older kids with progressive weakness:

- Think **SMA**.
- Think **DMD** (especially in boys).

For any boy with motor or global delays:

- Check a CK- If elevated → likely DMD.

⚠️ **These patients have complex needs—contact the neuromuscular team if they present to the ED or are admitted.**

Future Directions in Gene Therapies

For DMD
- 2 clinical trials for microdystrophin gene transfer
- Expansion to non-ambulatory kids

For SMA
- Intrathecal Zolgensma for patients >2y/o

For other diseases
- The list is long and will only continue to grow

Combination approaches
- Gene therapy + gene modulation + muscle growth agents

Long Term outcomes and Durability
- Need data

Equity, access, and healthcare costs
- Global access: affordability, infrastructure in low-resource settings
- Culturally and linguistically tailored delivery of care
- Policy and insurance frameworks to ensure sustainability

What is the cost of Elevidys?

A) 5K
B) 50K
C) 500K
D) 1 million
E) None of the above

Questions?