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Newborn Screening for Duchenne Muscular Dystrophy

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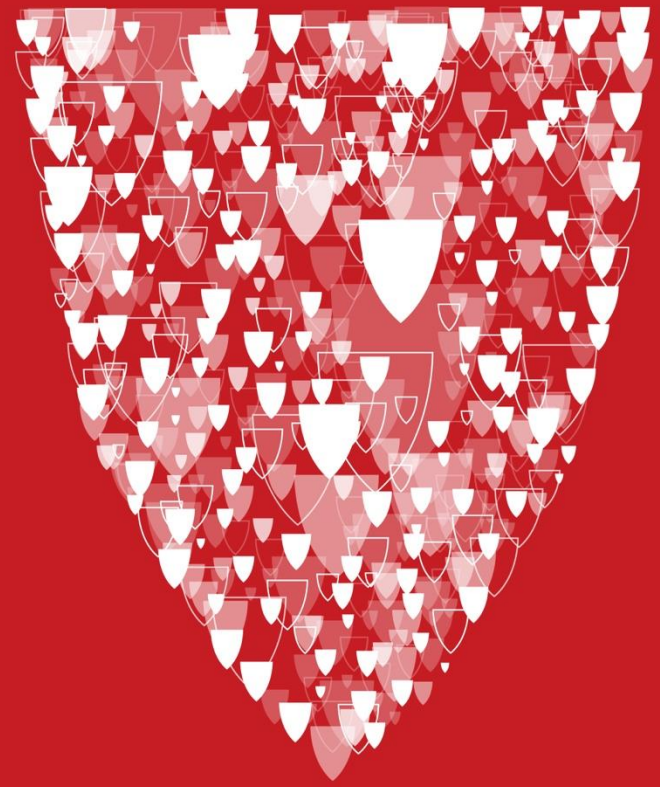
Ohio AAP Webinar

1/8/2025



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Ohio AAP DEI Toolkit Acknowledgement

- We have considered the Ohio AAP Diversity, Equity, and Inclusion standards in preparing this presentation.
- We invite your feedback in promoting equity within this learning space. If you have suggestions, please email Anna.Mitchell@UHhospitals.org

Disclosure

Anna Mitchell, MD, PhD, Brandon Hoff, DO, Rachel VanCoillie, faculty of this educational activity, have no relevant financial relationship(s) with ineligible companies to disclose.

Learning Objectives

1. Review the clinical features of Duchenne Muscular Dystrophy
2. Apply a systematic approach to the handling of an inconclusive newborn screen
3. Explain the rationale for adding DMD to the Ohio newborn screen
4. Discuss current therapies available for DMD

What is Duchenne Muscular Dystrophy?

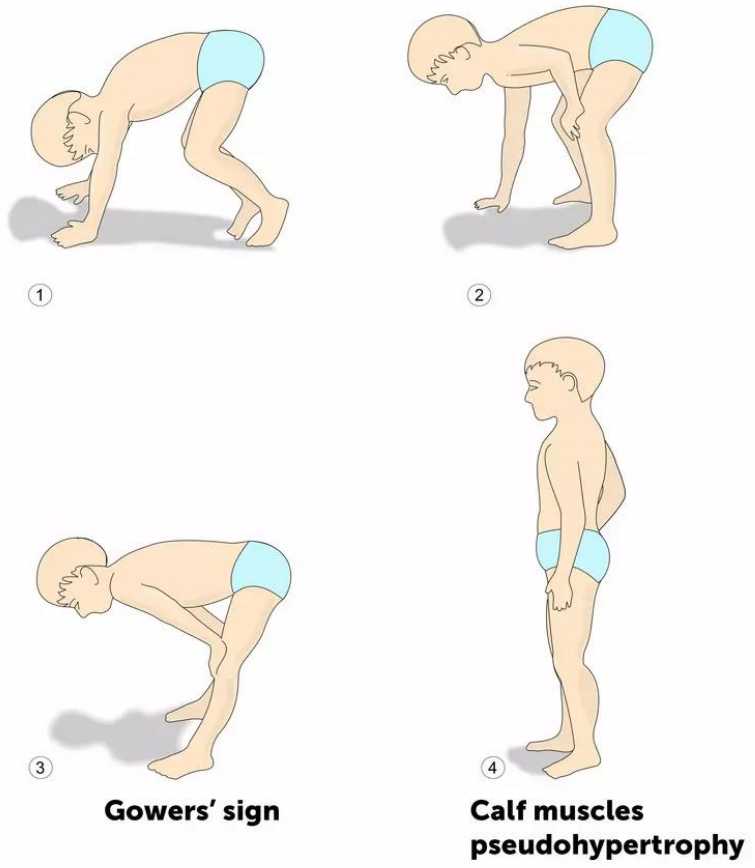
Duchenne Muscular Dystrophy (DMD)

- Part of the “Dystrophinopathy” spectrum

- Caused by variants (mutations) in the *DMD* gene, which codes for protein Dystrophin
  - “part of a protein complex that links the cytoskeleton with membrane proteins that in turn bind with proteins in the extracellular matrix”
- Prevalence
- X-linked
  - Primarily males affected
  - Is possible for females to be affected

Duchenne Muscular Dystrophy (DMD)

- Muscle weakness (predominantly proximal)
  - Delayed walking – mean age 18 months
  - Trouble getting to standing position
  - Waddling gait
  - Difficulty climbing stairs, running, jumping
  - Calf pseudohypertrophy
- Non-progressive cognitive impairment, ADHD, ASD
- Onset < 5 years of age
  - Mean age of diagnosis 41 months
- Progressive
  - Wheelchair dependent by early teens
  - Cardiomyopathy by late teens
  - Respiratory insufficiency



Newborn screening for DMD in Ohio

DMD on the Ohio Newborn Screen

- Added in April 2024
- Same dried blood spot specimen as remainder of newborn screen
- Measures CK-MM levels
    - Males with DMD often have CK-MM > 10x normal range
    - Females with DMD usually have elevated CK-MM, but often to a lesser degree than males

CK-MM Cutoff Levels (as of 6/2024)

Age at Collection	Cutoff (ng/mL)	Interpretation
0 - <48 hours	< 1,990	Within Range
48 - <72 hours	< 1,430	Within Range
72 - <168 hours	< 571	Within Range
≥168 hours	< 571	Within Range

Age at Collection	Cutoff (ng/mL)	Interpretation
0 - <48 hours	≥ 1,990	Inconclusive
48 - <72 hours	≥ 1,430	Inconclusive
72 - <168 hours	≥ 571	Inconclusive

Age at Collection	Cutoff (ng/mL)	Interpretation
≥ 168 hours	≥ 571	Elevated

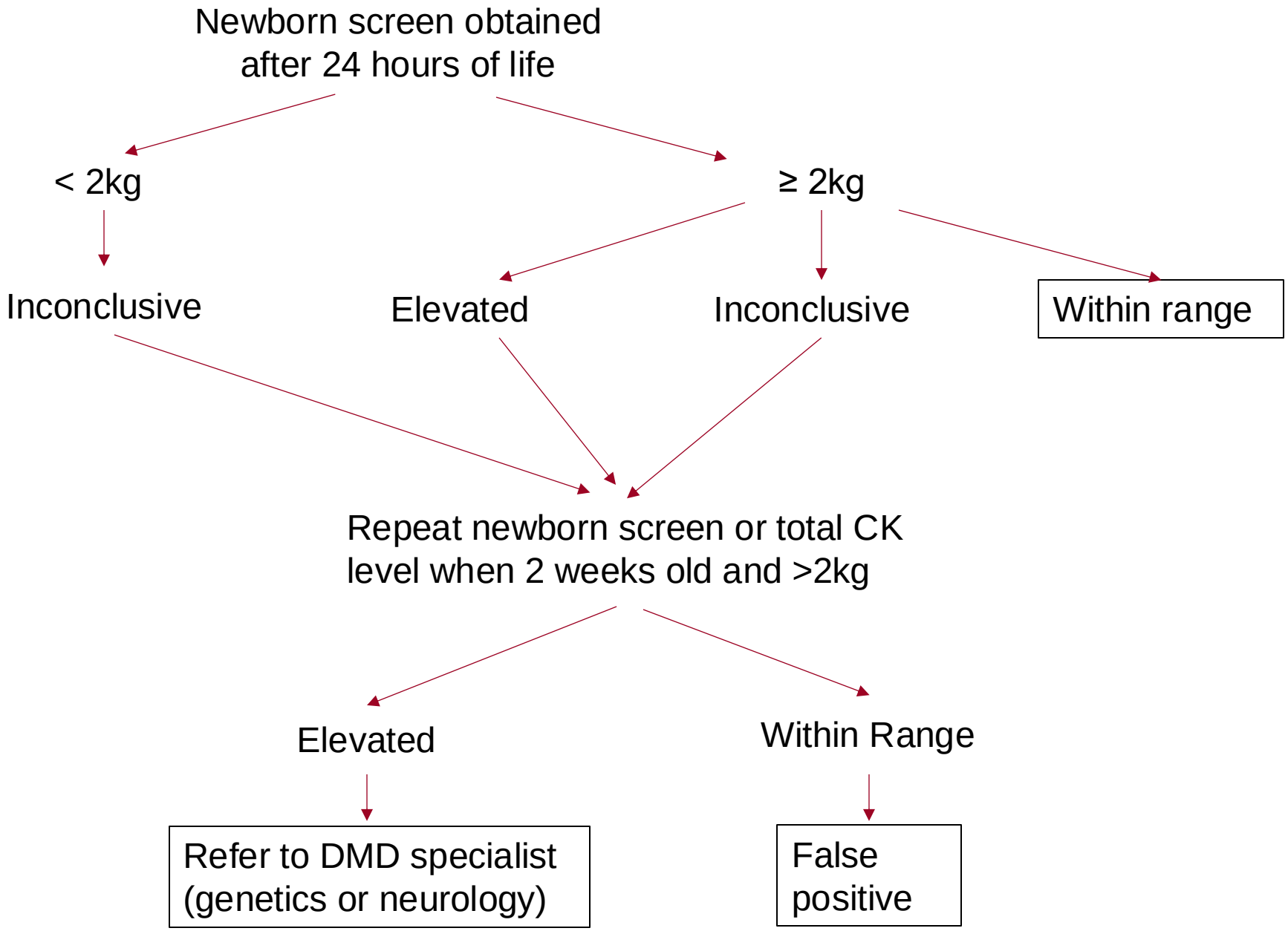
https://odh.ohio.gov/know-our-programs/Newborn-Screening/news/duchenne-muscular-dystrophy

Only validated for infants who are over 2kg! Will come back as inconclusive no matter what if infant is < 2kg.

PCP will receive NBS result and action required letter if inconclusive or elevated.

If “elevated,” ODH will also call PCP and regional specialty team

PCP should communicate screening results to the parent(s) or legal guardian and indicate that additional testing is needed to determine if their infant has a genetic muscle condition or if the increased CK-MM level has returned to “within range”.



CK may be elevated for reasons other than DMD

Birthing process

Gestational age

Other type of muscular dystrophy

*If patient is showing abnormal neurologic signs (hypotonia, lethargy, seizures, etc.) they should be referred immediately to specialist or to ER depending on severity. In these cases, likelihood of DMD is low and other etiologies should be investigated.

Why was DMD added to the newborn screen?

Wilson and Jungner Screening Principles (1968)

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with a recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case finding should be a continuing process and not a “once and for all” project.

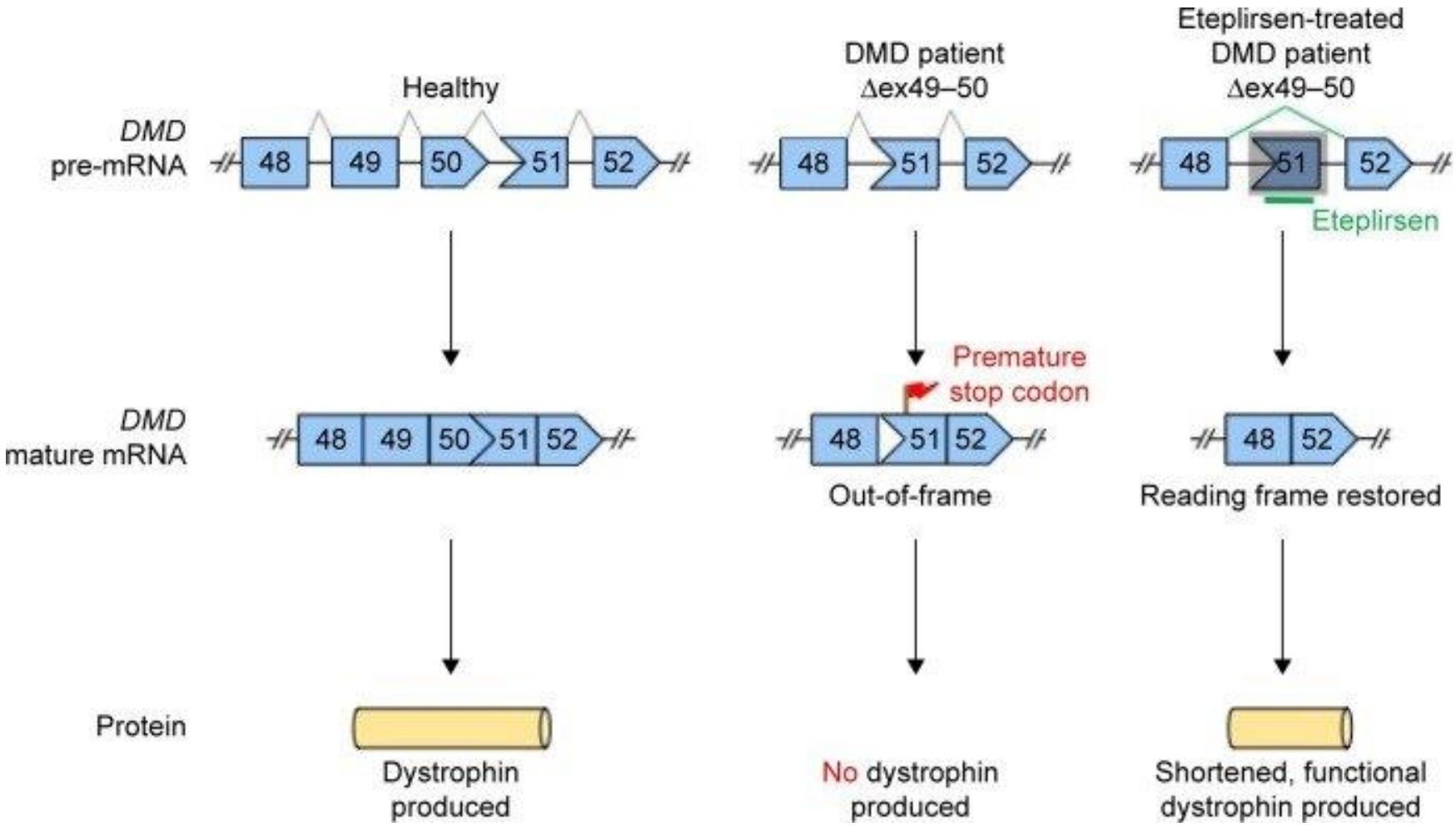
Classic treatments

- Cardiomyopathy
  - ACE inhibitors
  - Beta blockers
  - Diuretics and supplemental O2 for congestive heart failure
  - Cardiac transplantation if no skeletal muscle involvement
- Scoliosis
  - Bracing
  - Surgery
- Physical therapy
- Calcium, vitamin D to maintain bone strength
- Corticosteroids

Developing / Novel Therapies

- Exon Skipping
- Gene Therapy

Exon-Skipping Antisense Oligonucleotide (ASO) Therapy



Lim et al, Drug Design Development and Therapy, 2017

Exon-Skipping Antisense Oligonucleotide (ASO) Therapy

Targeted to the dystrophin pre-messenger RNA to skip out-of-frame variants

•**Eteplirsen (Exon 51 variants).** Exon 51 skipping restores the reading frame in these variants and is applicable to about 13% of individuals with DMD

- Eteplirsen received accelerated conditional United States Food and Drug Administration (FDA) approval in 2016 based on a clinical trial of 12 individuals with DMD who demonstrated a 23% increase in dystrophin-positive muscle fibers, an increase of dystrophin quantity by Western blot (0.08% to 0.93%), and a 151-meter difference in the decline of the six-minute walking distance (6MWD) compared to matched historical controls
- Eteplirsen is the first drug to get FDA approval using dystrophin quantification as a surrogate outcome measure for DMD.

•**Golodirsen, Viltolarsen (Exon 53 variants).** Approved by the FDA in December 2019 and is applicable to about 10% of individuals with DMD Viltolarsen, also an exon 53 skipping ASO, was approved in August 2020

•**Exon 52 deletion.** Individuals with deletion of exon 52 (accounts for ~2% of those with DMD) are amenable to either exon 51 or 53 skipping

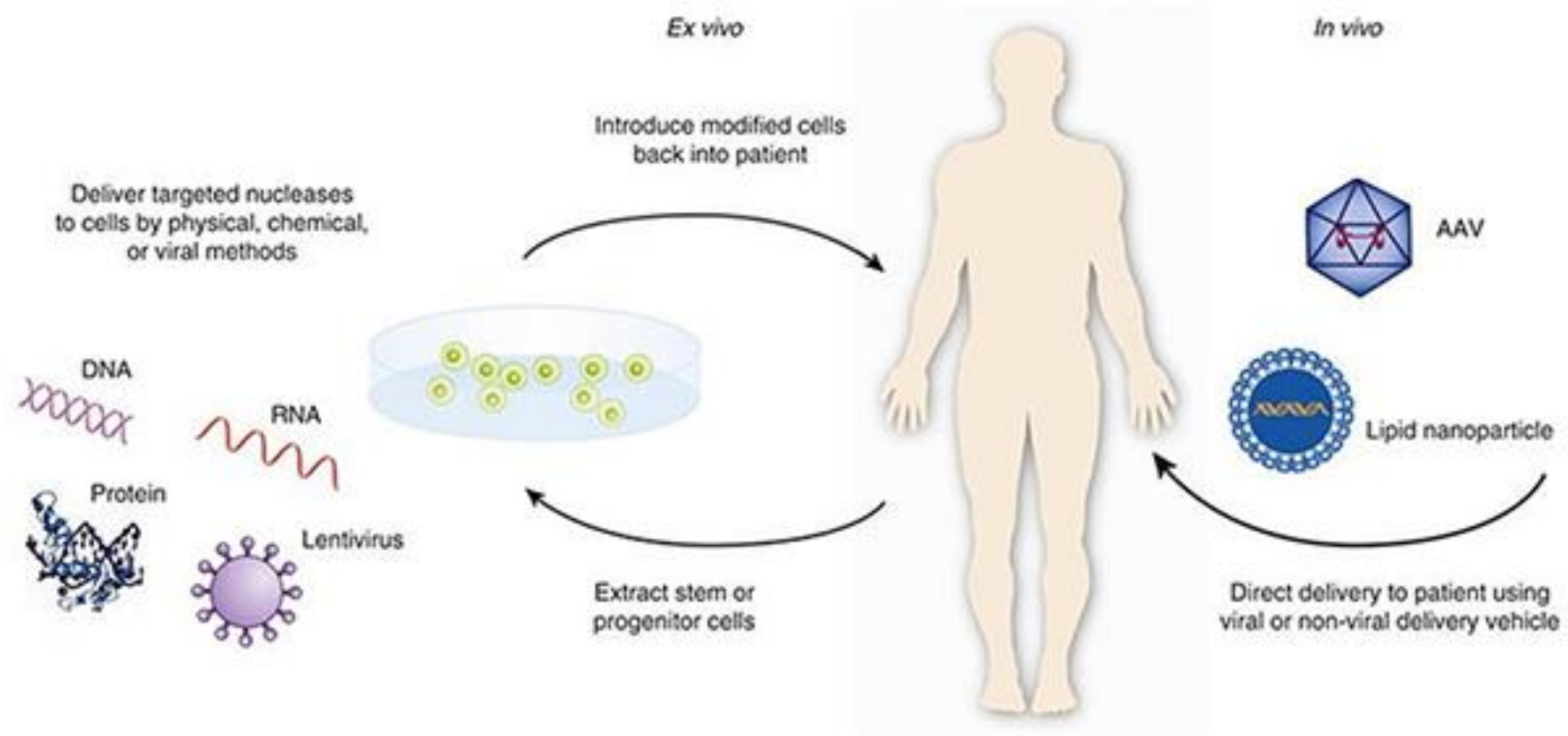
•**Casimersen (Exon 45 variants).** was approved by the FDA in February 2021.

- Currently approved treatments apply to ~30% of persons w/DMD; well tolerated; good safety profile
- Weekly intravenous infusions; variant specific

Gene Therapy

- Elevidys (delandistrogene moxeparvovec-rokl)
  - Approved by FDA in 2023 for boys 4 years of age or older with confirmed molecular diagnosis of DMD.
- Gene transfer therapy (currently in clinical trials)
  - Micro-dystrophin constructs are inserted into AAV vectors to drive high levels of transgene expression & produce enough potentially functional micro-dystrophin.
  - Variant nonspecific; single intravenous administration
  - Cannot restore full-length dystrophin; durability of therapeutic response; safety concerns (possibility of integration into host genome & risk of mutagenesis)

Gene Therapy

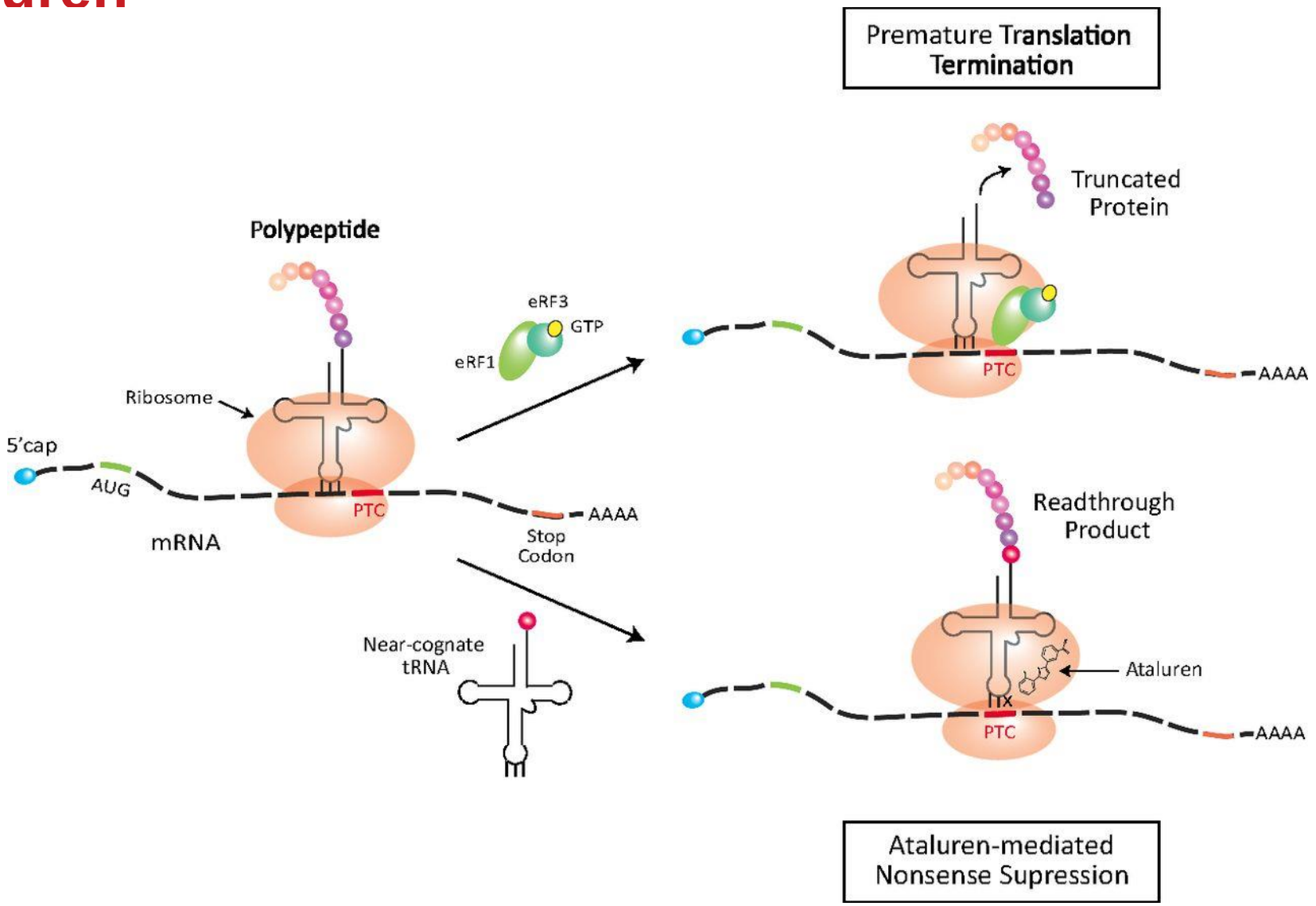


US FDA

Therapies in Development

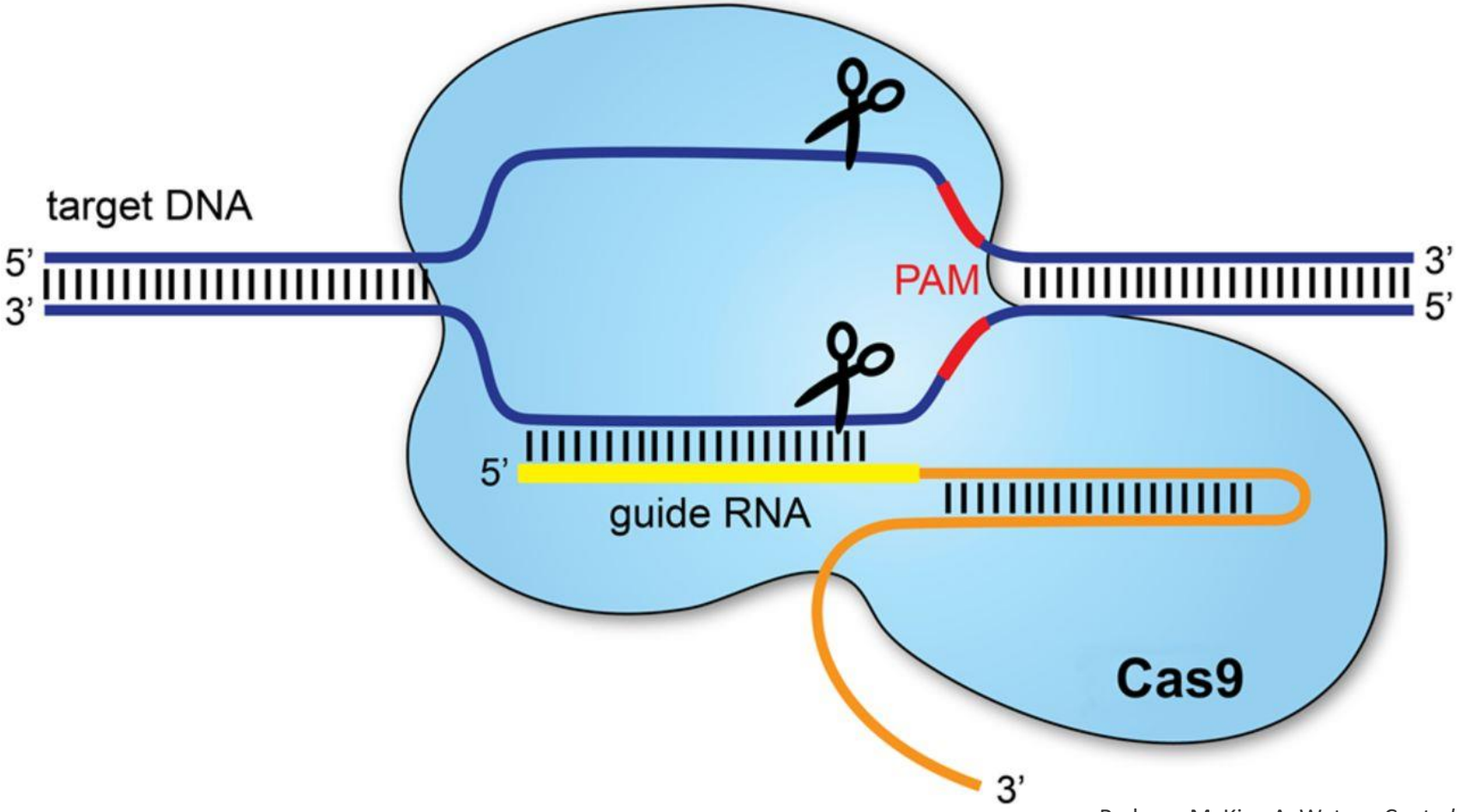
- Ataluren (approved by European Medicines Agency; not FDA approved)
  - 10-15% of patients
  - Stop codon read-through strategy for nonsense variants - promoting ribosomal read-through, allowing bypass of the pathogenic variant and continuation of the translation process to production of a functioning protein
  - Orally administered; well tolerated; good safety profile
  - Variant specific
- CRISPR/Cas9-mediated gene editing (preclinical phase)
  - Programmable nucleases to correct a gene defect
  - Variant nonspecific
  - Off-target effects; safety & tolerability concerns

Ataluren



N Siddiqui and N Sonenberg, PNAS, October 2016

CRISPR- Cas



Redman M, King A, Watson C, *et al*
Archives of Disease in Childhood - Education and Practice 2016;**101:**213-215.

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Your friendly neighborhood geneticists are here to help!

- You will likely get many initial inconclusive results, which can be frustrating.
- Over time this will likely improve as ODH reviews data on appropriate cutoffs
- Please reach out to a geneticist with any questions

1 Division of Human Genetics

Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue, MLC 4006
Cincinnati, OH 45229

(513) 636-4760
www.cincinnatichildrens.org

Dayton Outreach Sites: Westchester and Mason

2 Division of Medical Genetics

Dayton Children's Hospital
One Children's Plaza
Dayton, OH 45404

(937) 641-3800

www.childrensdayton.org

Dayton Outreach Sites: Beavercreek, Franklin, and Spri

3 Toledo Children's Hospital

2150 W. Central Avenue
Toledo, OH 43606

(419) 291-5599

www.utoledo.edu

4 Nationwide Children's Hospital

700 Children's Drive
Columbus, OH 43205

(614) 722-3535

www.nationwidechildrens.org

Columbus Outreach Sites:
Athens | Waverly | Marietta | Zanesville | Lima

5 Department of Pediatrics

MetroHealth Medical Center
2500 MetroHealth Drive
Cleveland, OH 44109

(216) 778-4444

https://www.metrohealth.org/genetics

6 University Hospitals Cleveland Medical Center

11100 Euclid Avenue, Lakeside 1500
Cleveland, OH 44106

(216) 844-3936

7 Center for Personalized Genetic Healthcare

Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland, OH 44195

(216) 636-1768

https://my.clevelandclinic.org/departments/genomics/about#overview-tab

8 Akron Children's Hospital

215 West Bowery Street
Akron, OH 44308

(330) 543-8792

www.akronchildrens.org

Akron Outreach Sites: Ravenna

Satellite site:
Aultman Maternal Fetal Medicine
2600 Tuscarawas St. W, Suite 300
Canton, OH 44708

(330) 363-6296

Reference: https://odh.ohio.gov/know-our-programs/genetic-services/resources/locations-of-clinical-genetic-services

Thank you!

References and Resources:

- Ohio Department of Health Newborn Screening Program: https://odh.ohio.gov/know-our-programs/newborn-screening/welcome-to-newborn-screening
- Genereviews – Dystropinopathies: https://www.ncbi.nlm.nih.gov/books/NBK1119/
- ClinicalTrials.gov: https://clinicaltrials.gov/
- FDA Drug Labels / Package Inserts: https://labels.fda.gov/

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