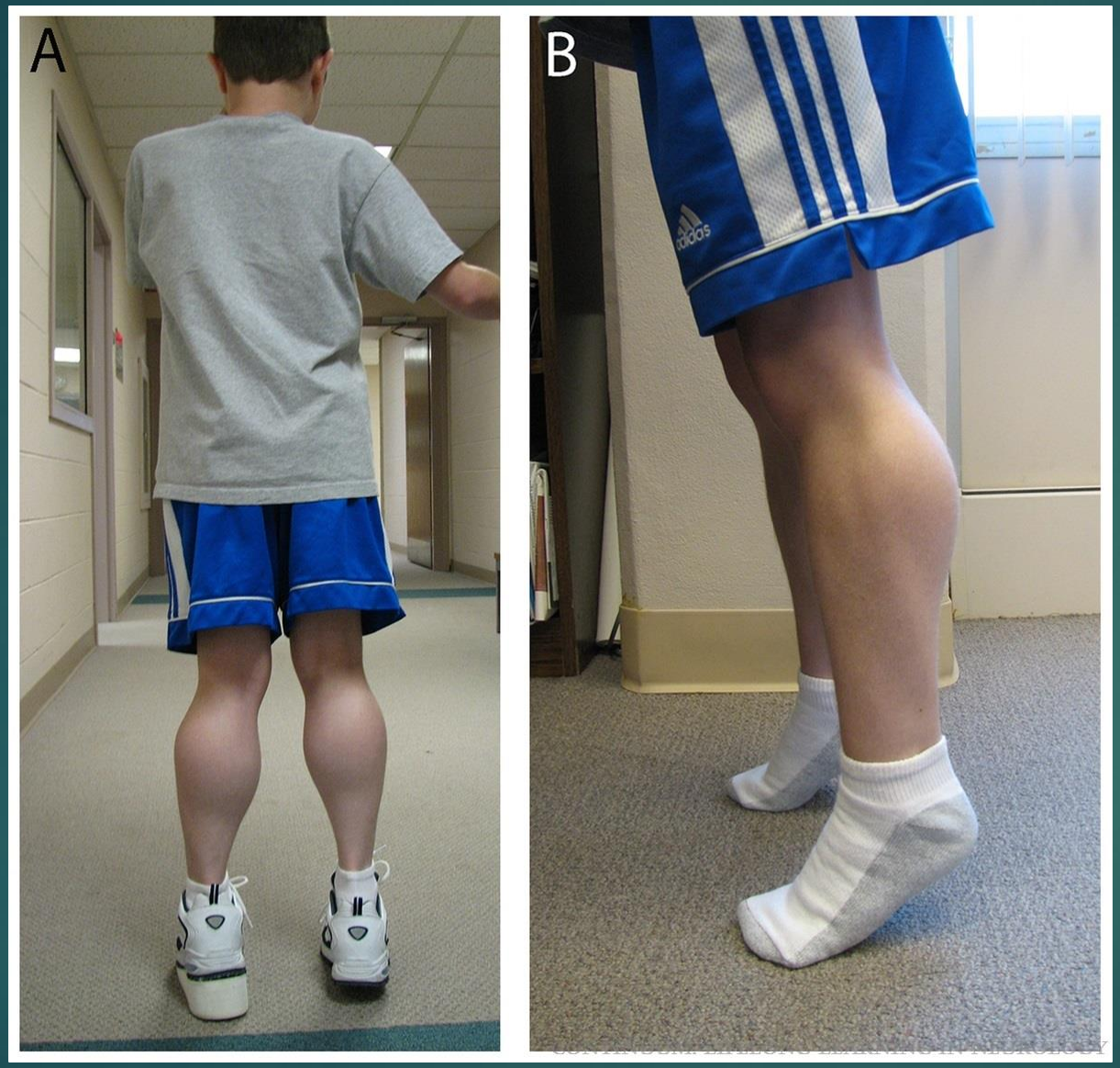
Muscular Dystrophy

DEBORAH YOUNG BRADSHAW, MD
PROFESSOR, DEPARTMENT OF NEUROLOGY
UPSTATE MEDICAL UNIVERSITY

Case: William

- 5 year old boy
- Brought to pediatrician due to difficulty running
- Normal pregnancy and birth
- Walked at 16 months (late)
- Mom noticed William had large calves
- A brother had died of heart problems at age 12 (brother had similar calves)

FIGURE 10-3



The Limb-Girdle Muscular Dystrophies and the Dystrophinopathies

Iyadurai, Stanley Jones P.; Kissel, John T.

CONTINUUM: Lifelong Learning in Neurology22(6):1954-1977, December 2016.

doi: 10.1212/CON.0000000000000406

Images of a 6-year-old boy with Duchenne muscular dystrophy showing calf hypertrophy evaluated from posterior view (A) and from lateral view, further accentuated by standing on toes (B).

Process of Medical Diagnosis

- Patient complaints: **Symptoms**
- Examination (physician's observations): **Signs**
- Combination of above usually indicate which body system is affected:
  - Cough/sore throat: red throat on exam and swollen glands = upper respiratory system
  - Abdominal pain/diarrhea and tender belly on exam = gastrointestinal

When is a symptom due to problems with the nervous system?

- Problems with
  - Thinking/speaking
  - The senses: vision, touch, hearing
  - Movement/coordination
  - Autonomic (unconscious functions): bowel, bladder

Neurological Localization

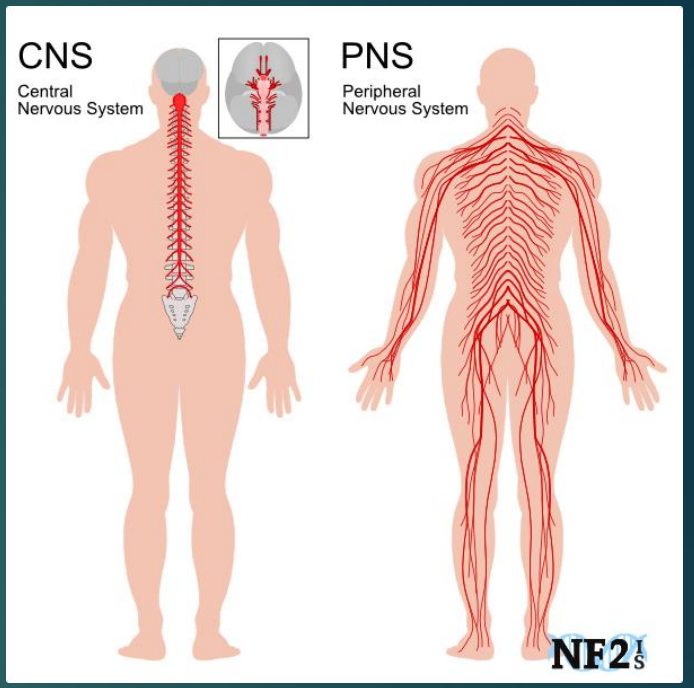
- Where is the problem?
  - Brain
  - Spinal cord
  - Nerves
  - Muscle

Localization

- Where is the problem?
  - Brain
  - Spinal cord
  - Nerves
  - Muscle

Central nervous system

Peripheral Nervous system



CNS diseases

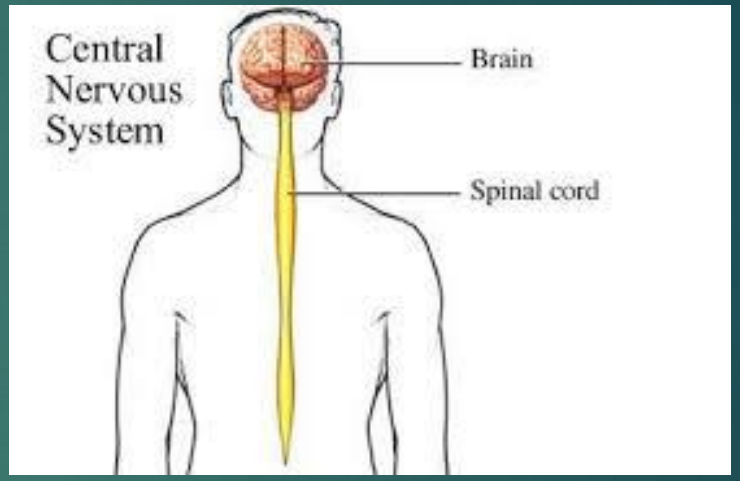
Epilepsy

Stroke

Multiple sclerosis

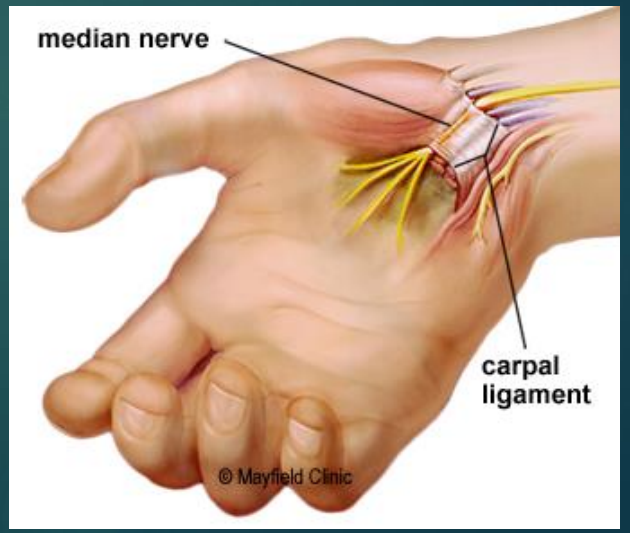
Migraine

Quadriplegia/paraplegia



Peripheral nervous system diseases

- Pinched nerves (carpal tunnel syndrome)
- Neuropathy (numb feet and hands)
- Myasthenia gravis (disconnection between nerve and muscle
- Muscle disease
  - **Muscular dystrophy**



How can doctors tell if it is a disease of the CNS or PNS?

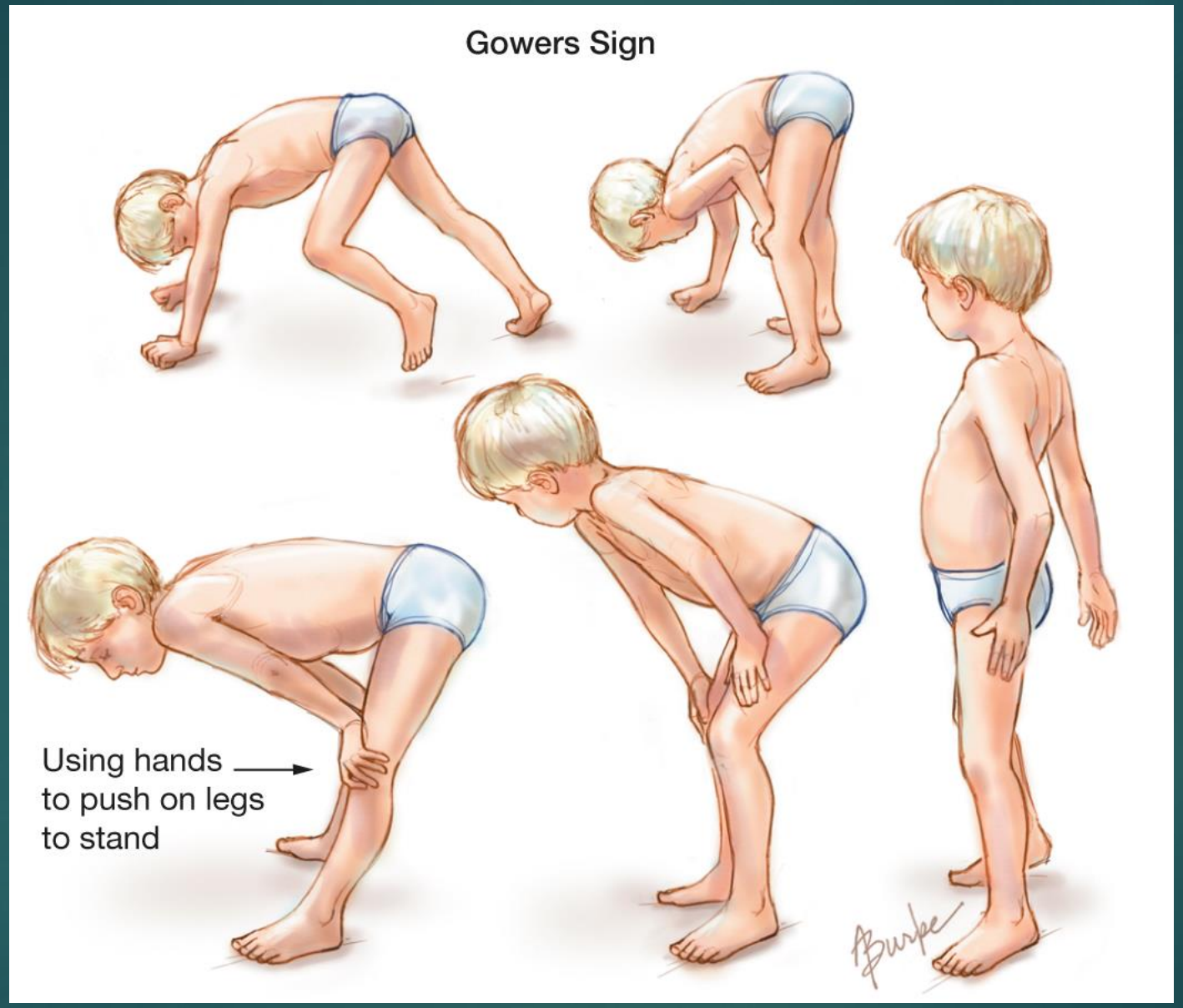
- If thinking is abnormal = brain
- If special senses (hearing/vision/taste/smell) are affected = brain or nerve to brain
- Reflexes help a lot:
  - Over-active reflexes = CNS
  - Under-active reflexes = PNS

William

- Parents describe William's interactions and use of language normal for age. "Cognitive" milestones on target
- Eyes, hearing, speech, swallowing all normal.
- Only problem is "motor" so we are already thinking of a peripheral nervous system/muscle problem.

William's Physical Examination

- Normal thinking and speech
- Normal eyes, ears, nose and mouth
- **Proximal** muscles are weak
  - Movement at the shoulders and elbows (biceps & triceps) weak
  - Movement at hips and knees weak
  - Wrists, hands and ankles are strong
- Normal sensation (touch, pinprick, etc)
- Reflexes are slightly reduced
- Waddling gait
- POSITIVE GOWER'S MANEUVER



https://jamanetwork.com/journals/jama/fullarticle/1104723


Gowers Sign
A 5-year-old boy with Duchenne muscular dystrophy demonstrating the Gowers sign. Notice how he "climbs on himself" to stand up.
CONTINUUM
AMERICAN ACADEMY OF NEUROLOGY

TESTING

ADDS DIAGNOSTIC CERTAINTY TO PHYSICIAN'S TENTATIVE DIAGNOSIS

CPK: CREATINE PHOSPHOKINASE

- Enzyme (protein that has important action in the body) which is abundant in in muscle tissue
- When muscle is damaged, CPK leaks out of muscle and into bloodstream.
- Diseases that damage muscle like muscular dystrophy cause increased levels
- Elevated CPK is a good test to confirm if a patient has a muscle disease

WILLIAM'S CPK

- **3,000** units/liter (normal is less than 200)
- Confirms the preliminary diagnosis of a muscle disease.

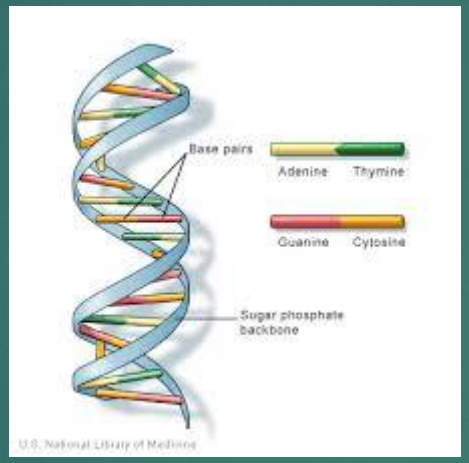
MUSCLE DISEASE

ISOLATED "PROXIMAL" WEAKNESS

ELEVATED CPK

WHICH MUSCLE DISEASE?

- HEREDITARY

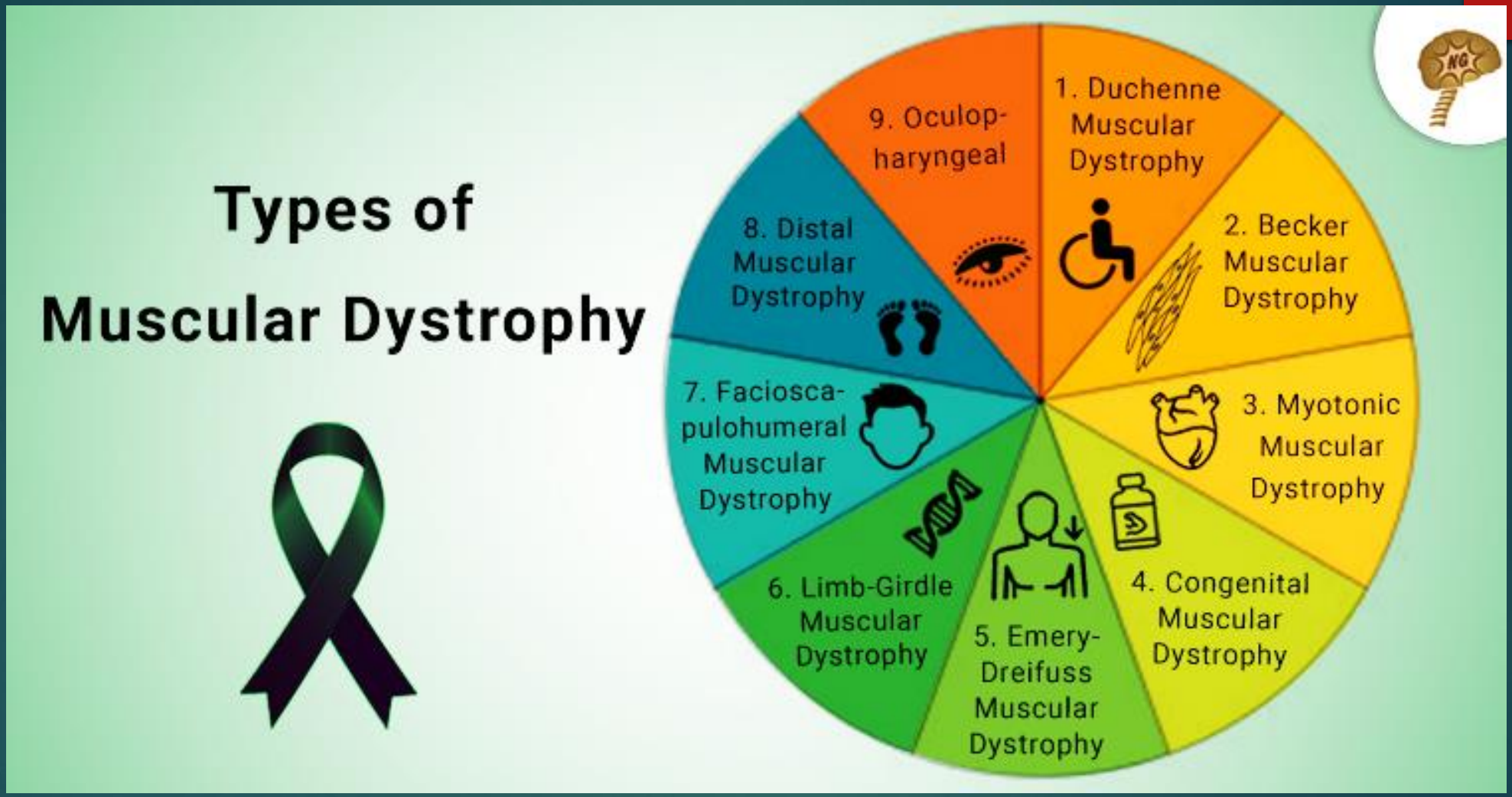


- AQUIRED
  - MUSCLES ATTACKED BY IMMUNE SYSTEM
  - TOXIC SUBSTANCES

When serious diseases occur early in life (childhood)they are usually inherited (in the DNA).

INHERITED MUSCLE DISEASE = **MUSCULAR DYSTROPHY**

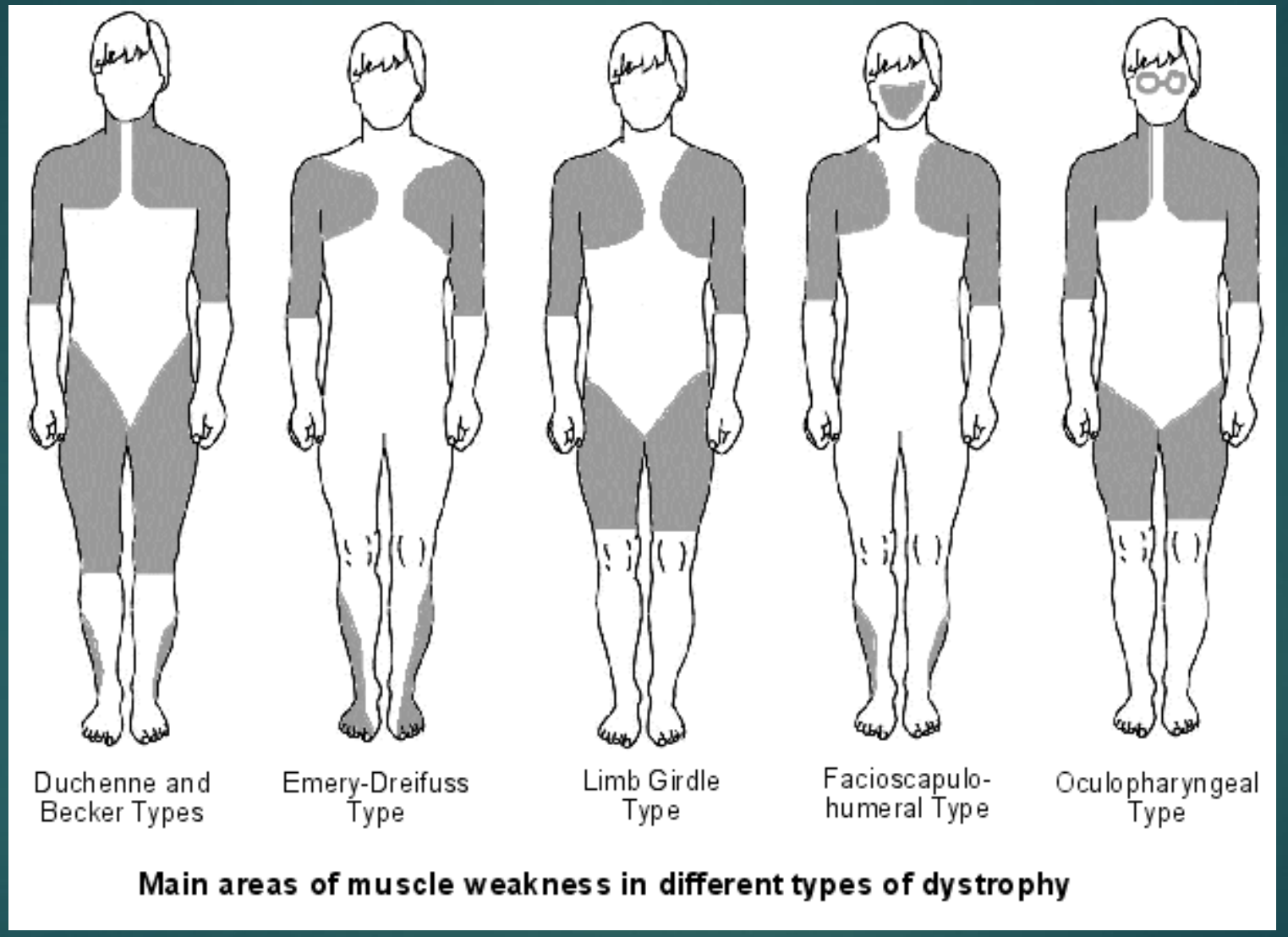
Types of Muscular Dystrophy



https://www.neurogenbsi.com/new-hope-for-muscular-dystrophy/

TYPES OF MUSCULAR DYSTROPHY

- GENDER
- AGE OF ONSET
- WEAKNESS PATTERN
- FAMILY HISTORY
- DEGREE OF CPK ELEVATION



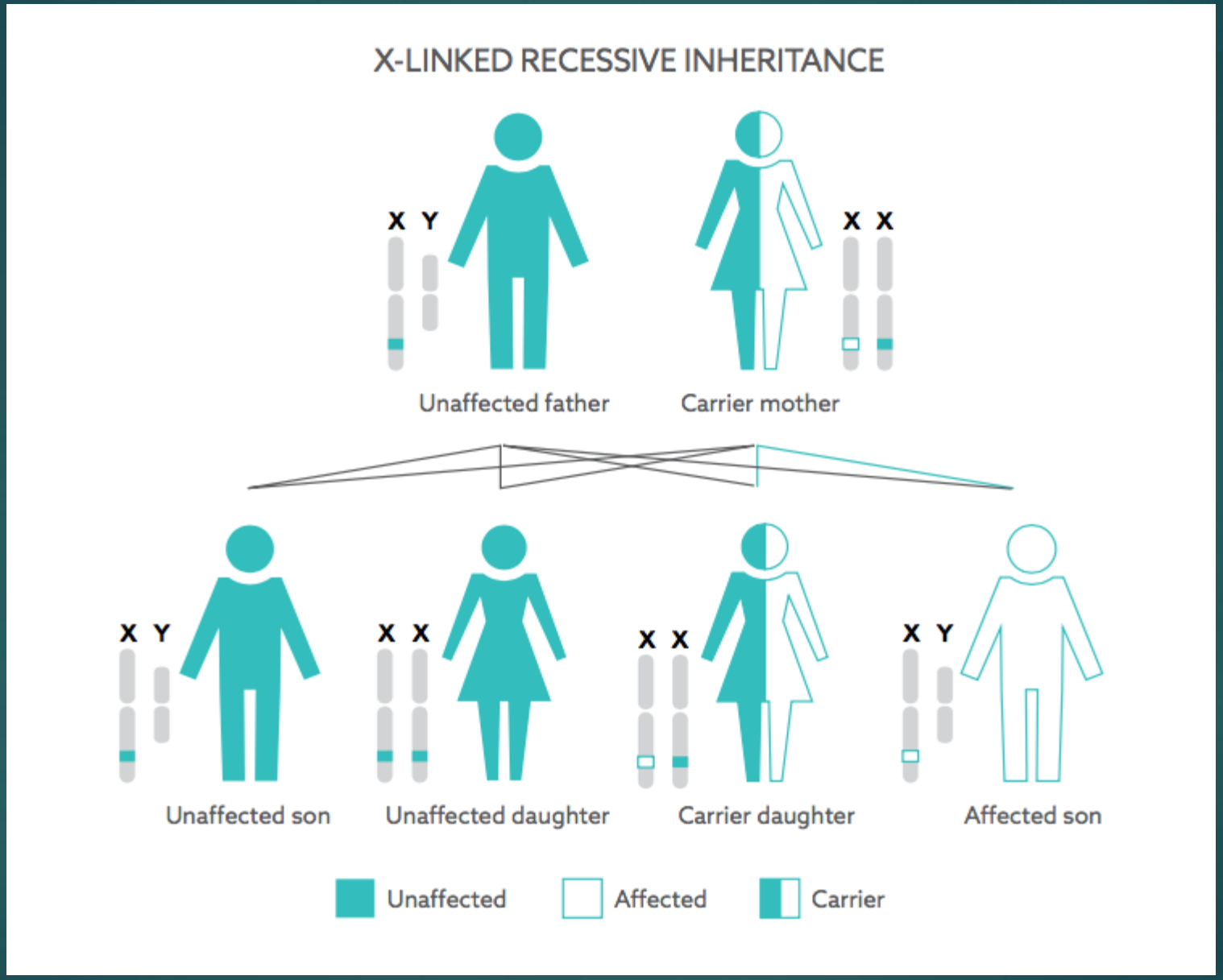
Main areas of muscle weakness in different types of dystrophy

WILLIAM

- Symptoms began before 5
- Proximal weakness with normal facial muscles
- Big calves
- Family history?
  - Parents normal but mom has muscle pain
  - Older brother died at age 12 of unknown cardiac conditions
- Very high CPK
- **Duchenne muscular dystrophy**

Duchenne muscular dystrophy (DMD)

- Most common muscular dystrophy
- 1/3500-5000 boys
- Passed by mother on “X chromosome”

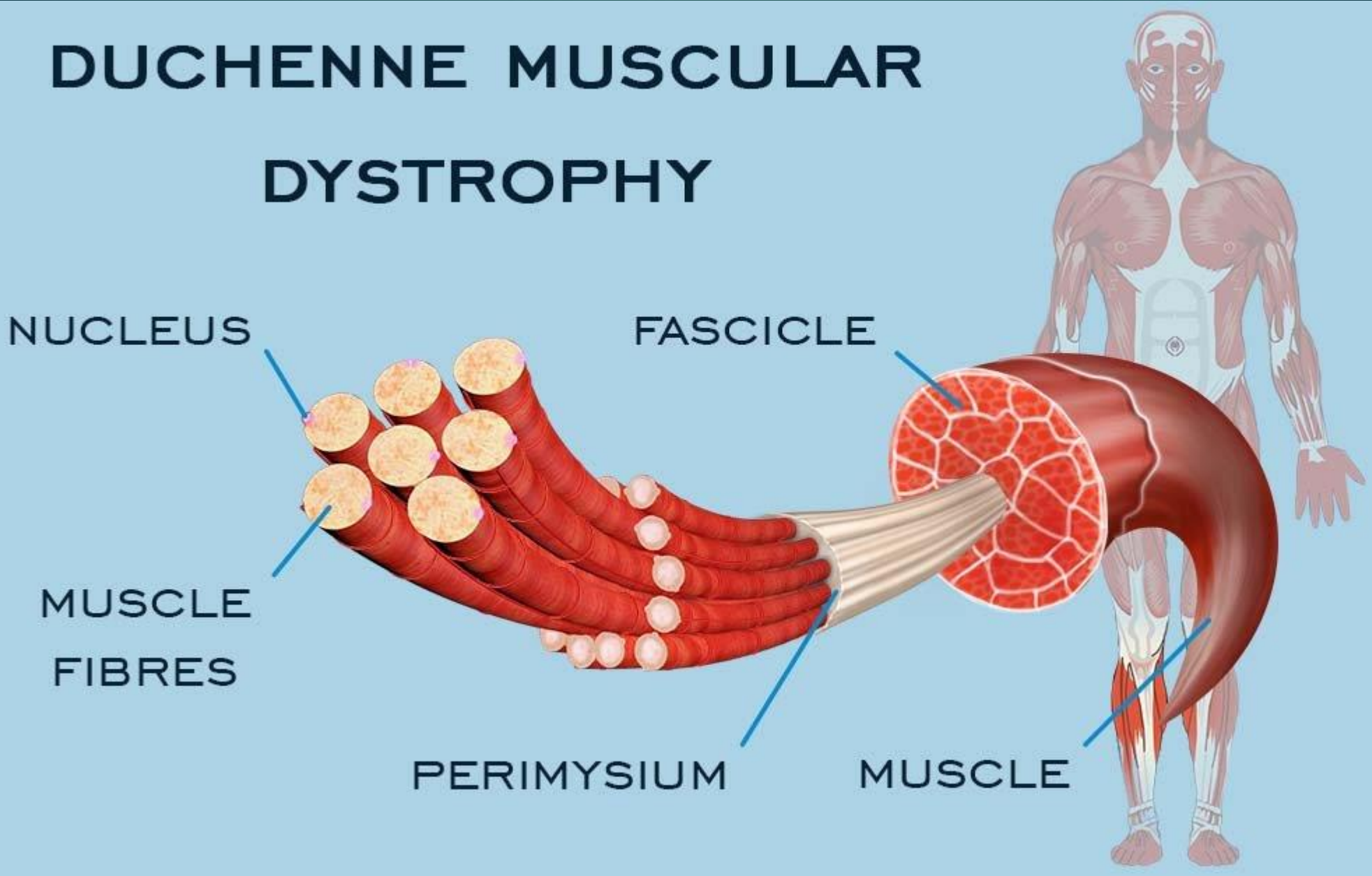


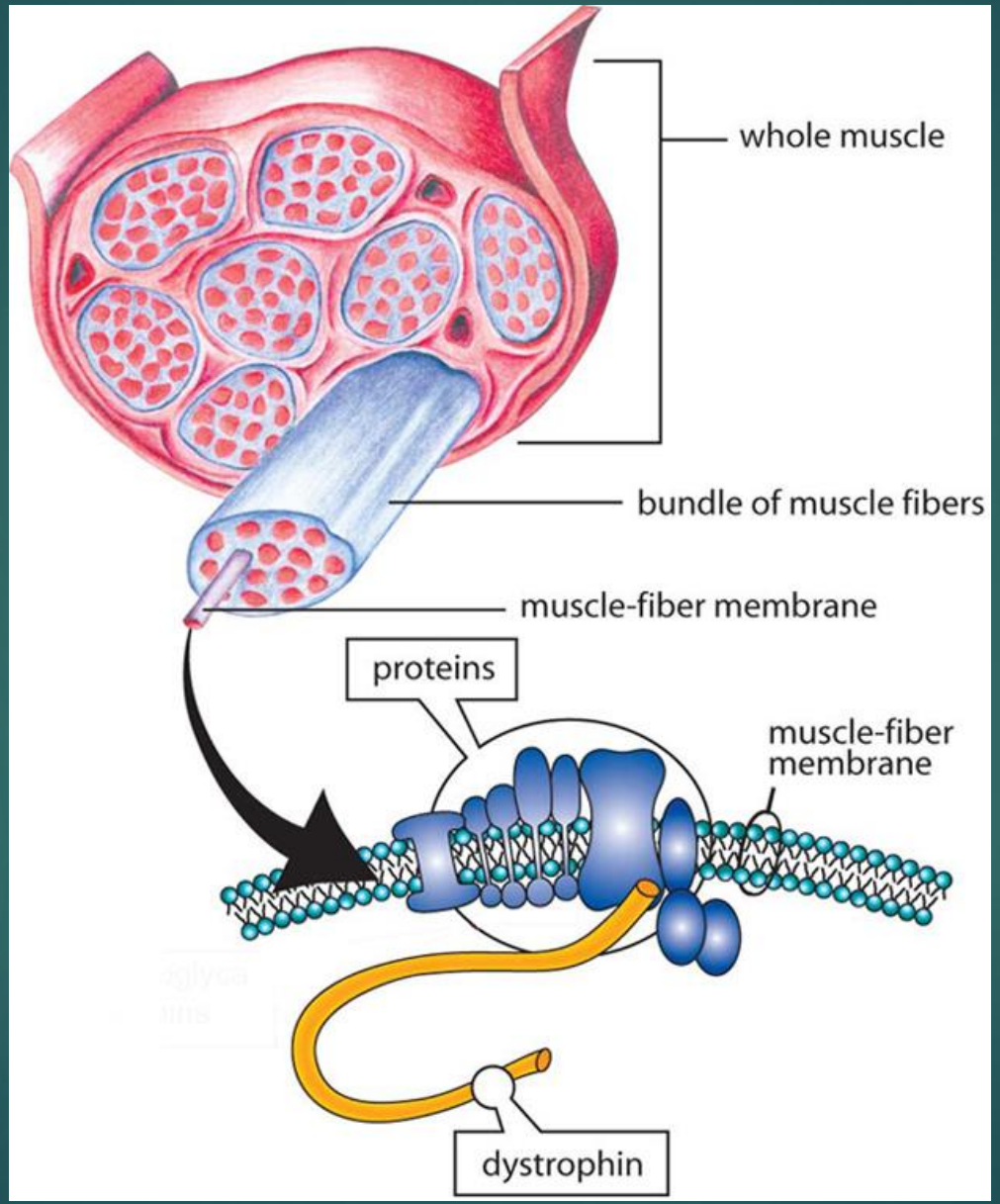
https://duchennecanada.org/disease-treatment/how-duchenne-is-inherited/

HOW TO DIAGNOSE MUSCULAR DYSTROPHY

- MUSCLE BIOPSY
- GENETIC TESTING

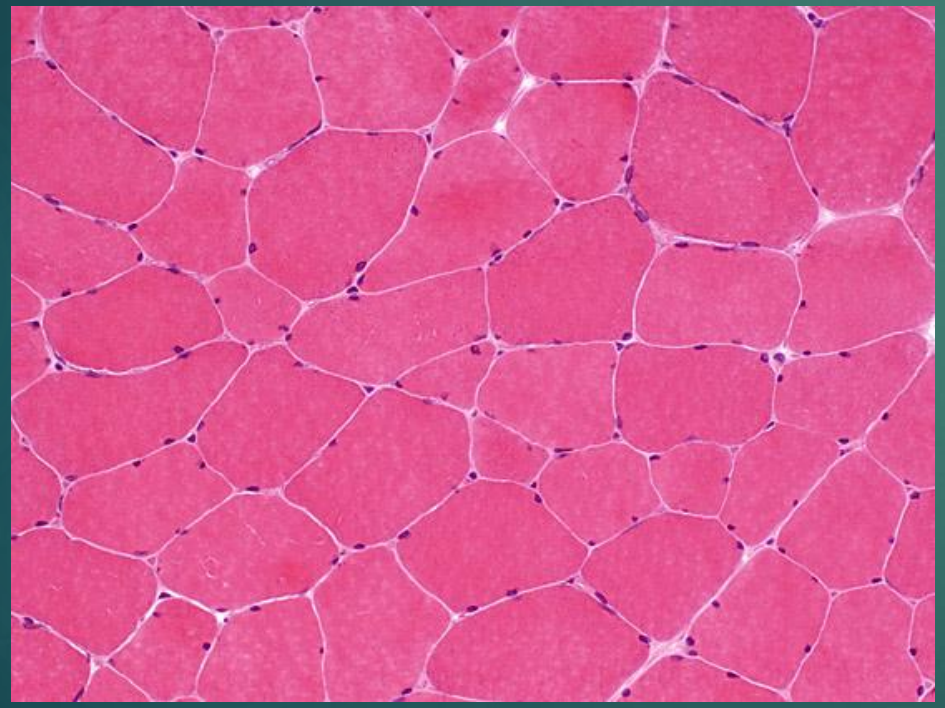
DUCHENNE MUSCULAR DYSTROPHY



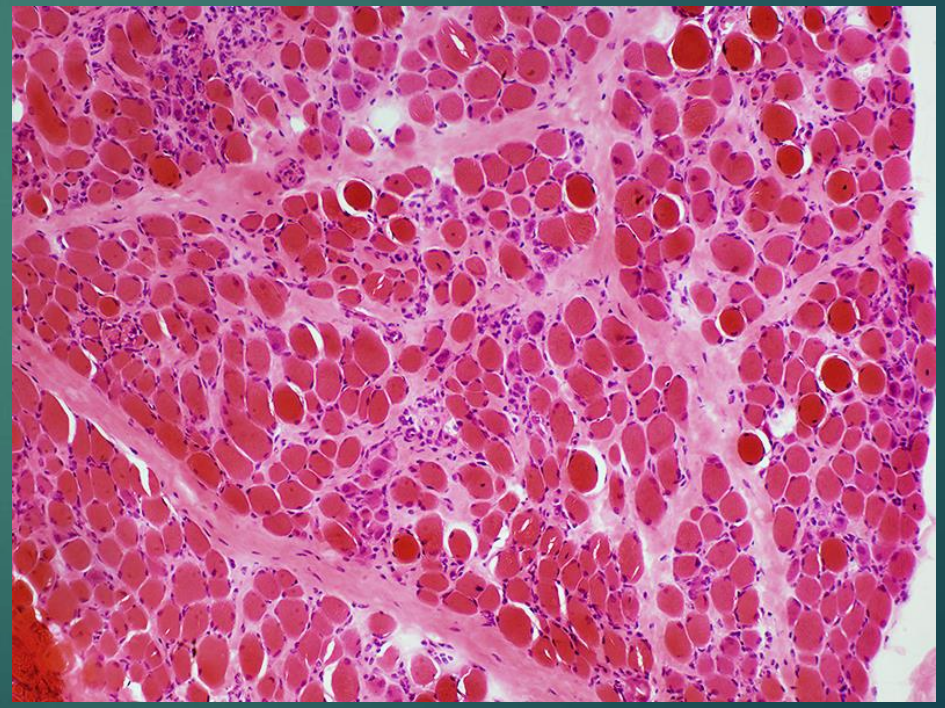

whole muscle
bundle of muscle fibers
muscle-fiber membrane
proteins
muscle-fiber membrane
dystrophin

MUSCLE UNDER THE MICROSCOPE

NORMAL

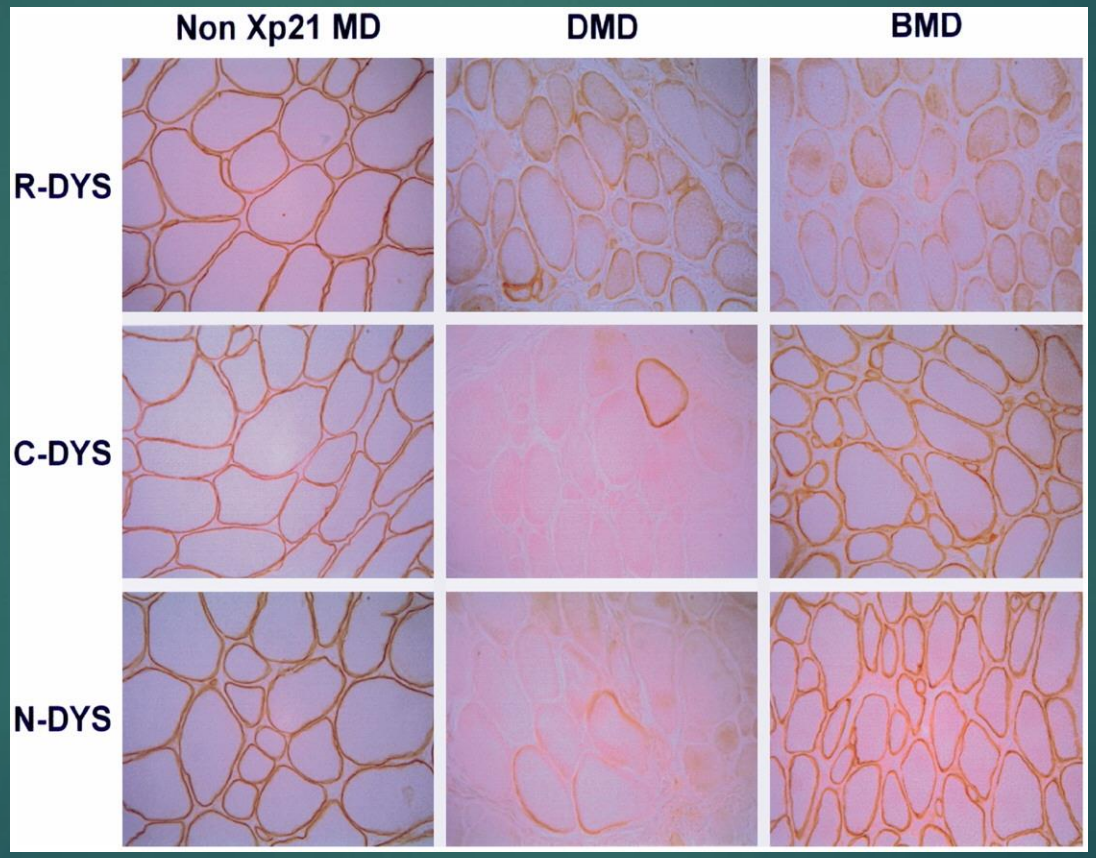


DMD



https://neuromuscular.wustl.edu/pathol/dmdpath.htm#dmdolder

We can stain muscle samples with antibodies to **dystrophin**



Vogel, H Zamecnik J. Diagnostic Immunohistology of Muscle Diseases. J Neuropath Exp Neurol Volume 64(3), March 2005, pp 181-193

HOW TO DIAGNOSE MUSCULAR DYSTROPHY

- MUSCLE BIOPSY
- GENETIC TESTING

Genetic testing is now preferred

- Blood or saliva
- 100% sensitive and specific when the mutation is known
- Increasingly available through free programs

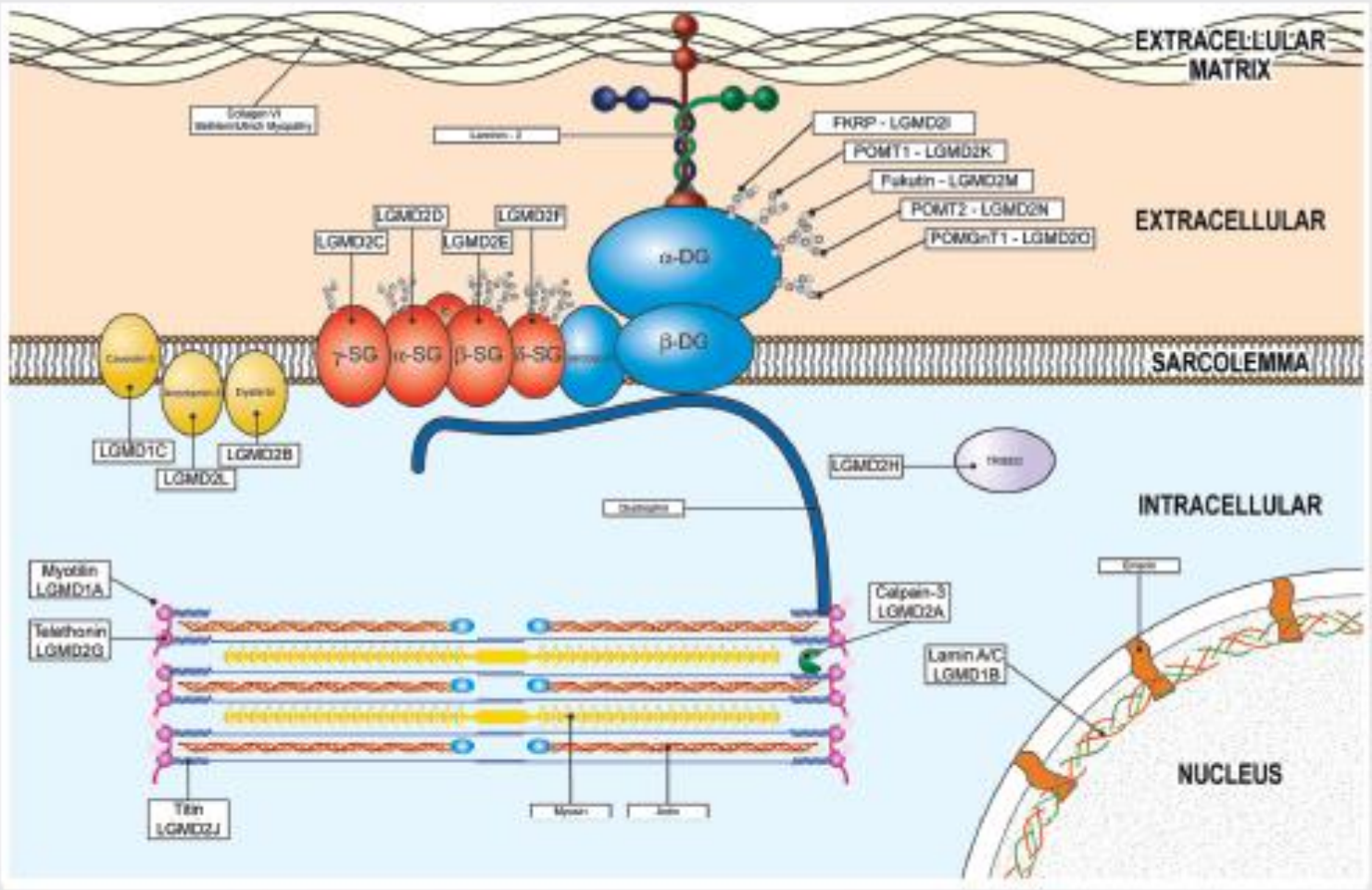
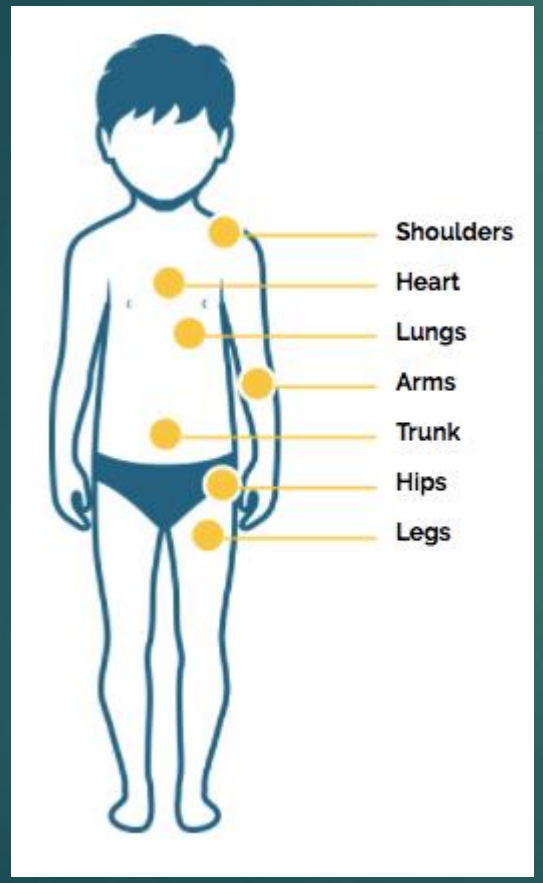


FIGURE 2-13 Subcellular localization of the limb-girdle muscular dystrophies.

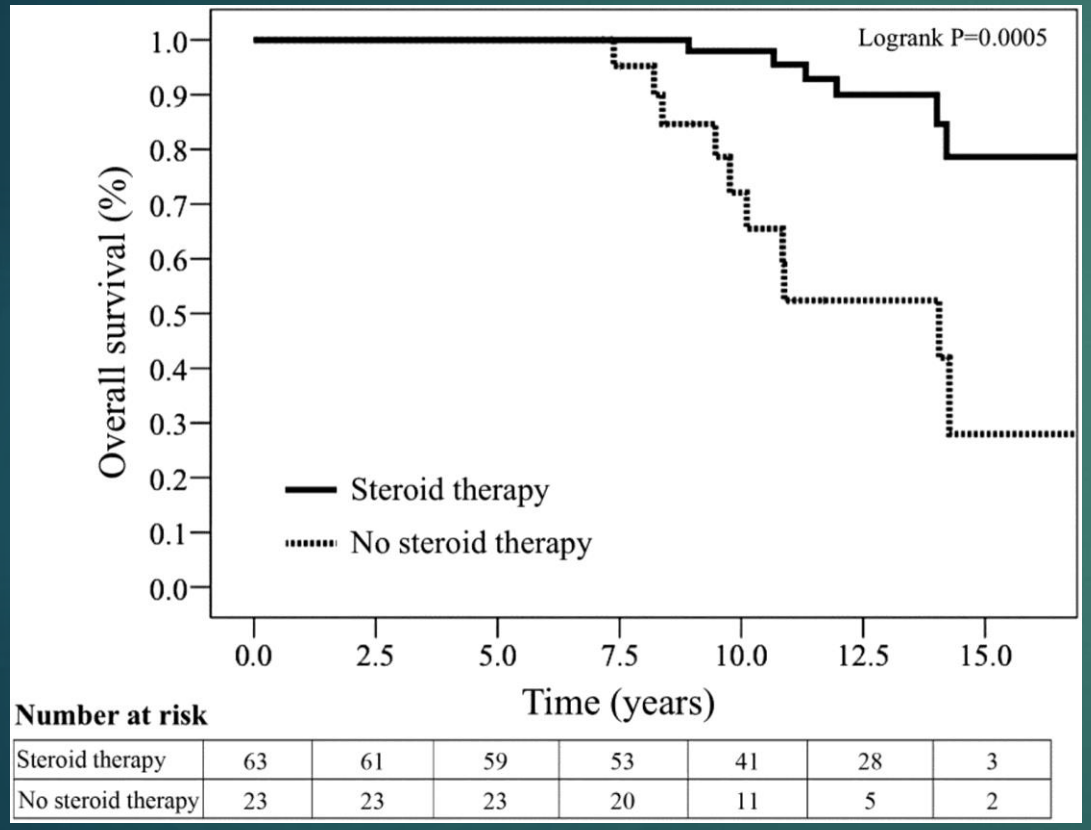
FKRP = fukutin-related protein; LGMD = limb-girdle muscular dystrophy; POMT = protein-O-mannosyltransferase; DG = dystroglycan; POMGnT1 = protein-O-linked mannose β1, 2-*N*-acetylglucosaminyltransferase; SG = sarcoglycan; TRIM32 = tripartite motif containing protein 32.

Advancing DMD



- Loss of walking by age 12
- Progressive curvature of the spine
- Heart muscle becomes weak and electrical system misfires
- Breathing weakens
- Death usually occurs late 20s or early 30s.

Treatment: Steroids are beneficial in DMD



Number at risk

Steroid therapy	63	61	59	53	41	28	3
No steroid therapy	23	23	23	20	11	5	2

- Prolongs walking
- Prolong time free of ventilator
- Delays scoliosis
- Prolongs life

Journal of the American College of Cardiology
Volume 61, Issue 9, March 2013

FDA News Release

FDA grants accelerated approval to first drug for Duchenne muscular dystrophy

For Immediate Release

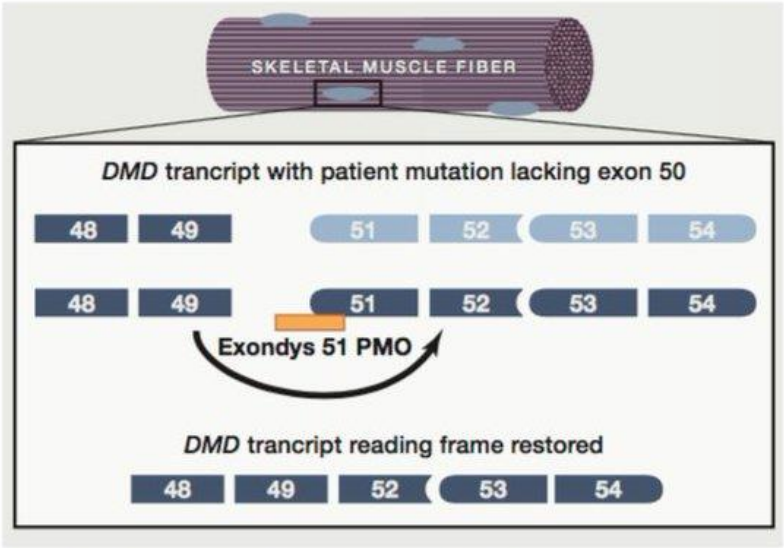
September 19, 2016

The accelerated approval of Exondys 51 is based on the surrogate endpoint of dystrophin increase in skeletal muscle observed in some Exondys 51-treated patients.

How Exondys works:

Exon Skipping Therapy

Courtney S. Young[1] and April D. Pyle[1,2,*]
[1]Molecular Biology Interdepartmental Program, Center for Duchenne Muscular Dystrophy, Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research, University of California, Los Angeles, Los Angeles, CA 90095; [2]Department of Microbiology, Immunology and Molecular Genetics, University of California, Los Angeles, Los Angeles, CA 90095
*Correspondence: apyle@mednet.ucla.edu
http://dx.doi.org/10.1016/j.cell.2016.10.050



Exondys 51 is the first therapy for Duchenne muscular dystrophy (DMD) to have been granted accelerated

NAME
Exondys 51 (Eteplirsen)

APPROVED FOR
Patients with Duchenne muscular dystrophy who have a confirmed mutation applicable to exon 51 skipping

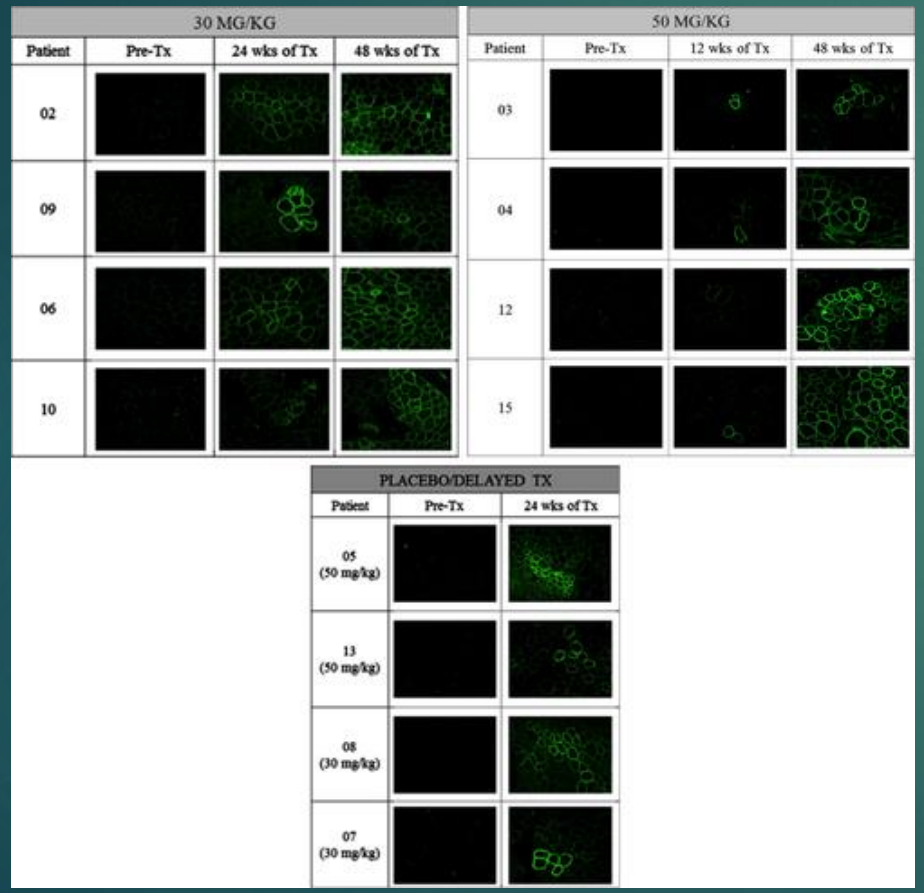
TYPE
Phosphorodiamidate morpholino oligomer (PMO)

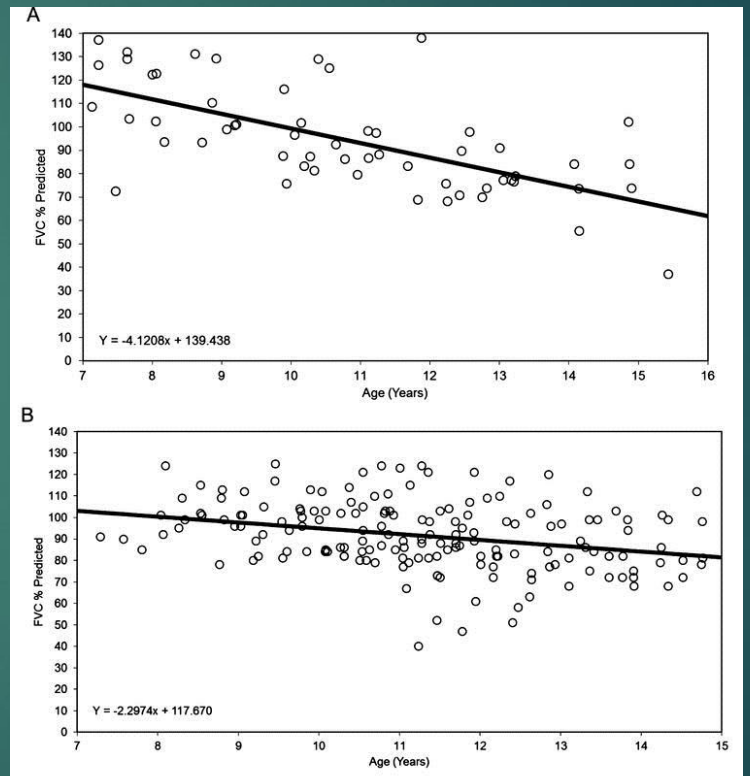
MOLECULAR TARGETS
RNA transcript of *DMD*, exon 51

CELLULAR TARGETS
Skeletal muscles expressing *DMD* transcript

EFFECTS ON TARGETS
Causes *DMD* transcript exon 51 to be skipped, putting the RNA back in frame and creating an internally deleted but somewhat functional dystrophin protein

Exondys: Exon-skipping therapy





	Natural History Control (Age 7–15.5 years)	Eteplirsen-Treated (Age 7–15.5 years)
% Annual Decline (95% CI)	4.1% (1.9%, 6.3%)	2.3% (1.2%, 3.4%)

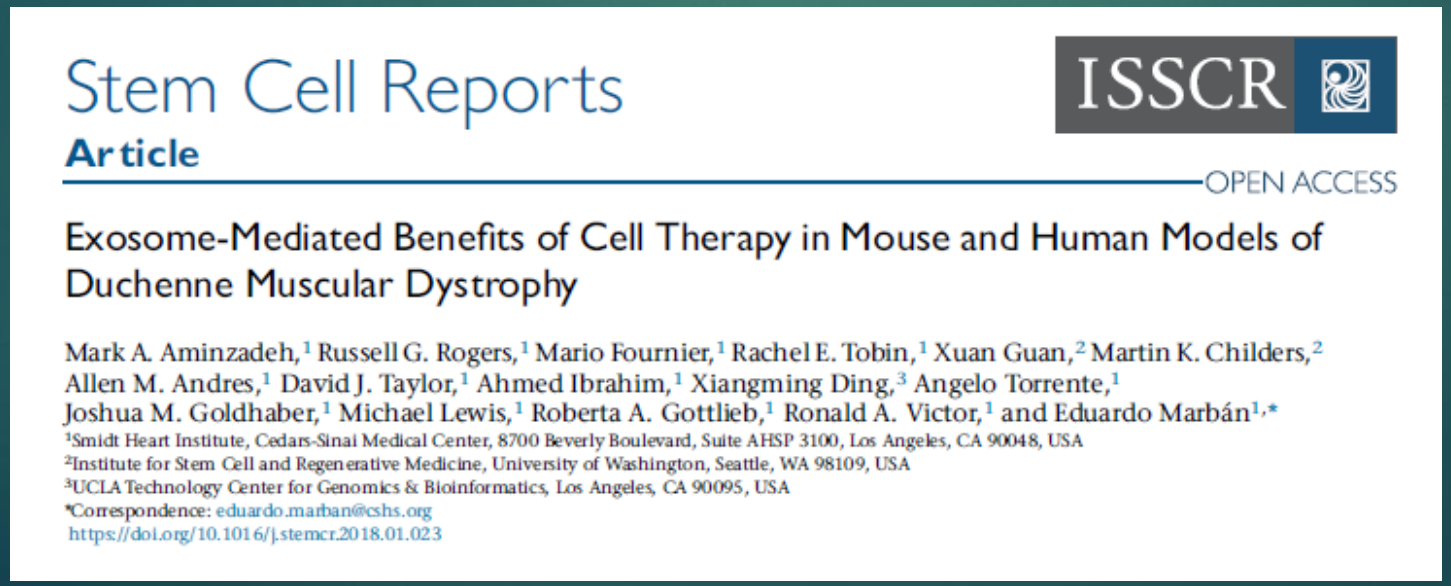
Journal of Neuromuscular Diseases, vol. 5, no. 1, pp. 47-58, 2018

Treatment

- Multidisciplinary care teams: MDA Care Center
  - Neurologist/Physical Medicine physician
  - Physical therapist
  - Occupational therapist
  - Social work
  - MDA coordinator
  - Genetic counselor
  - Pulmonary and cardiac physicians
  - Equipment (bracing, power chairs)

Future treatments

- Harmless virus to deliver missing gene
  - Preliminary results show success of this method in spinal muscular atrophy
- Stem cell treatments



Stem Cell Reports
Article
OPEN ACCESS

Exosome-Mediated Benefits of Cell Therapy in Mouse and Human Models of Duchenne Muscular Dystrophy

Mark A. Aminzadeh,[1] Russell G. Rogers,[1] Mario Fournier,[1] Rachel E. Tobin,[1] Xuan Guan,[2] Martin K. Childers,[2] Allen M. Andres,[1] David J. Taylor,[1] Ahmed Ibrahim,[1] Xiangming Ding,[3] Angelo Torrente,[1] Joshua M. Goldhaber,[1] Michael Lewis,[1] Roberta A. Gottlieb,[1] Ronald A. Victor,[1] and Eduardo Marbán[1,*]
[1]Smidt Heart Institute, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Suite AHSP 3100, Los Angeles, CA 90048, USA
[2]Institute for Stem Cell and Regenerative Medicine, University of Washington, Seattle, WA 98109, USA
[3]UCLA Technology Center for Genomics & Bioinformatics, Los Angeles, CA 90095, USA
*Correspondence: eduardo.marban@cshs.org
https://doi.org/10.1016/j.stemcr.2018.01.023

How about other muscular dystrophies?

- Pompe disease: due to missing enzyme. Now treatment by replacing enzyme
- None are curable
- With success of viral vectors, search is underway for gene therapies for many types

Thank you!

Questions?