
# Duchenne Muscular Dystrophy: Then and Now

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# Disclosures

- Financial disclosures
  - 04/08/2022 Institutional Site Readiness Advisory Board for Gene Therapy, Sarepta Therapeutics, Denver, CO.
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- I will be discussing some off-label use of therapies for Duchenne Muscular Dystrophy.

# Learning concepts today

Duchenne disease incidence and genetics

Presenting symptoms and trajectory

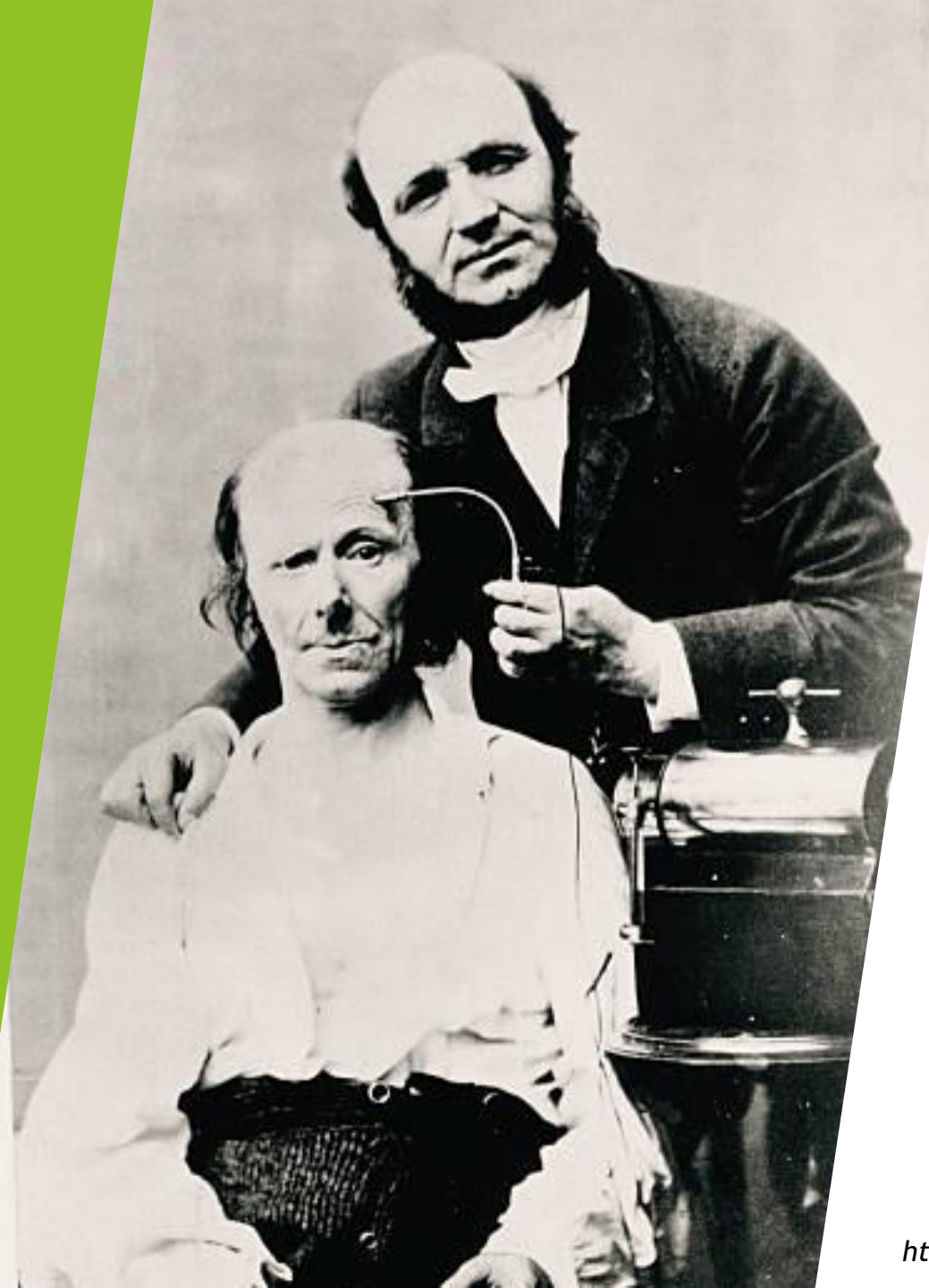
Duchenne cultural timelines

Current standard of care & therapies

School resources and Support

# What is Duchenne Muscular Dystrophy?

- X-linked progressive neuromuscular disorder
- 1 in 3,500 male live births worldwide
  - 20,000 children are diagnosed globally each year
- Lack of dystrophin, an important structural protein to maintain muscle
- Muscle cells weaken over time with loss of ambulation followed by declined in heart and lung function.
- Diagnosis 4-6 years of age
- Average life span 2nd-3rd decade
- No cure

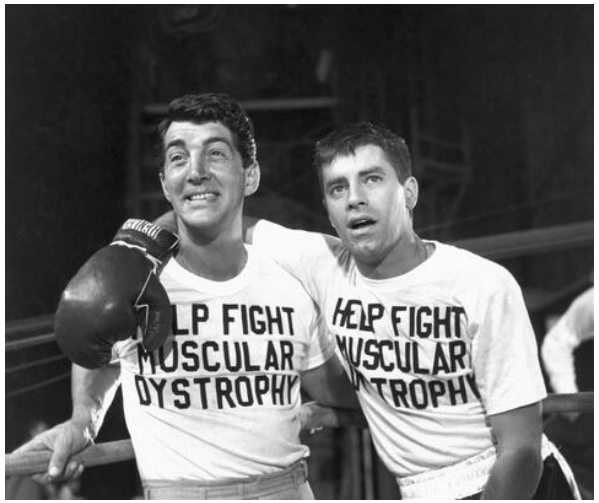


# 1861 Guillaume Benjamin Amand Duchenne

- First to describe disease in young boy
- First to practice muscle biopsy
- Formalized the diagnostic principles of electrophysiology
- Photo: Dr. Duchenne stimulating a patient's facial muscle with a low voltage current, ca. 1862.

*https://www.gettyimages.com/photos/guillaume-duchenne*

# Muscular Dystrophy Association: 1950 – 1960's




- 1952 The Porch Light Brigade: National Association of Letter Carriers becomes first sponsor of MDA
- 1954 Jerry Lewis and Dean Martin during a fundraising boxing match.
- 1961 Lady Bird Johnson visits with Muscular Dystrophy Association's National Poster Child Lola Lucas
- 1963 President John F. Kennedy with National Poster Children for the Muscular Dystrophy Associations of America, Inc.

(NALC/Bert Parry/JFKLibrary Archives)

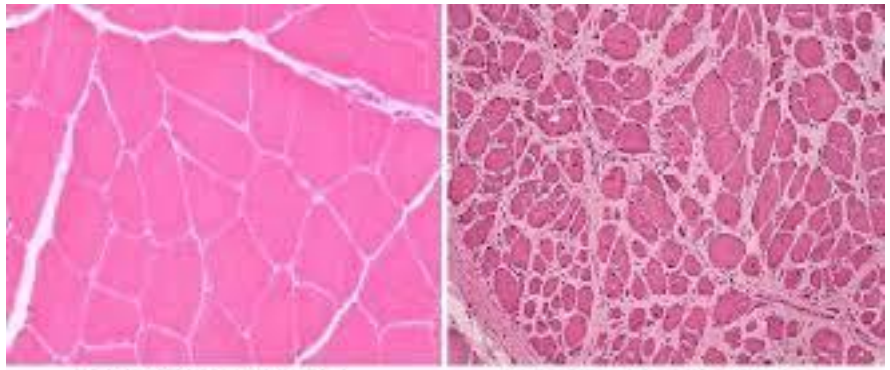
# Labor Day Telethons & Jerry's Kids

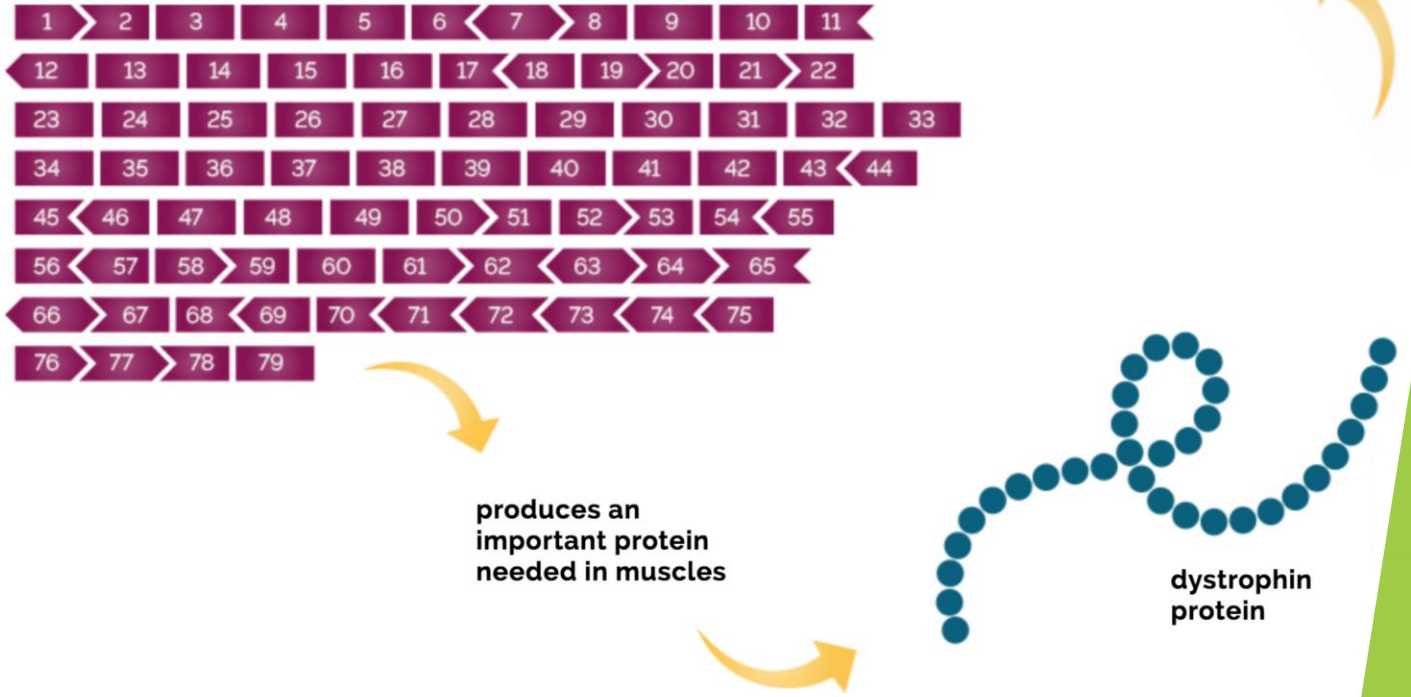
- 1956 - Jerry Lewis and Dean Martin co-hosted a live TV show benefiting fledgling MDA
- 1956-2014: Spanning 60 years Jerry Lewis and  guests performed an annual Labor Day telethon
- In total, $2.5 billion was raised, lending to breakthrough scientific discoveries for the disease

# 1986 The Genetics of Duchenne

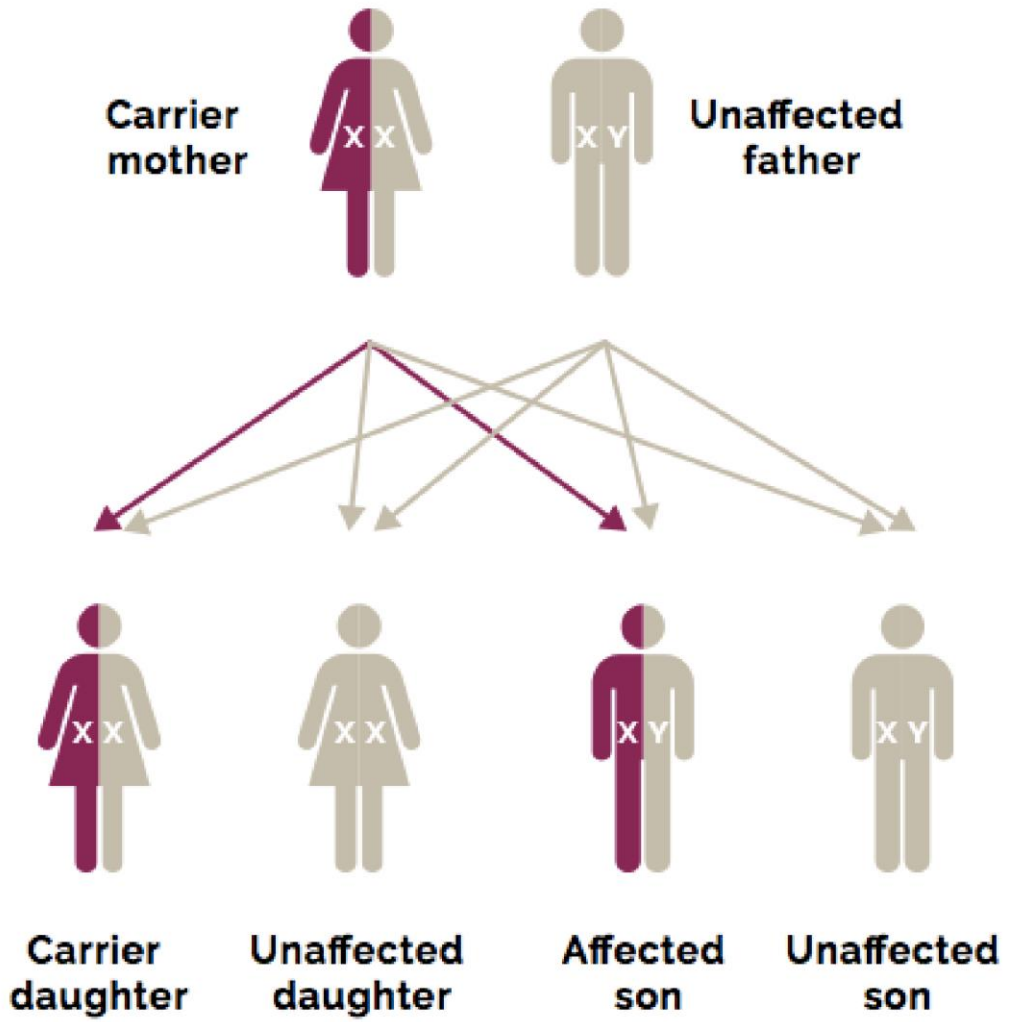
- Single gene affected. - *DMD*
- *X-linked (Xp21.2 region)*
- *7,000+ known mutations*
  - *65% deletions*
  - *10% duplications*
  - *25% point-mutations*
- *Severity of disease follows frame-reading rules*

https://www.mda.org.au/information/md101/




https://www.duchenne.com/understanding-duchenne/role-genetics-duchenne




# Inheritance

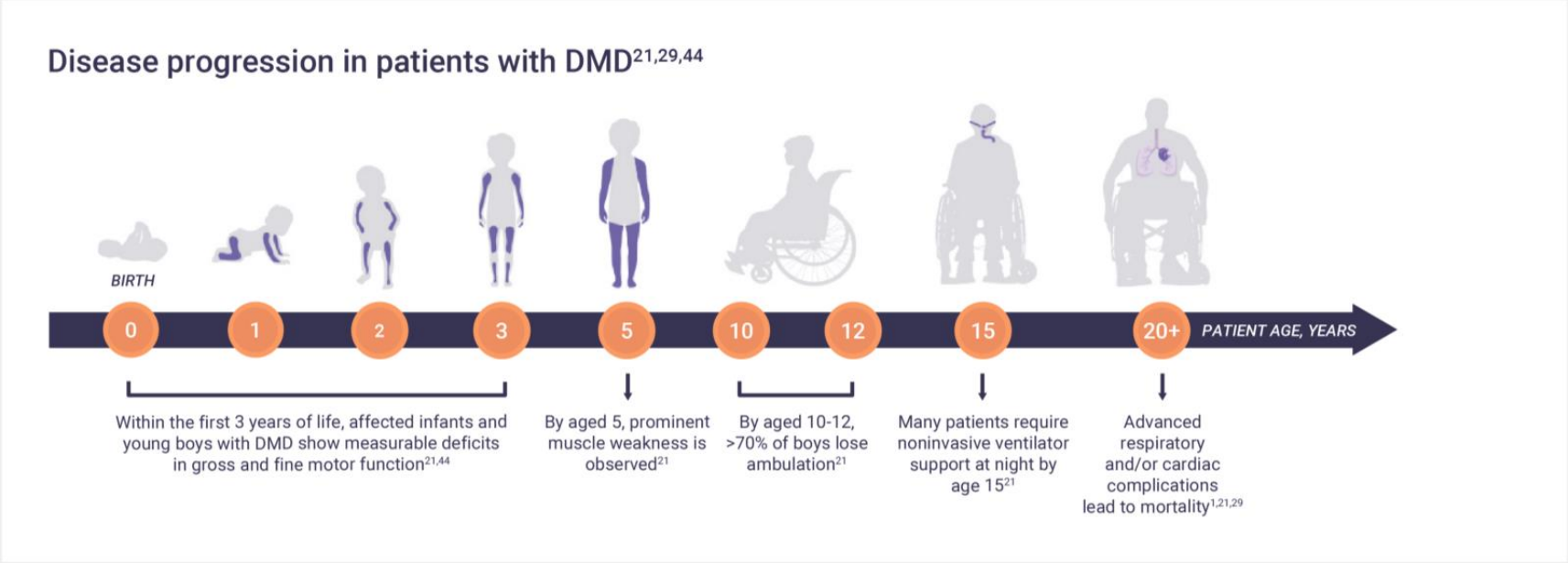
- X-linked
- 30% de novo or new mutation
- 70% familial

- Males are predominantly affected
- Women are carriers but can be symptomatic - typically with cardiomyopathy in adulthood

https://www.duchenne.com/hcp/dmd-overview/role-genetics-dmd

# Clinical Recognition of DMD

- **Slower gait or run, difficulty with stairs**
- Toe walking
- **+Gowers sign**
- **Elevated CK (5-10,000+) (usually investigated after elevation in liver enzymes)**
- Lordotic or “waddling” gait
- Calf hypertrophy
- Later onset cardiomyopathy and respiratory disease
- 30% have intellectual difficulties




*https://medhub.ptcbio.com/neuromuscular/dmd/*

# Duchenne progression

Myopathic gait

*https://www.youtube.com/watch?v=b46xmMgdtnY*


Gowers

***http://www.worldduchenneday.org***

# 2001–2018: DMD Legislation & Care Guidelines

- 2001 MD-Care Act
- 2010 & 2018:The DMD Care Considerations Working Group: a consortium of NM and related specialty-experts released the first DMD Care Guide
  - Corticosteroid therapy
  - Respiratory support
  - Cardiovascular
  - Rehabilitation eval/PT/OT
  - Gastroenterology
  - Orthopedic/Endocrinology
  - School support
  - Anesthesia precautions (avoid Succinylcholine and volatile anesthetics ->severe hyperkalemia and severe rhabdomyolysis)

Public Law 107–84
107th Congress

An Act

To amend the Public Health Service Act to provide for research with respect to various forms of muscular dystrophy, including Duchenne, Becker, limb girdle, congenital, facioscapulohumeral, myotonic, oculopharyngeal, distal, and Emery-Dreifuss muscular dystrophies.

Dec. 18, 2001
[H.R. 717]

Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psy

Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management

David J Birnkrant, Katharine Bushby, Carla M Bann, Susan D Apkon, Angela Blackwell, David Brumbaugh, Laura E Case, Paula R Clemens, Stasia Hadjiyannakis, Shree Pandya, Natalie Street, Jean Tomezsko, Kathryn R Wagner, Leanne M Ward, David R Weber, for the DMD Care Considerations Working Group*

Since the publication of the Duchenne muscular dystrophy (DMD) care considerations in 2010, multidisciplinary care of this severe, progressive neuromuscular disease has evolved. In conjunction with improved patient survival, a shift to more anticipatory diagnostic and therapeutic strategies has occurred, with a renewed focus on patient quality of life. In 2014, a steering committee of experts from a wide range of disciplines was established to update the 2010 DMD care considerations, with the goal of improving patient care. The new care considerations aim to address the needs of patients with prolonged survival, to provide guidance on advances in assessments and interventions, and to consider the implications of emerging genetic and molecular therapies for DMD. The committee identified 11 topics to be included in the update, eight of which were addressed in the original care considerations. The three are primary care and emergency management, endocrine management, and transitions of part 1 of this three-part update, we present care considerations for rehabilitation, endocrine (growth, puberty, and adrenal
dysphagia) management.

# School support

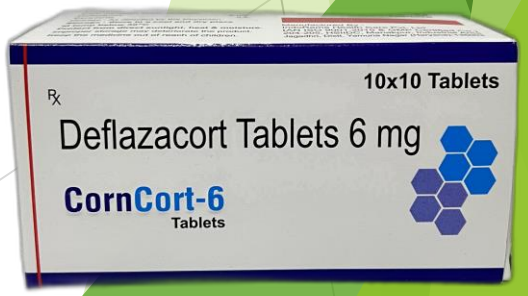
- Individualized Education Plan
- 504 for both physical and scholastic accommodations
- Resources on
  - Adaptive P.E.
  - Books and talking with peers
  - Educational tips and guidance for educators


https://www.parentprojectmd.org/care/for-families/school-resources/

# DMD Therapies

# 1974-present: Glucocorticosteroids

- Glucocorticoids theorized and used as DMD therapy since early 1970's
- First clinical trial (1974) was small (n=14): results suggested a slowed loss of strength compared to those not taking steroids.
- Repeat trials with larger cohorts confirmed up 3 years delay in LOA with delays in cardiopulmonary decline and scoliosis
- Pathophysiology:
  - improves muscle cell membrane repair by secondary gene promotion
  - reduces muscle necrosis and inflammation through reduced cytokine release
  - increases total muscle mass and strength by enhanced myoblast production
- Prednisone: off-label for DMD
- 2017: Deflazacort (prednisone derivative): FDA-approved for DMD for ≥2yo

# Prednisone/Deflazacort

Standard of care for DMD ≥2 yo; Timed typically when motor milestones plateau ~2 yo; best if BEFORE decline

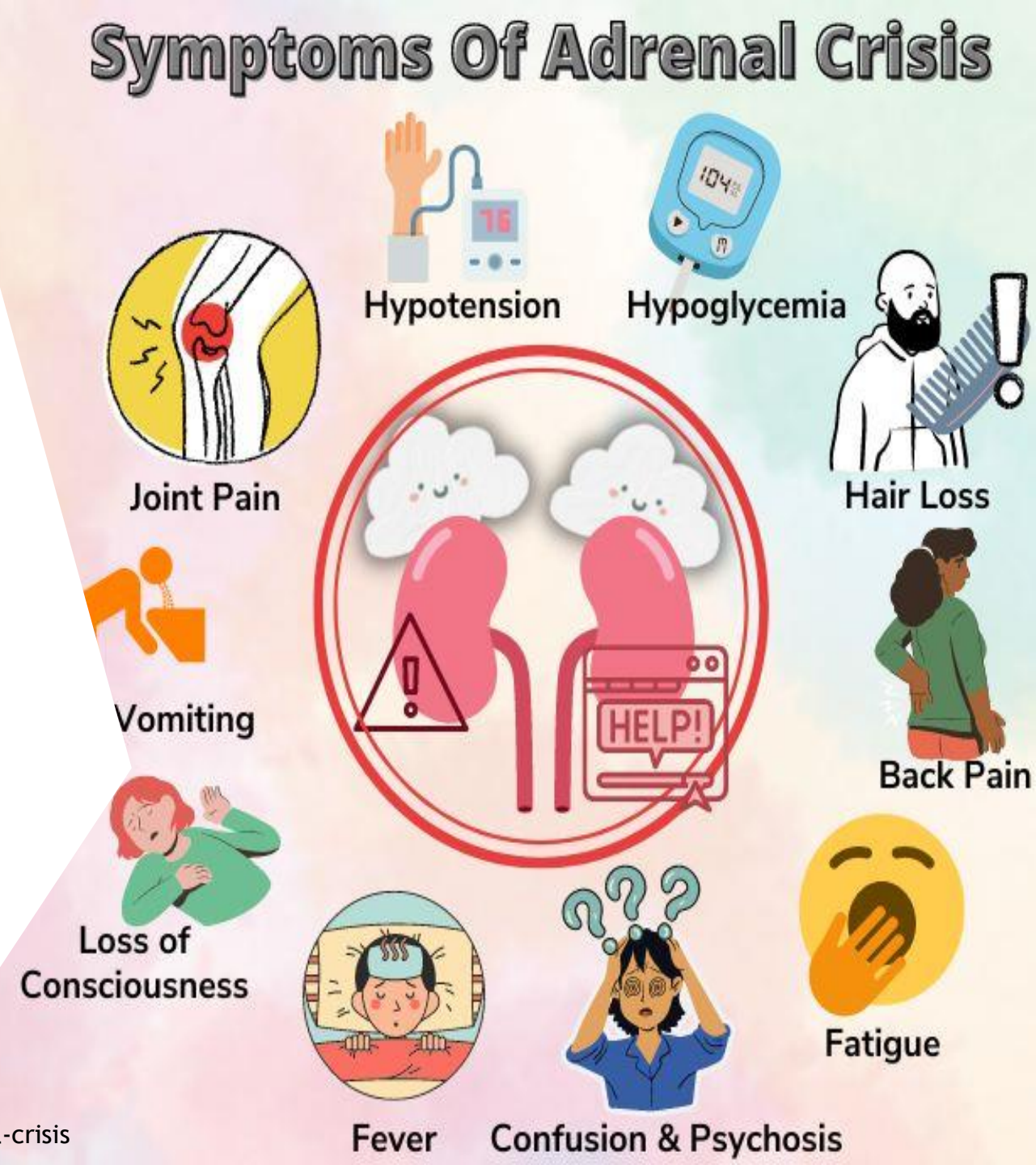
| | |
|---|---|
| Prednisone | 0.75mg/kg/day (max 30mg/day) |
| Deflazacort | 0.9mg/kg/day (max 36mg/day) |

| Potential side effects are numerous: | |
|---|---|
| Increased appetite/weight gain | Acute mood changes/mental health decline |
| Osteoporosis | Glaucoma/cataracts |
| Delayed wound healing/Infection risks (shingles, measles, chickenpox) | Reduced growth in children |
| Hypertension | Diabetes or worsening insulin resistance |
| Cushing's syndrome: moon face, kyphosis, acne, diffuse striae | Adrenal Crises |

# Prednisone/Deflazacort

*Prescribing considerations*

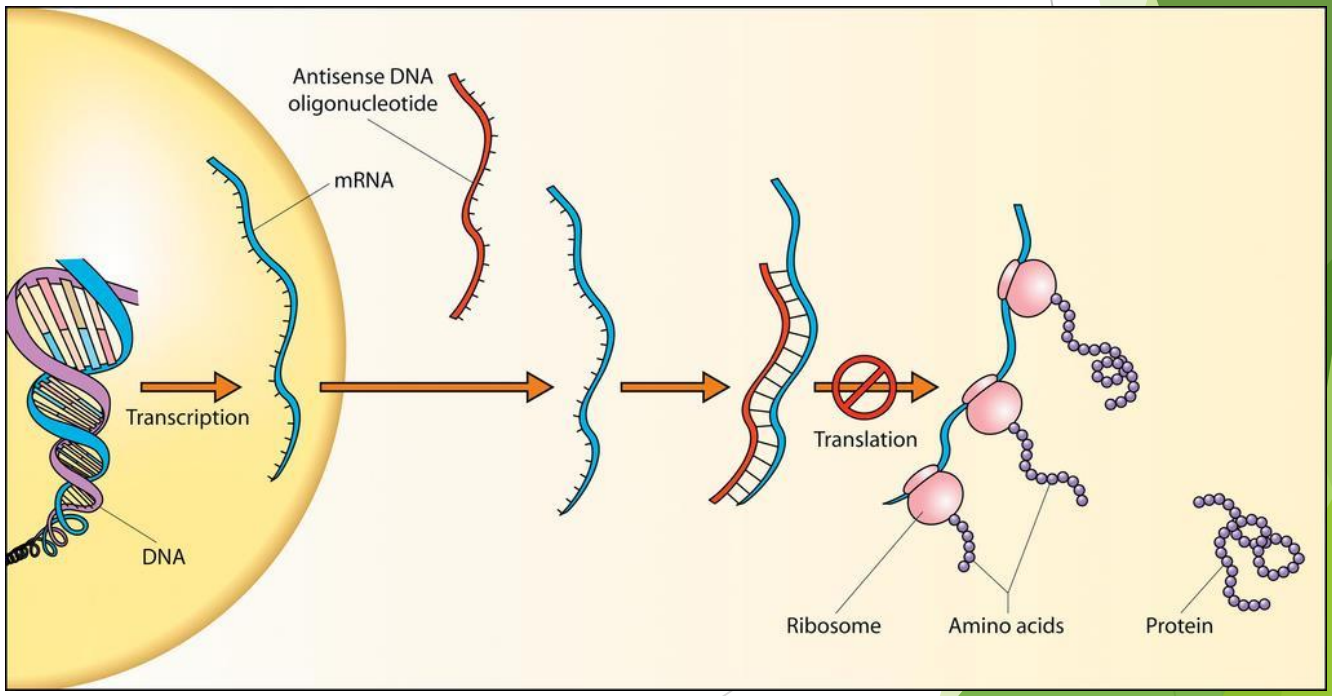
- Counseling on potential adverse effects and anticipated benefits
- Pre-steroid labs: renal and liver function studies, cell counts and vaccination titers for varicella and tuberculosis
- Steroid titration ~ 6-10 weeks
- Transition to deflazacort if there are significant adverse symptoms
- Counseled on avoiding stopping therapy abruptly or stress-dosing during surgery--> Adrenal crisis
- **Adrenal Crisis: Insufficient cortisol for daily function**
  - ACTH (cosyntropin) stimulation test, Cortisol level, Blood glucose, Serum potassium, Serum sodium, Serum pH
  - Treat initially with 50-100 mg/m$^2$ IV hydrocortisone/Solu-Cortef©
  - Taper to baseline with IV or oral prednisone or prednisolone
  - Needs emergency card or handout to provide outside providers




https://www.icliniq.com/articles/endocrine-diseases/adrenal-crisis

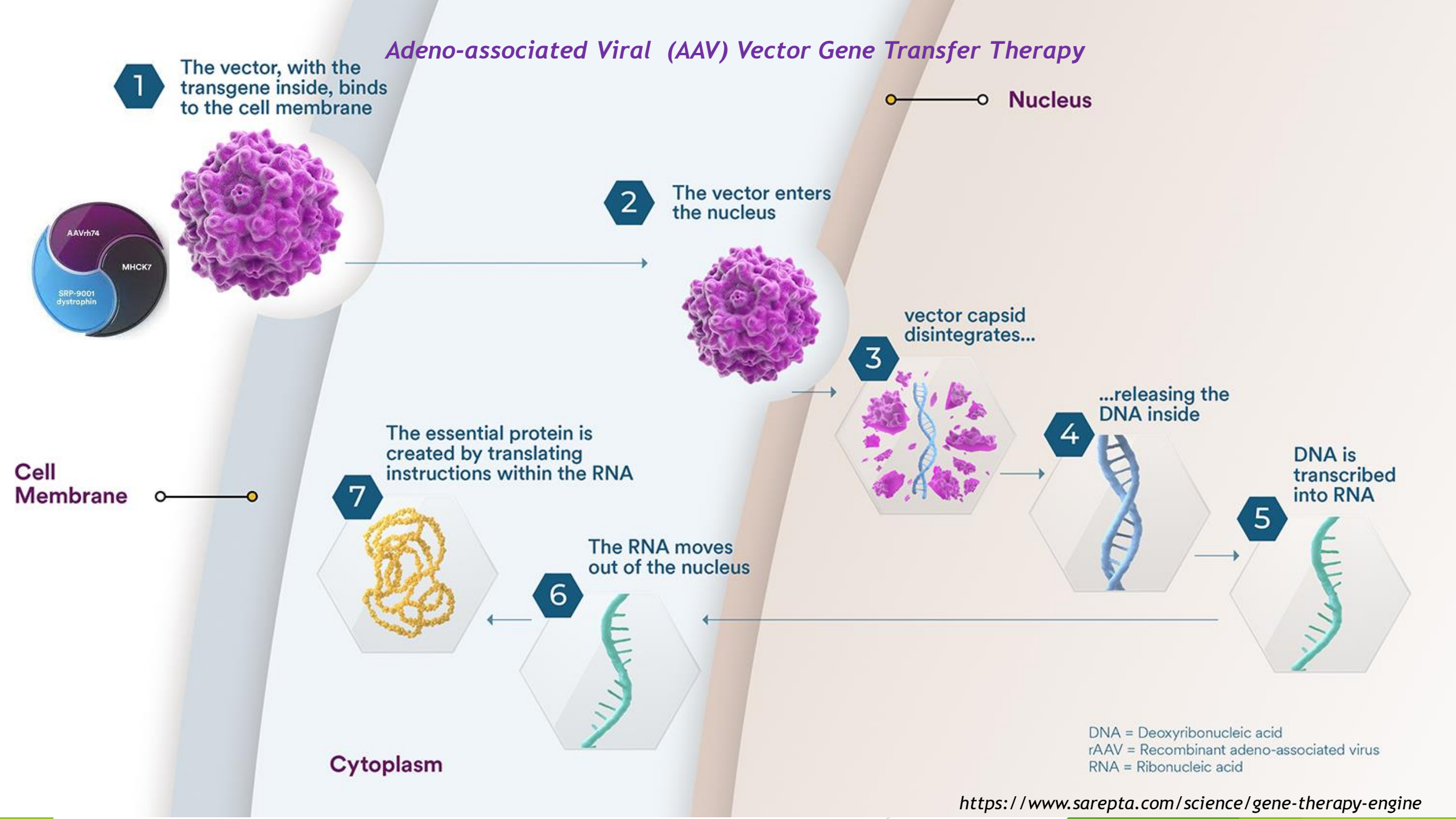
# 2016: Antisense Oligonucleotide “Exon Skipping” therapies


- Mutation-specific
  - Eteplirsen (Exondys 51) 14% of patients with DMD mutations
  - Golodirsen (Vyondys 53), Vitolarsen (Viltepso) 8-14%
  - Casimersen (Amondys 45) 4-8%
- RNA splicing:
  - After transcription
  - Before Translation (outside the nucleus)
  - Corrects the reading frame at the **mRNA level** by splicing out an adjacent exon -> in-frame code and shortened but functional dystrophin product
- Does not alter original DNA, degrades quickly
- Weekly infused therapy. - lifelong




***Robinson R, https://www.als.net/news/aso-therapy/***

# *Adeno-associated Viral (AAV) Vector Gene Transfer Therapy*




DNA = Deoxyribonucleic acid
rAAV = Recombinant adeno-associated virus
RNA = Ribonucleic acid

*https://www.sarepta.com/science/gene-therapy-engine*

Elevidys

delandistrogene moxeparvovec-rokl

suspension for intravenous infusion

# Gene Transfer therapy

- ELEVIDYS has been specifically approved for the treatment of individuals between the ages of 4 and 5 who have been diagnosed with Duchenne muscular dystrophy
- Single dose therapy
- Must be viral antibody antigen negative
- Specific Duchenne mutations are excluded


Faith Fortenberry & Justin Moy
MDA National Ambassadors

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