Implementing Genetics/ Genomic Medicine into Clinical Practice

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AAPA Annual Meeting

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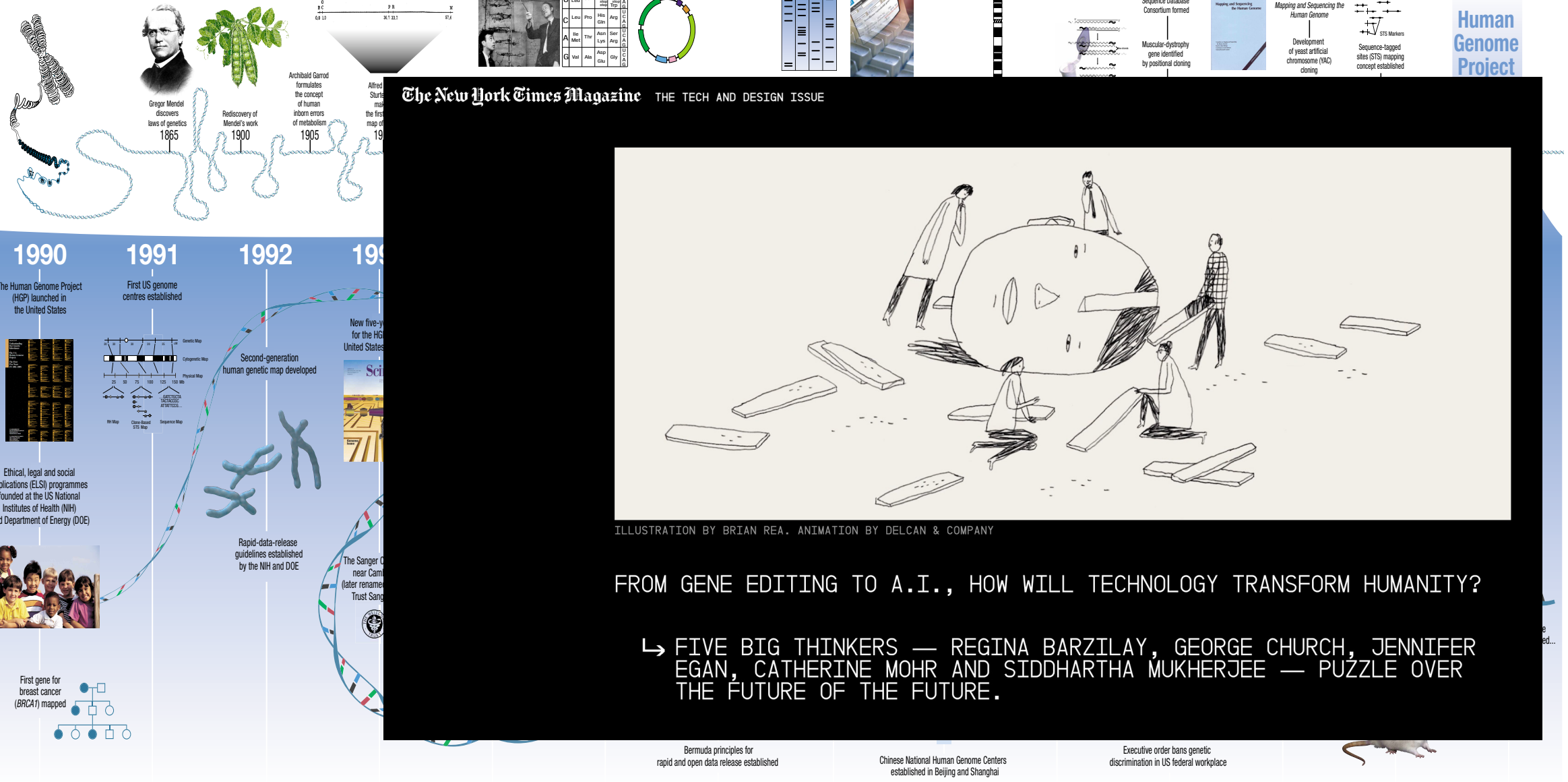
Disclosures

- Non-Declaration Statement: I have no relevant relationships with ineligible companies to disclose within the past 24 months. (Note: Ineligible companies are defined as those whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.)

Educational Objectives

- Identify the characteristics of a patient's medical condition that may raise concerns for a possible genetic disease
- Outline what a PA can do to help streamline and enhance the efficacy of a genetics referral
- Encourage 'thinking genetics' when you might not have done before

Landmarks in genetics and genomics



The New York Times Magazine THE TECH AND DESIGN ISSUE

ILLUSTRATION BY BRIAN REA. ANIMATION BY DELCAN & COMPANY

FROM GENE EDITING TO A.I., HOW WILL TECHNOLOGY TRANSFORM HUMANITY?

↳ FIVE BIG THINKERS — REGINA BARZILAY, GEORGE CHURCH, JENNIFER EGAN, CATHERINE MOHR AND SIDDHARTHA MUKHERJEE — PUZZLE OVER THE FUTURE OF THE FUTURE.

PEAS COURTESY J. BLAMIRE, CITY UNIV. NEW YORK; WATSON & CRICK COURTESY A. BARRINGTON BROWN/SPL; *SCIENCE* COVERS COURTESY AAAS

https://www.genome.gov/sites/default/files/media/files/2020-09/HGP_Timeline.pdf

https://www.nytimes.com/interactive/2018/11/16/magazine/tech-design-medicine-phenome.html 11/16/2018

What are the challenges of implementation into clinical practice?

Challenges and strategies for implementing genomic services in diverse settings: experiences from the Implementing GeNomics In pracTicE (IGNITE) network

Nina R. Sperber,[1,7,16] Janet S. Carpenter,[2] Larisa H. Cavallari,[3] Laura J. Damschroder,[4] Rhonda M. Cooper-DeHoff,[5] Joshua C. Denny,[6] Geoffrey S. Ginsburg,[7] Yue Guan,[8] Carol R. Horowitz,[9] Kenneth D. Levy,[2] Mia A. Levy,[6] Ebony B. Madden,[10] Michael E. Matheny,[11] Toni I. Pollin,[8] Victoria M. Pratt,[2] Marc Rosenman,[2] Corrine I. Voils,[12,13] Kristen W. Weitzel,[5] Russell A. Wilke,[14] R. Ryanne Wu,[7,15] and Lori A. Orlando[7]

1. Increase the relative priority of integrating genomics within the health system EHR
2. Strengthen clinicians' knowledge and beliefs about genomic medicine
3. Engage patients in the genomic medicine projects

Sperber NR, 2017

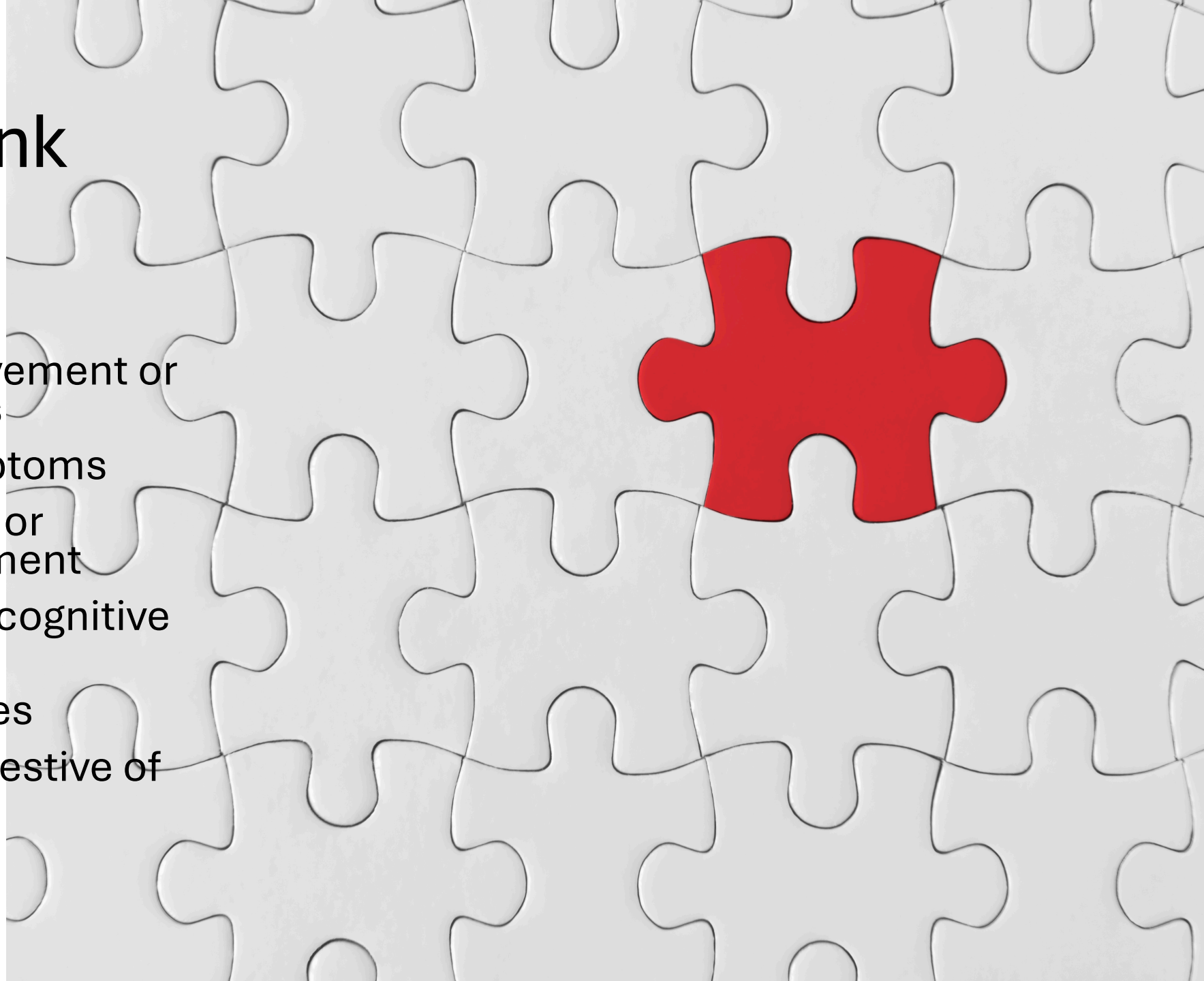
Role of primary health care team

PCPs have a key role in identifying patients and families who may benefit from being referred for a genetic evaluation

PCPs are involved with managing, caring, and supporting families at risk for genetic conditions

When to “think genetic”?

- Multi-system involvement or multiple anomalies
- Unconnected symptoms
- Progressive course or abnormal development
- Unexplained neurocognitive impairment
- Dysmorphic features
- Family history suggestive of hereditary disease



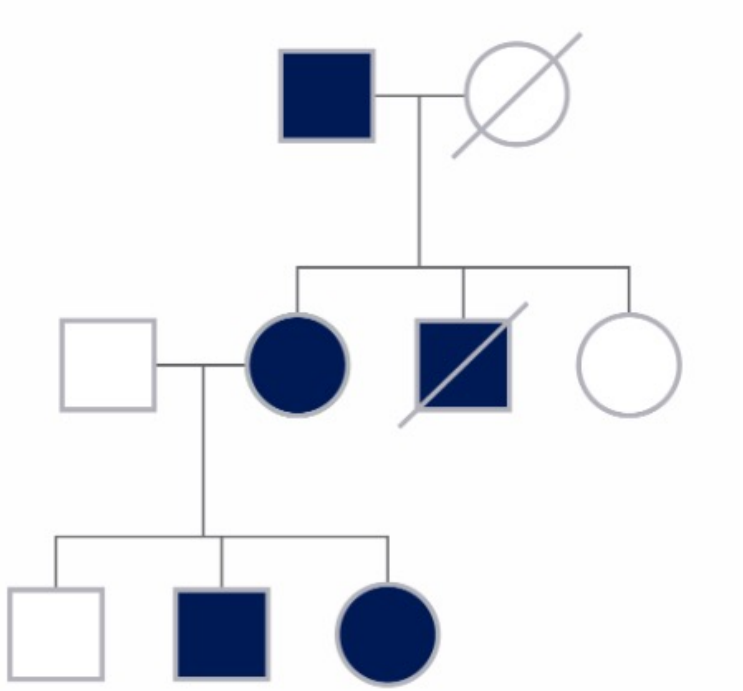
HPI PEARLS

Birth history

- Prenatal and neonatal history
- Fetal movements
- Polyhydramnios or oligohydramnios
- Breech presentation or failure to progress
- Abnormal position to the hands/ feet, frog-leg position, dislocated hips, scoliosis
- Respiratory and/ or feeding difficulties at birth

Family history

- Consanguinity and ethnicity – ask EVERYONE!
- Death at an early age/ unknown reason
- Remote family members with similar symptoms
- Multiple miscarriages
- Anything weird



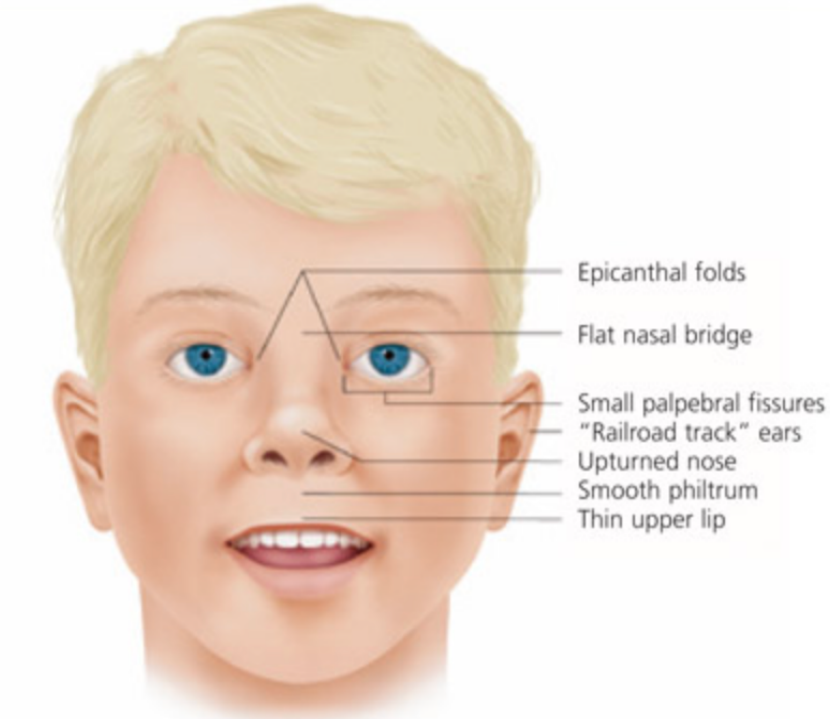
https://www.genome.gov/genetics-glossary/Pedigree

Early developmental milestones	Age of symptom onset	Progression of symptoms	Other systemic involvement
• Don’t believe “normal” • Regression or plateau	• Neonatal • Congenital • Childhood • Adolescent • Adult	• Progressive, static, improving • Acute vs. chronic	• Cardiovascular • Hepatomegaly • Skeletal anomalies • Arthrogryposis

PHYSICAL EXAM

Dysmorphic features

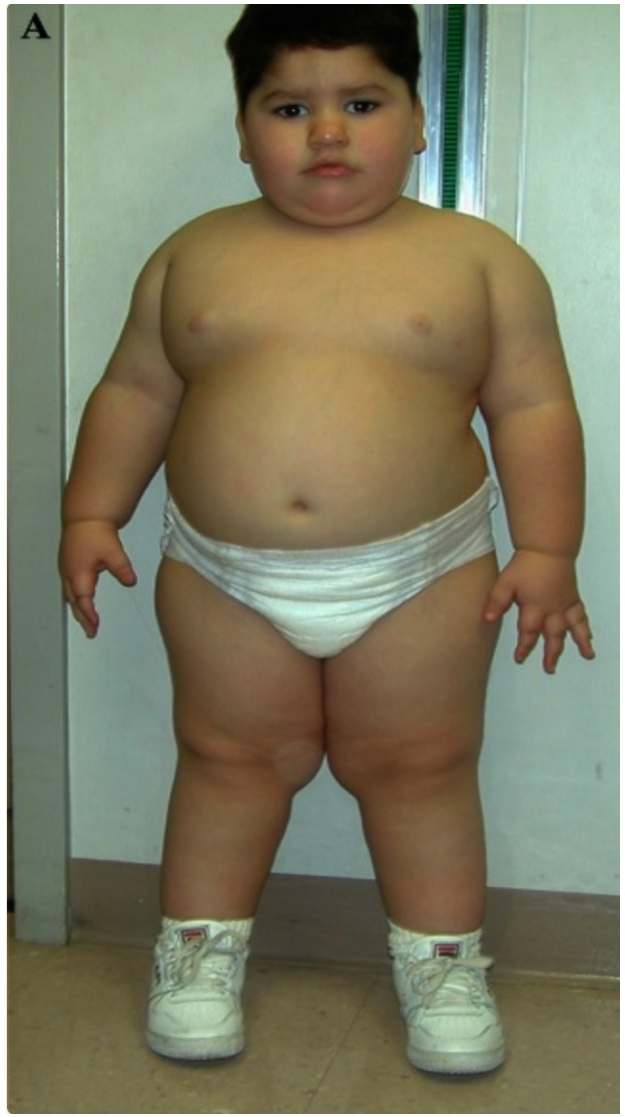
- Distinctive facial features
- Ear shape and position
- Eye spacing
- Body proportions and symmetry
- Spine or sacral anomalies
- Limbs/ digits
- Palmar creases



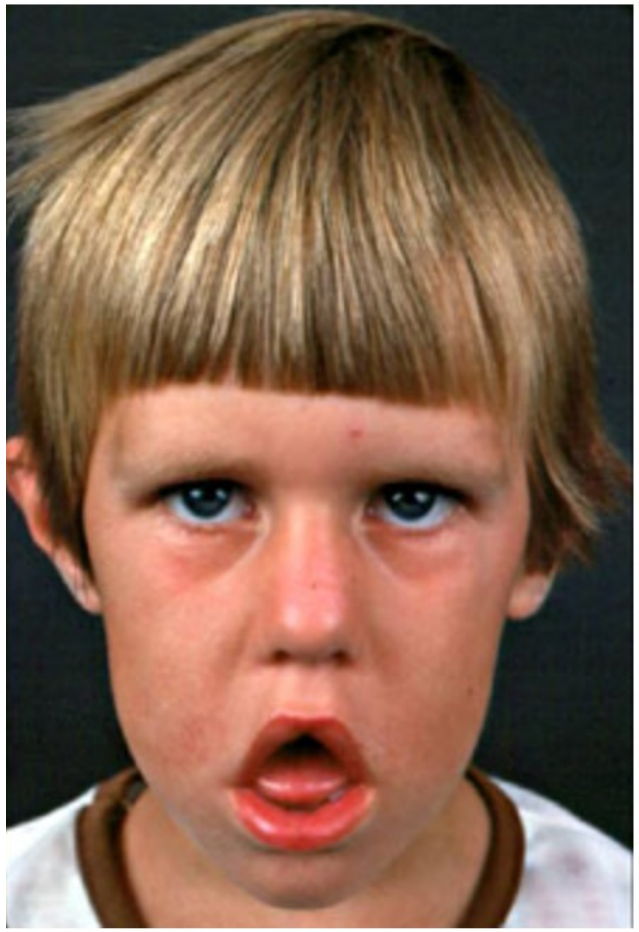
May involve taking measurements: height, weight, and head circumference – even in adults!

Note any change in findings over time

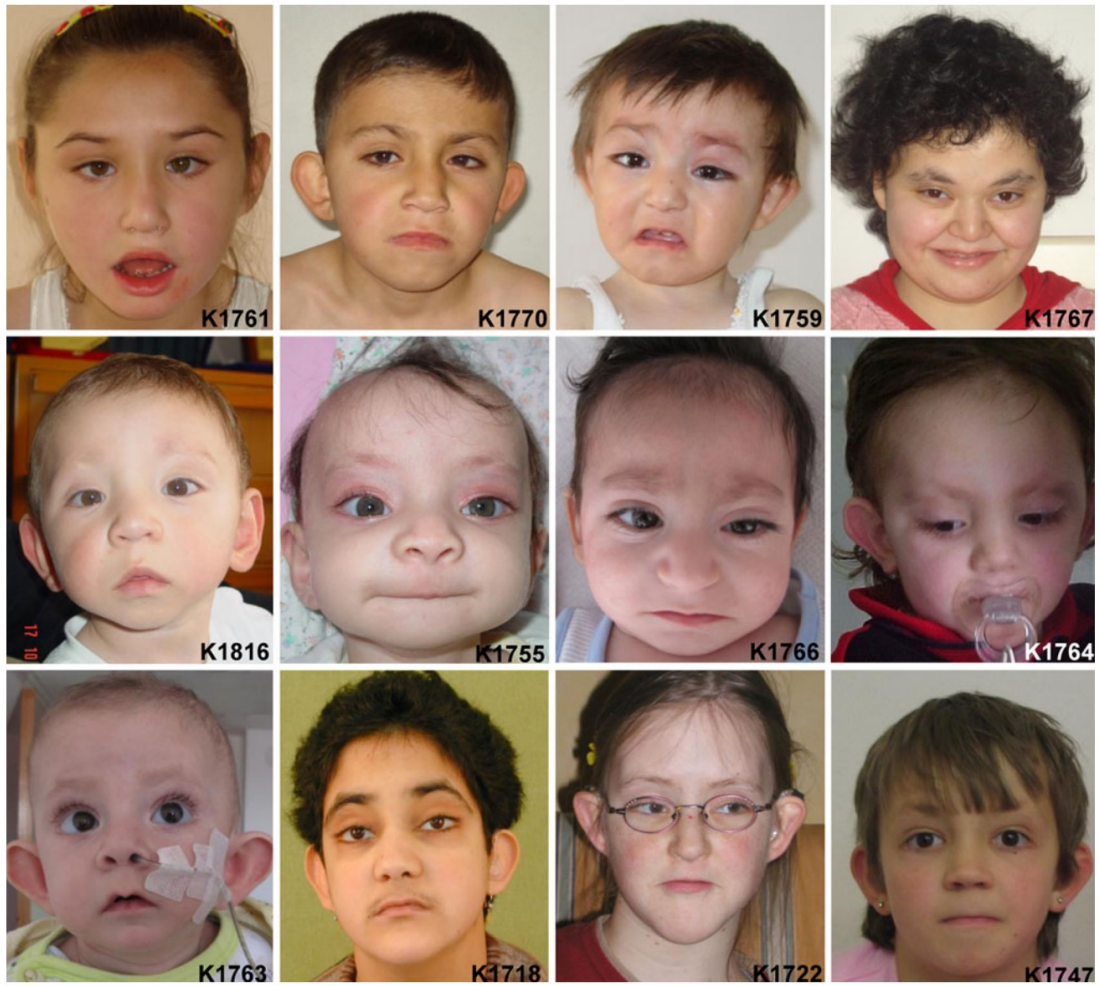
Depending on patient, specialized exam (neurological exam) may be performed



Angulo MA, 2015.



https://neuromuscular.wustl.edu/musdist/pe-eom.html


K1761
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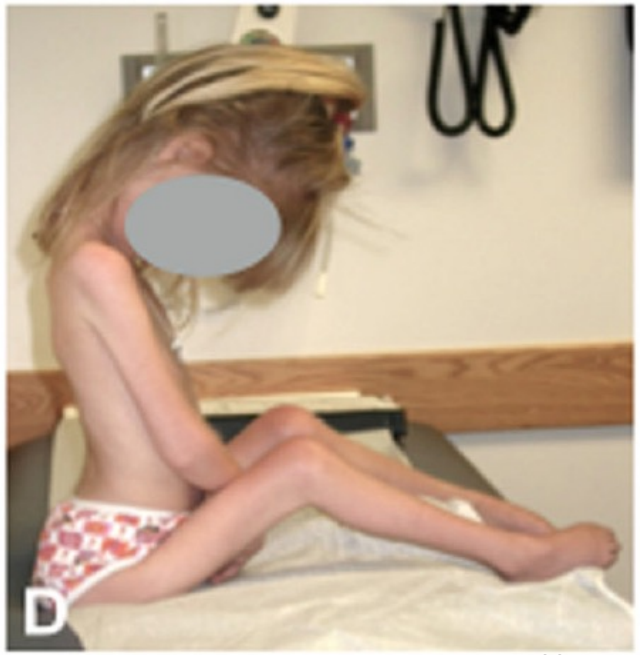
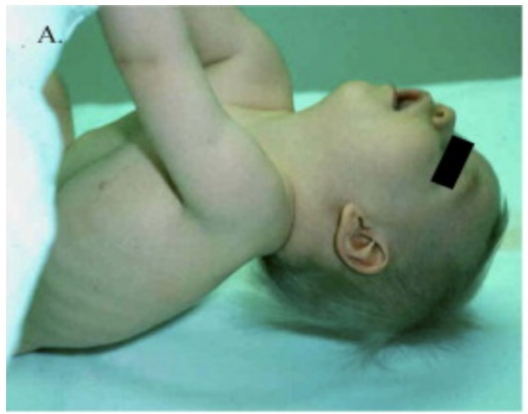
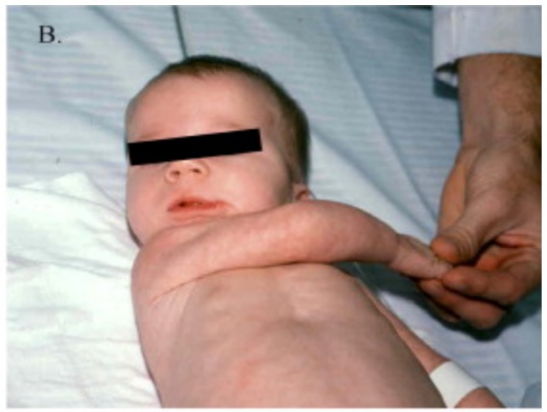
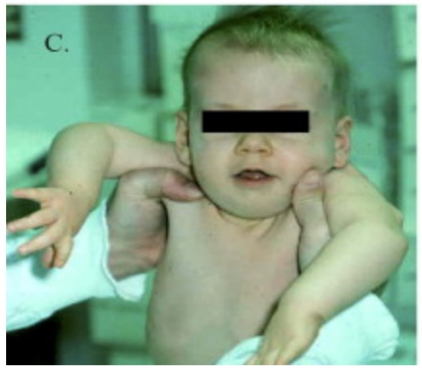
Li, Y, 2011.

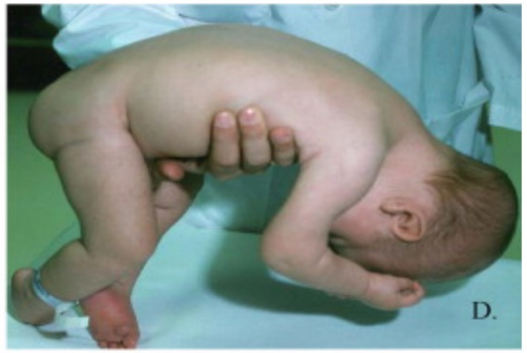


Bonnemann, CG, 2014.

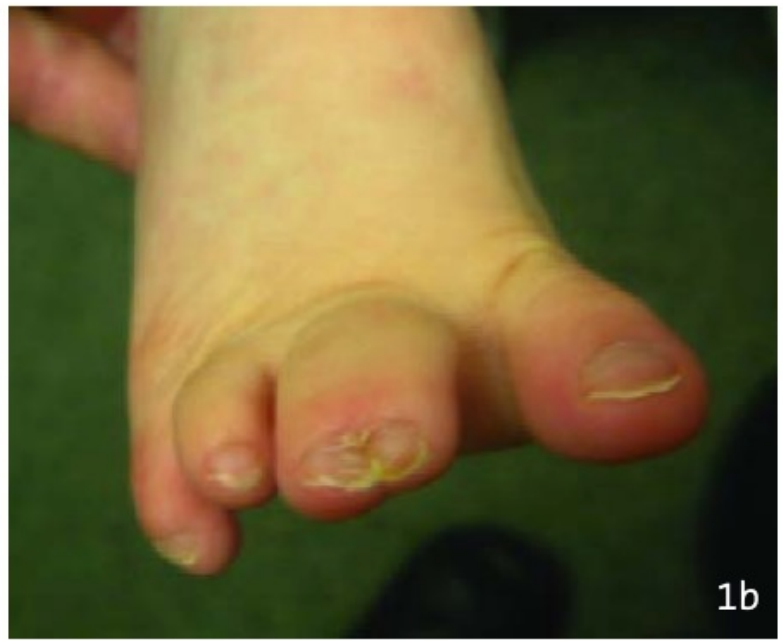


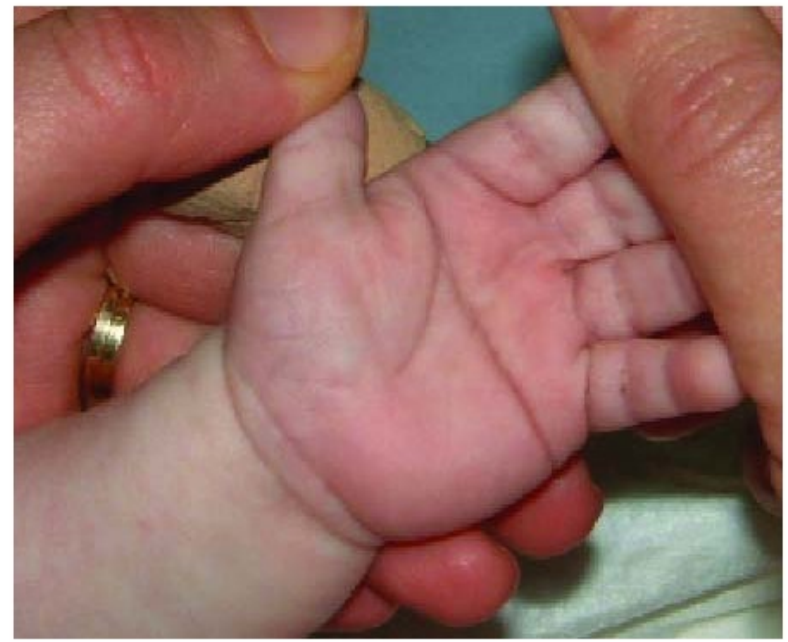






Bodenseiner, JB, 2008.





Clayton-Smith, J, 2008.

Labs To Consider

- General investigation: CBC, CMP, vitamin D
- Low tone or weakness
  - Creatine Kinase (CK or CPK)
  - Thyroid function
  - Acute onset consider: toxins (heavy metals, drugs, botulism), infections (CBC, ESR)
- Metabolic
  - Lactate/ pyruvate, plasma amino acids, acylcarnitine profile, free/ total carnitine, urine organic acids
- Pain
  - CBC/ ferritin, CMP, Mg/ Phos
- Other
  - Fasting blood glucose, hemoglobin A1C, vitamin E/ B12

Case #1

Chief complaint: “Need note for school PE, walking funny”

History

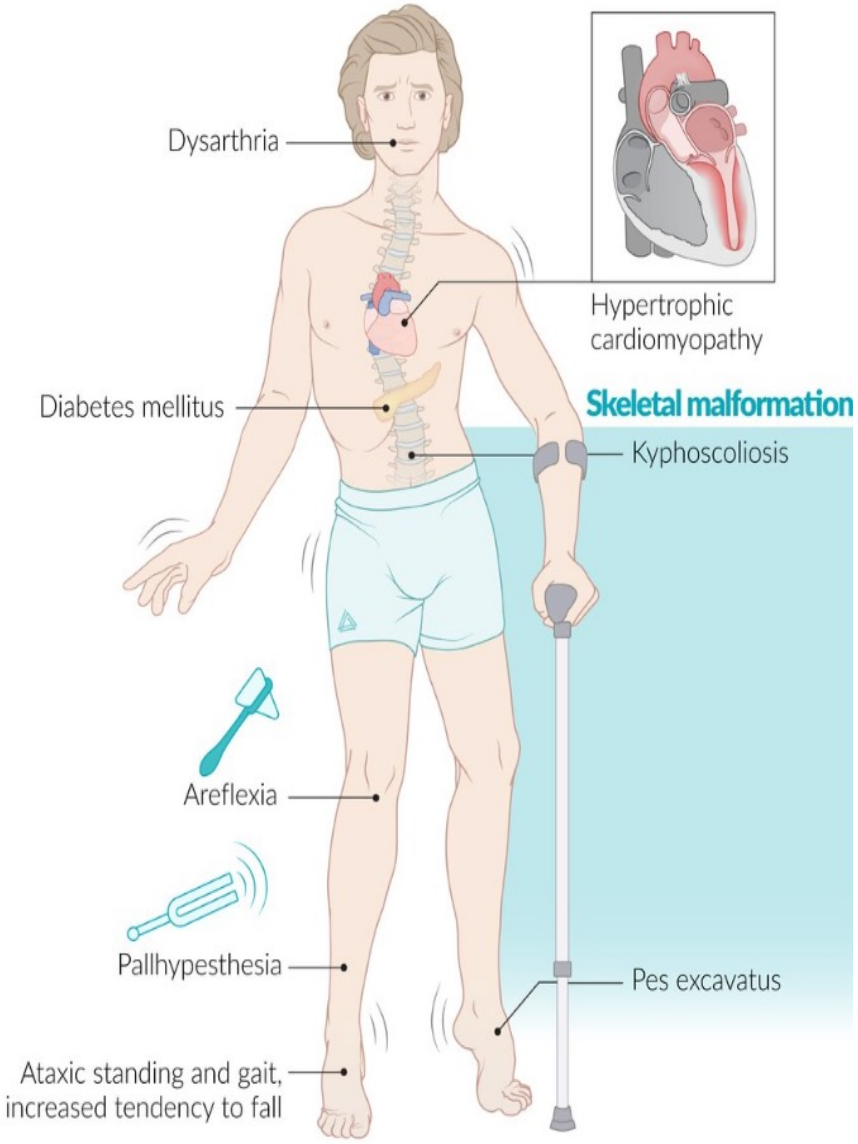
- 10 yo boy with history of hypertrophic cardiomyopathy referred for gait disturbance
- Normal developmental history except mild speech delay
- Started walking “funny” starting 2 years ago
- Appears clumsy
- Younger siblings outrunning him
- Slurred speech

Work up

- Exam findings
  - +Dysarthria
  - Incoordinated limb movements
  - LE: Muscle atrophy and weakness
  - Bilateral ankle contractures and scoliosis
  - Sensory: Decreased vibration
  - Reflexes: 1+ in UE, absent in LE
  - Cerebellum: +Dysmetria (FTN), slow RAM, +nystagmus
  - Gait: Severely ataxic, difficulty with tandem and balance
  - +Romberg
- Labs:
  - Normal CBC, CMP, CK, TSH/ free T4, metabolic studies
- Prior genetic testing
  - Invitae hypertrophic cardiomyopathy panel – negative

Friedreich's Ataxia

- Common form of inherited ataxia
- Autosomal recessive
- Affects approximately 1:40,000 live births with mean age of onset at 16 years
- Neurodegenerative disorder caused by mutations in *frataxin* (*FTX*) gene
- Primary involvement include CNS, spinal cord/ peripheral nerves, and heart



https://www.amboss.com/us/knowledge/friedreich-ataxia

Case #2

Chief complaint: “Falling a lot”

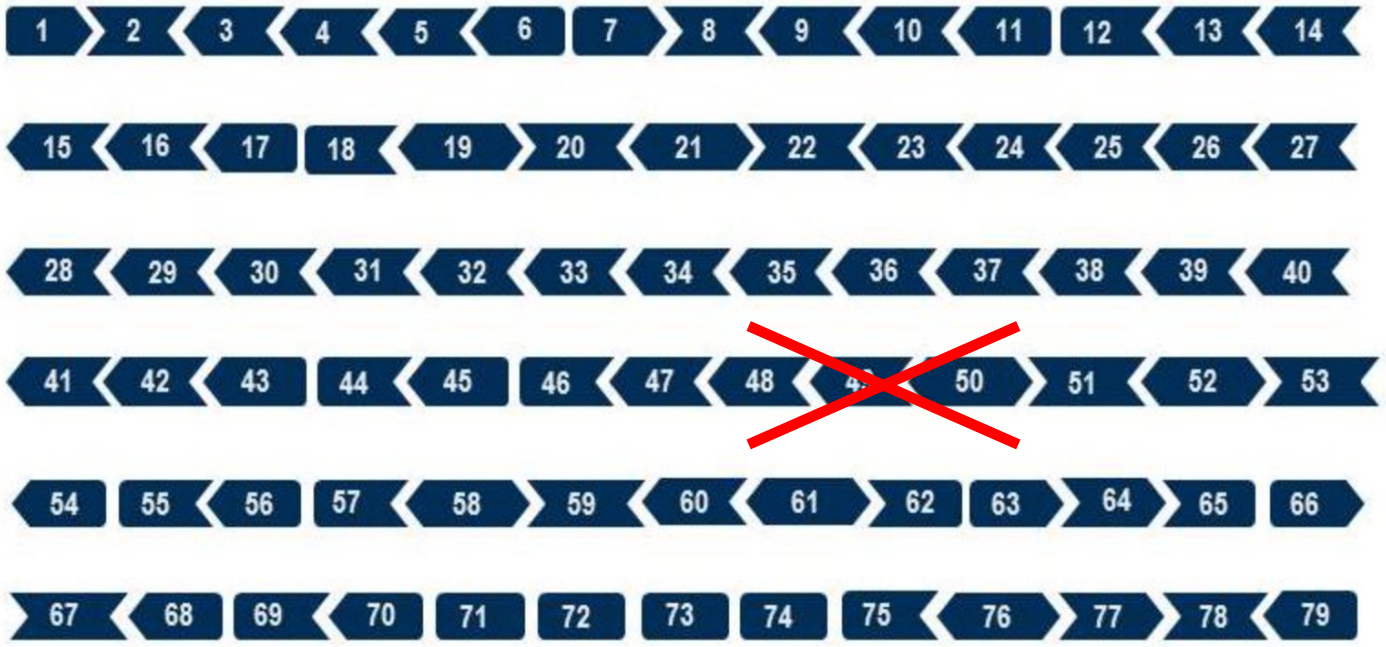
History

- 5 yo boy referred for progressive muscle weakness x 9-10 months
- Normal development except mild toe-walking
- Seems slower compared to peer group
- Frequent falling, fatigue
- Difficulty with climbing stairs

Work up

- Exam findings
  - Calf pseudohypertrophy, bilateral ankle contractures
  - Proximal muscle weakness
  - Waddling/ Trendelenburg gait and toe-walking
  - Difficulty walking up > down stairs
  - +Gowers Sign
- Labs
  - Elevated CK level = 30,000 (normal < 120)
  - AST and ALT elevated in 300's
- Pediatrician referred to gastroenterology
  - Normal hepatology work up, including liver biopsy
  - GI sent patient for neuromuscular evaluation

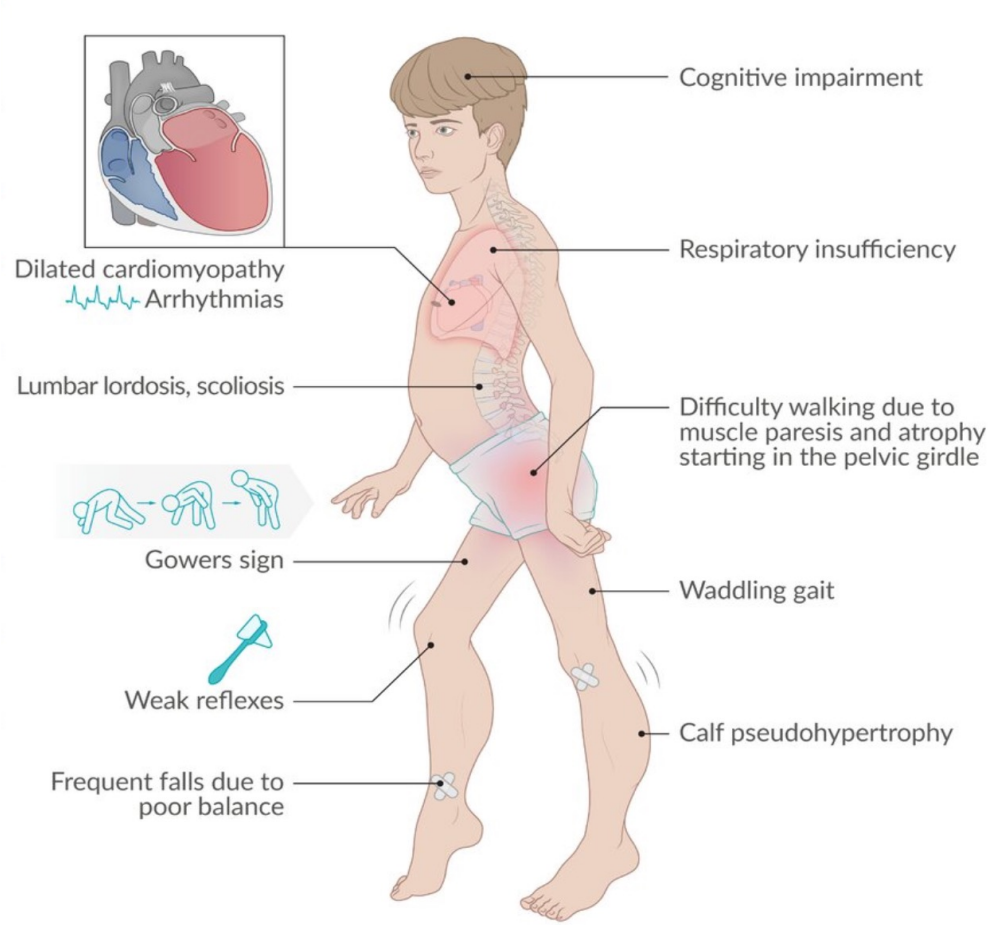
- Given history, physical exam findings, and CK elevation – immediately sent for genetic testing
- Patient was found to have deletion of exons 48-50 (out of frame mutation) in the *dystrophin* gene



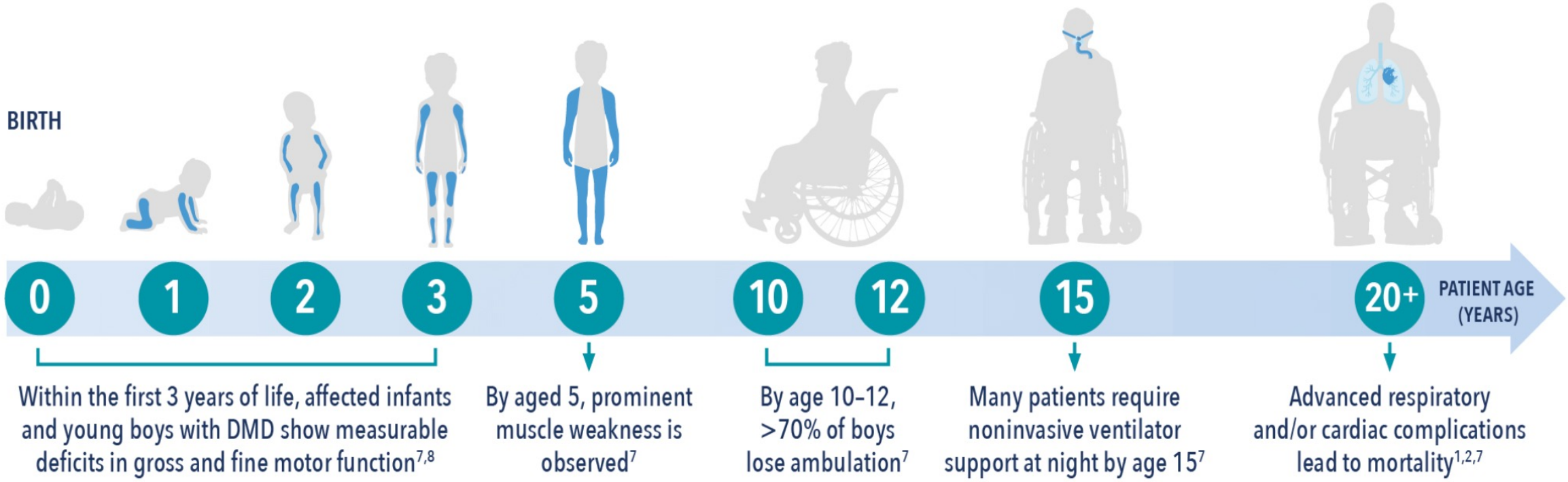
https://www.exonskipping.nl/reading-frame/

Duchenne Muscular Dystrophy

- X-linked recessive
- 1:5000 live male births – most common form of muscular dystrophy
- Common symptoms:
  - Progressive proximal weakness, calf pseudohypertrophy, scoliosis, respiratory muscle weakness, cardiomyopathy
- Standards of care
- FDA approved disease modifying therapies



https://www.amboss.com/us/knowledge/progressive-muscular-dystrophies



https://takeonduchenne.eu/what-is-duchenne-muscular-dystrophy/

Dystrophin restoration: Exon-skipping

Strategy: Restore the reading frame of out-of-frame (ie, DMD) dystrophin transcripts to produce partially functional dystrophins (akin to BMD)

- Different exons are skipped based on mutation size and location (mutation-specific)

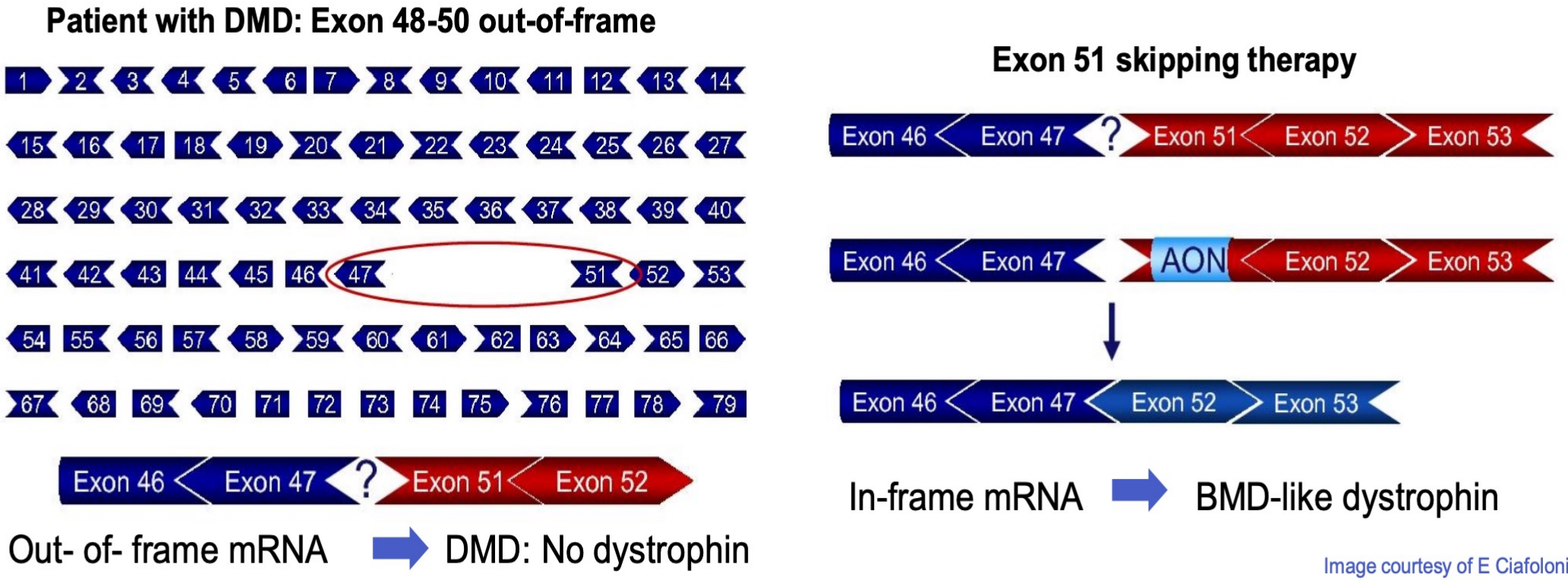


Image courtesy of E Ciafoloni

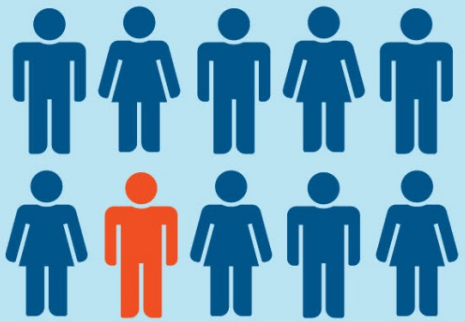
https://www.mda.org/sites/default/files/2022/06/meded/Whats%20New%20in%20DMD_FINAL_052422_0.pdf

When do I refer to genetics?

- Acute referral to clinic vs ER
- Non-urgent referrals
- Facilitate the referral – **don't rely on the system!!!**
- In the meantime….

1 in 10 } Americans has a RARE DISEASE

30 million people have a serious, lifelong condition.



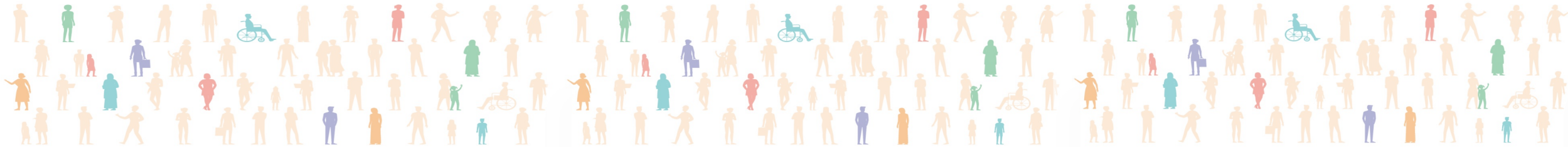
More than half are children[1]

Holding hands, they would circle the globe about 1.5 times

What is a RARE DISEASE ?

Any disease, disorder, illness or condition affecting fewer than 200,000people in the United States is considered RARE.[1]

https://rarekc.org/about/what-is-rare/



Multidisciplinary Care

Newsome SD, 2016.


NORD


RARE DISEASES
CLINICAL RESEARCH NETWORK


United Pompe Foundation


ALS
ASSOCIATION


RYR-I
FOUNDATION


cure
SMA


MDA
Muscular
Dystrophy
Association


ClinicalTrials.gov


UDN
Undiagnosed
Diseases Network

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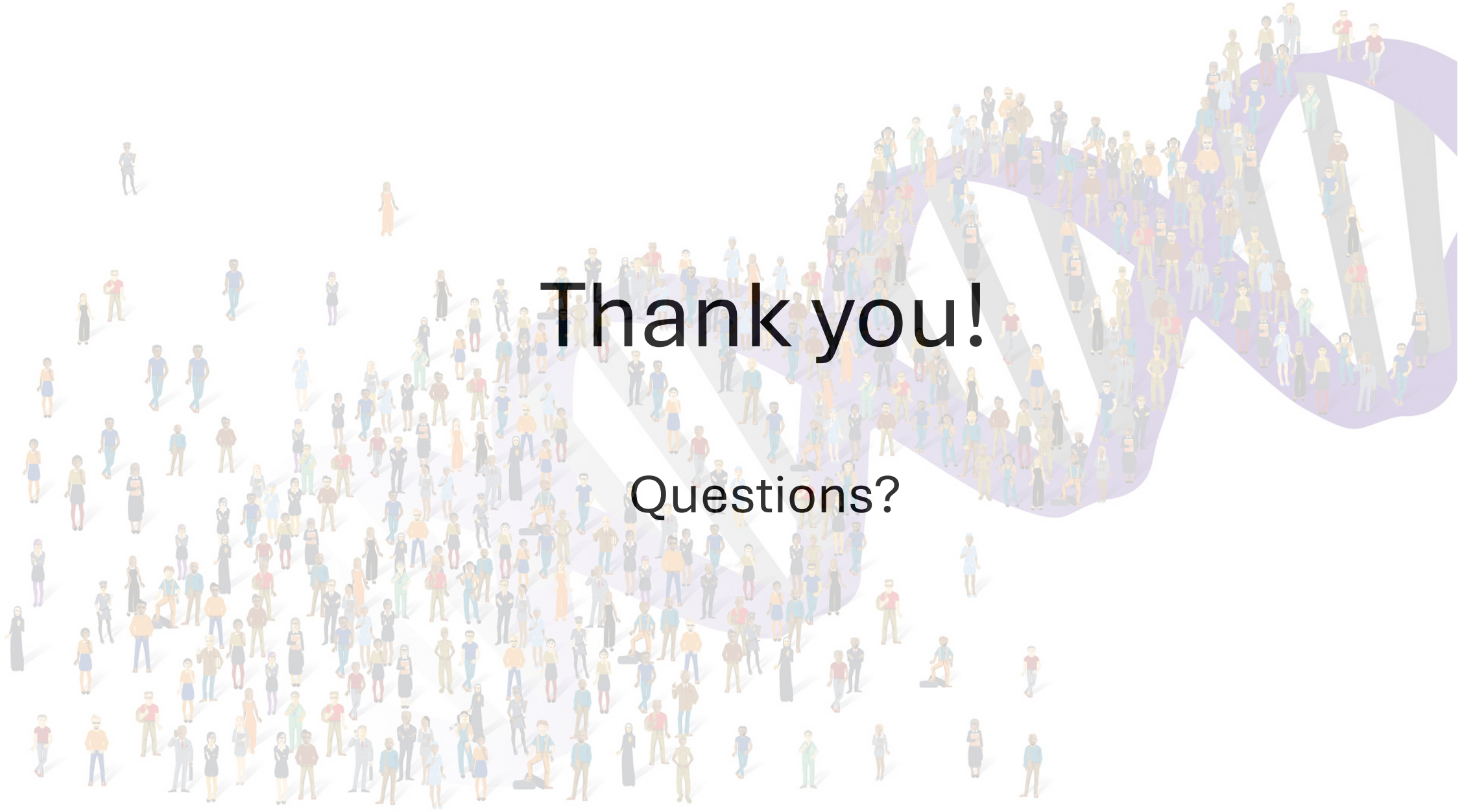
- https://bioresource.nihr.ac.uk/centres-programmes/rare-diseases-bioresource/

https://takeonduchenne.eu/what-is-duchenne-muscular-dystrophy/



Thank you!

Questions?