the FOUNDATION for PERIPHERAL NEUROPATHY®

Welcome!

FPN Webinar:

Hereditary Neuropathies *and* the Benefits of Genetic Testing

Wednesday, October 11, 2023

Sponsored by: Alnylam® PHARMACEUTICALS

We will begin our presentation shortly.

the FOUNDATION for PERIPHERAL NEUROPATHY®

Please join us in welcoming today's experts:

Moderator:

Lindsay Colbert
Executive Director
the Foundation *for* Peripheral Neuropathy

Presenters:

Amanda Peltier, MD, MS
Associate Vice Chair, Academic Affairs
Division Chief, Neuromuscular
Professor, Neurology
Vanderbilt University

Emily Brown, MGC, CGC
Patient Support Professional
Genetic Counselor
Johns Hopkins Hospital

the FOUNDATION for PERIPHERAL NEUROPATHY®

Before We Begin

This presentation is being recorded. The recording link will be emailed to you so you can view it again later.

Submit your questions anytime via the Questions Box. We will try to answer them during this webinar.

If you are having trouble with the audio using your computer, you can dial in by phone (check your email for dial-in instructions).

Hereditary Neuropathies and Genetics

Amanda Peltier, MD MS
Professor of Neurology

VANDERBILT UNIVERSITY
MEDICAL CENTER

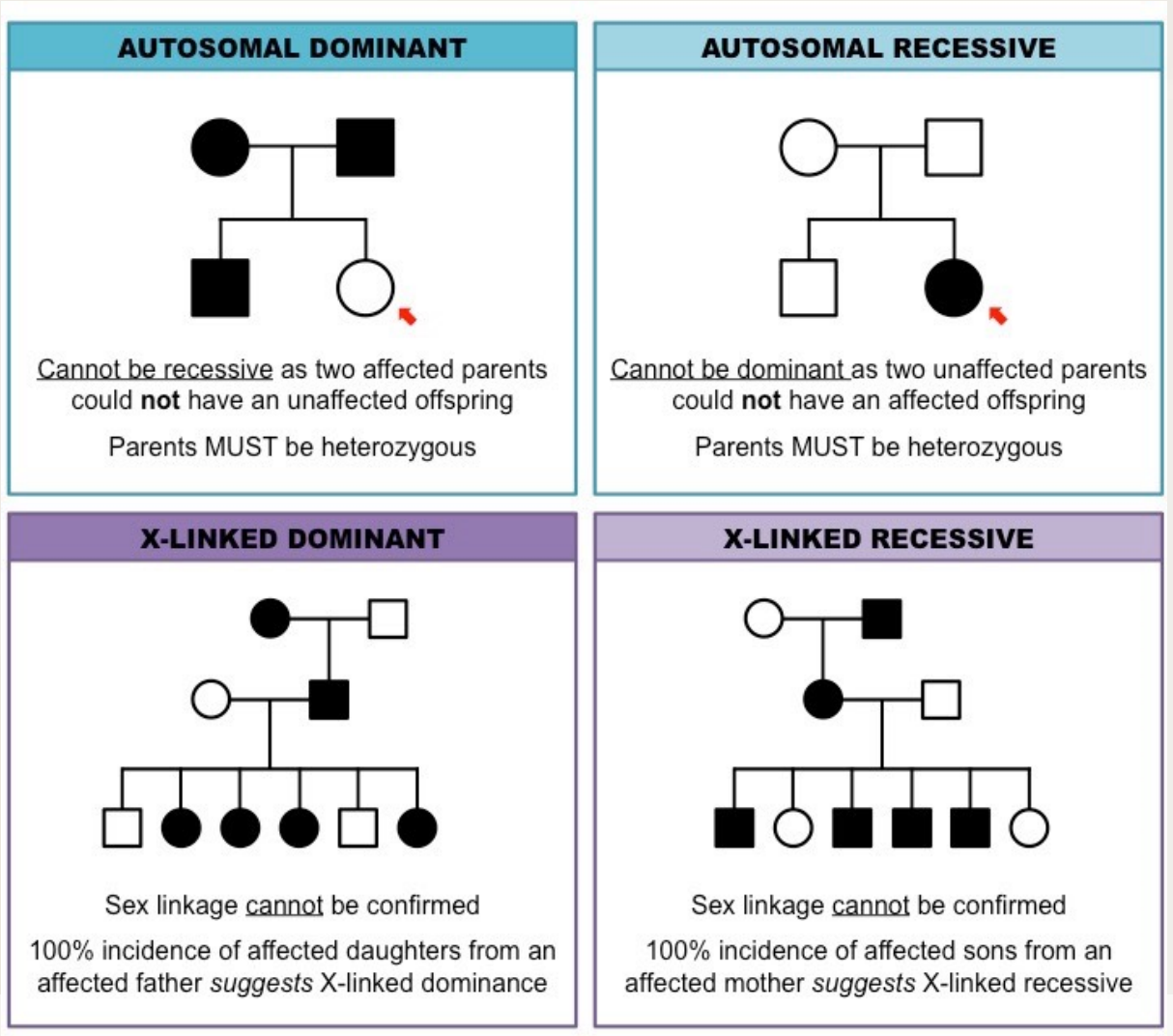
What are Inherited Neuropathies?

- Neuropathies caused by a single gene mutation or gene deletion, duplication.
- Account for about 7% of all neuropathy (125,000 patients of approximately 1.86 million people in the United States)
- Can be only motor, only sensory, sensory and motor (most common) sensory and autonomic (most rare), or sensory, motor and autonomic nerves involved.
- Originally described by Charcot, Marie, Tooth, 3 different neurologists in the 1800s.
- Hereditary amyloidosis first described in 1952 by Andrade in Portugal, affects about 50,000 worldwide.

Inherited Disorders

- Can be inherited as dominant,

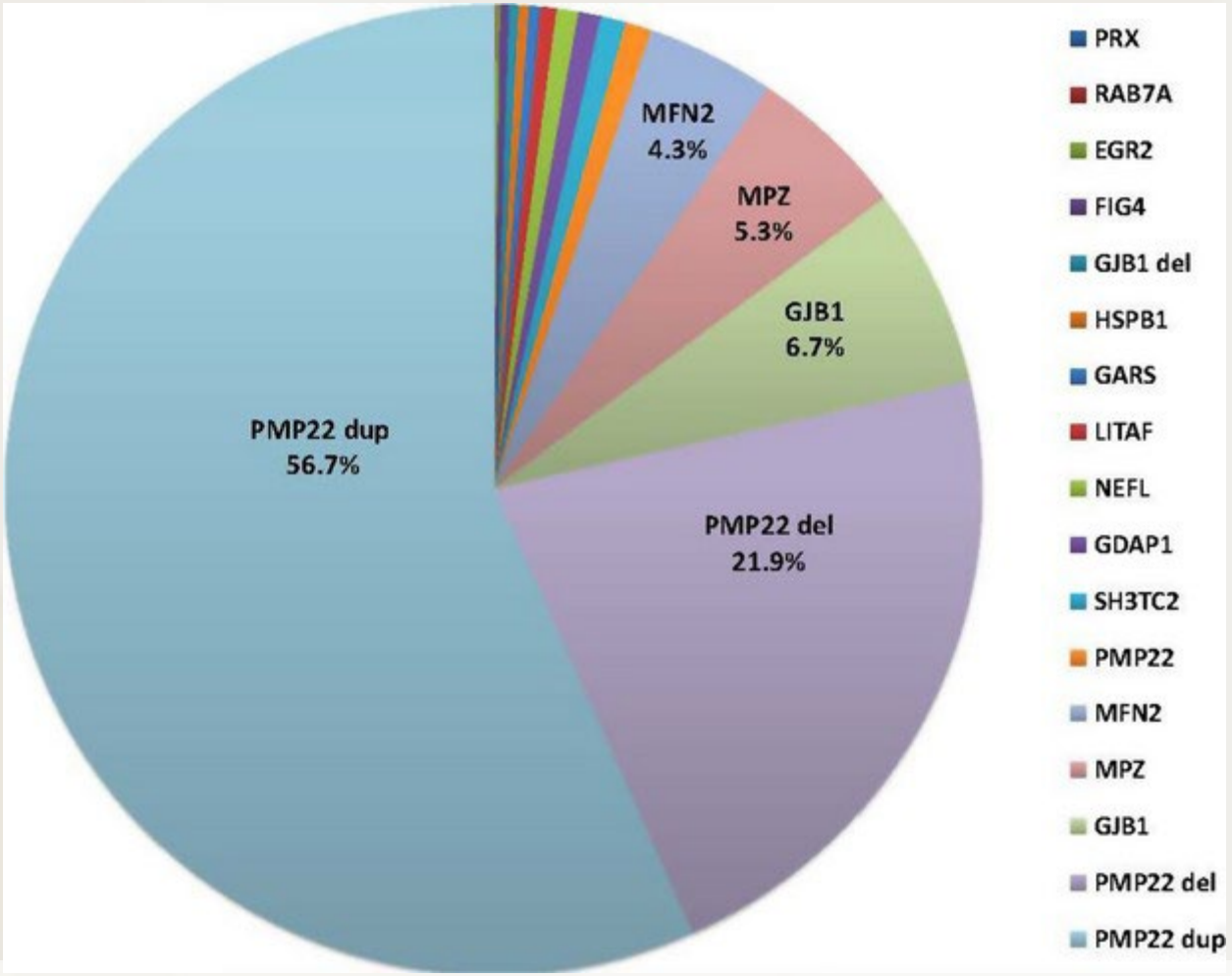
Recessive, X-linked depending on how many gene copies needed to have a disorder.



Pedigree Charts/Bioninja https://ib.bioninja.com.au/_Media/pedigree-charts_med.jpeg

Distribution of Common Mutations

- The most common mutation causing neuropathy is a duplication of the PMP gene, accounting for over half of all inherited neuropathies.



https://onlinelibrary.wiley.com/cms/asset/9f290b2b-64b0-4813-ade4-bf3c18506674/mgg3106-fig-0001-m.jpg

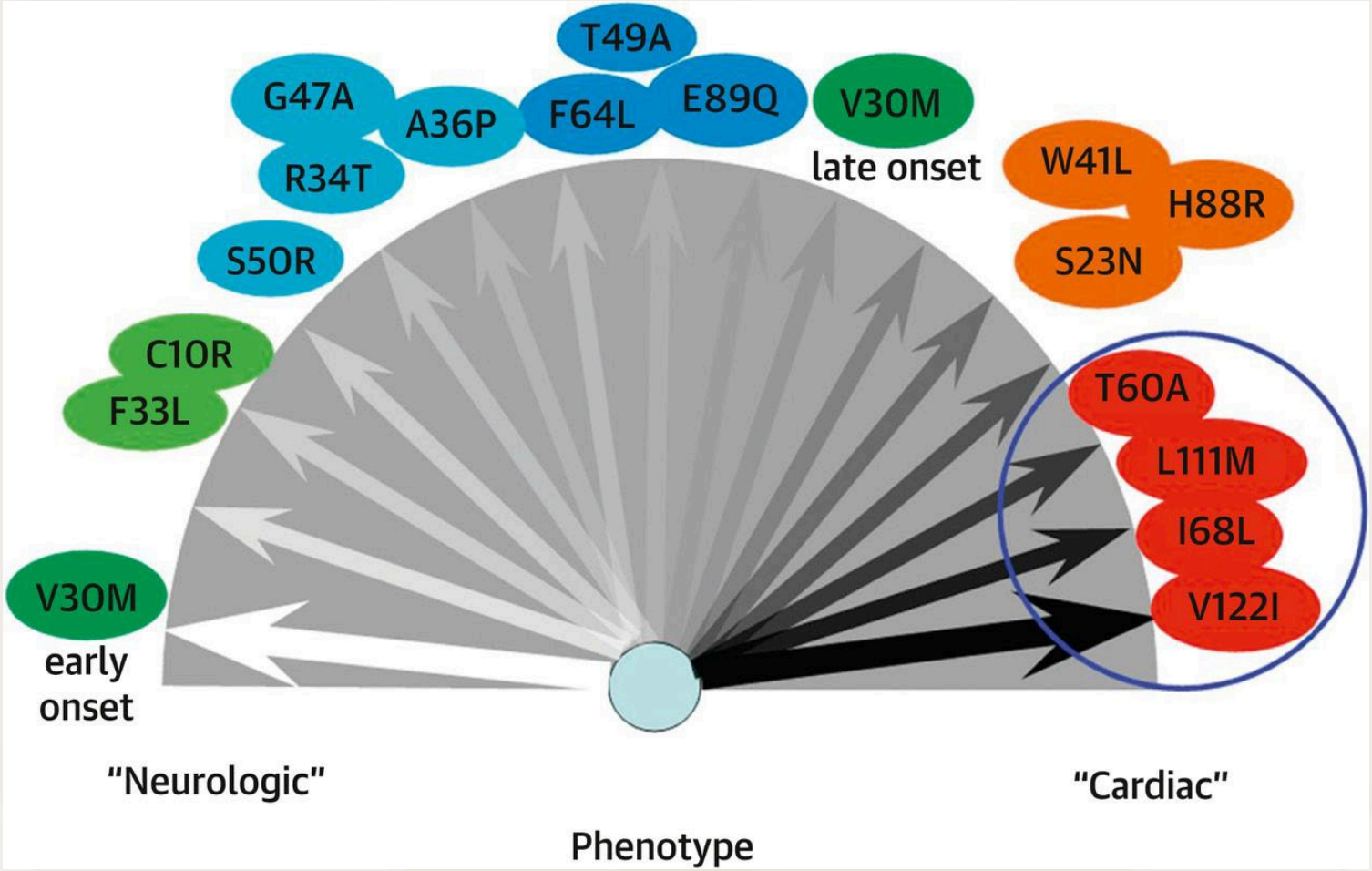
Types of Nerve Fibers and their Function

- Motor: large myelinated nerves which go to muscle. Cause weakness, atrophy (shrinkage) of muscles.
- Sensory fibers
  - Large myelinated sensory fibers convey vibration, light touch, proprioception (ability to know where your limb is in space)
  - Small non-myelinated sensory fibers found in the skin convey pain, temperature, also some light touch
- Autonomic fibers
  - Small non-myelinated sensory fibers go to different organs to control automatic functions like heart rate, blood pressure, ability to urinate, sexual function, gastrointestinal function.

Classification of Hereditary Neuropathies

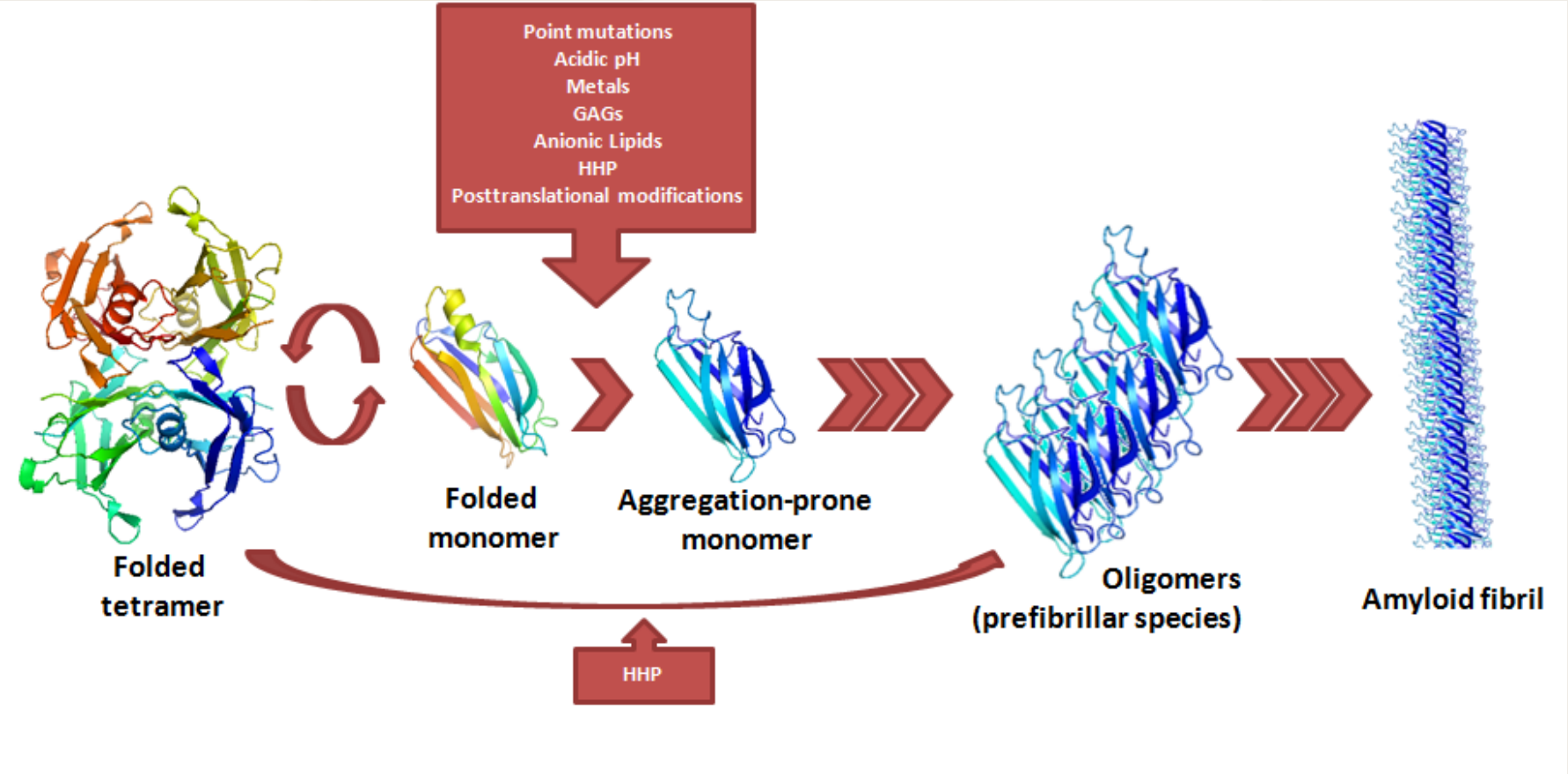
Class	Types of Fibers Involved	Inheritance Pattern	Typical age of presentation	Typical Symptoms	Nerve conduction findings
CMT1	Sensory and motor myelinated fibers	Autosomal dominant	Teens (rarely early childhood)	Weakness starting in feet and eventually affecting hands, sensory loss in same areas	Slowing of nerves to 10-20 m/s
CMT2	Sensory and motor myelinated fibers	Autosomal dominant	Childhood, Teens	Weakness starting in feet and eventually affecting hands, sensory loss in same areas	Normal to mildly slowed nerve fiber velocity (above 40 m/s), loss of nerve fiber responses
CMT 4	Sensory and motor myelinated fibers	Autosomal recessive	Childhood, Teens	Weakness starting in feet and eventually affecting hands, sensory loss in same areas	Normal to mildly slowed nerve fiber velocity (above 40 m/s), loss of nerve fiber responses
CMTX	Sensory and motor myelinated fibers	X-linked recessive	Teens, young adulthood	Weakness starting in feet and eventually affecting hands, sensory loss in same areas	Intermediate slowing 25-35 m/s
Hereditary Sensory and Autonomic Neuropathies	Sensory and autonomic non-myelinated fibers	Mostly autosomal recessive	Childhood	Pain or loss of pain, amputations, autonomic symptoms	Normal nerves (EMG only tests large fibers)
Hereditary Amyloidosis	Motor, Sensory, Autonomic myelinated and non-myelinated fibers	Autosomal dominant	Adulthood to 80s	Carpal tunnel syndrome, numbness, pain, weakness, autonomic symptoms	Can be normal (small fiber at first), can have mild to moderate slowing, loss of nerve responses

Familial Amyloidosis

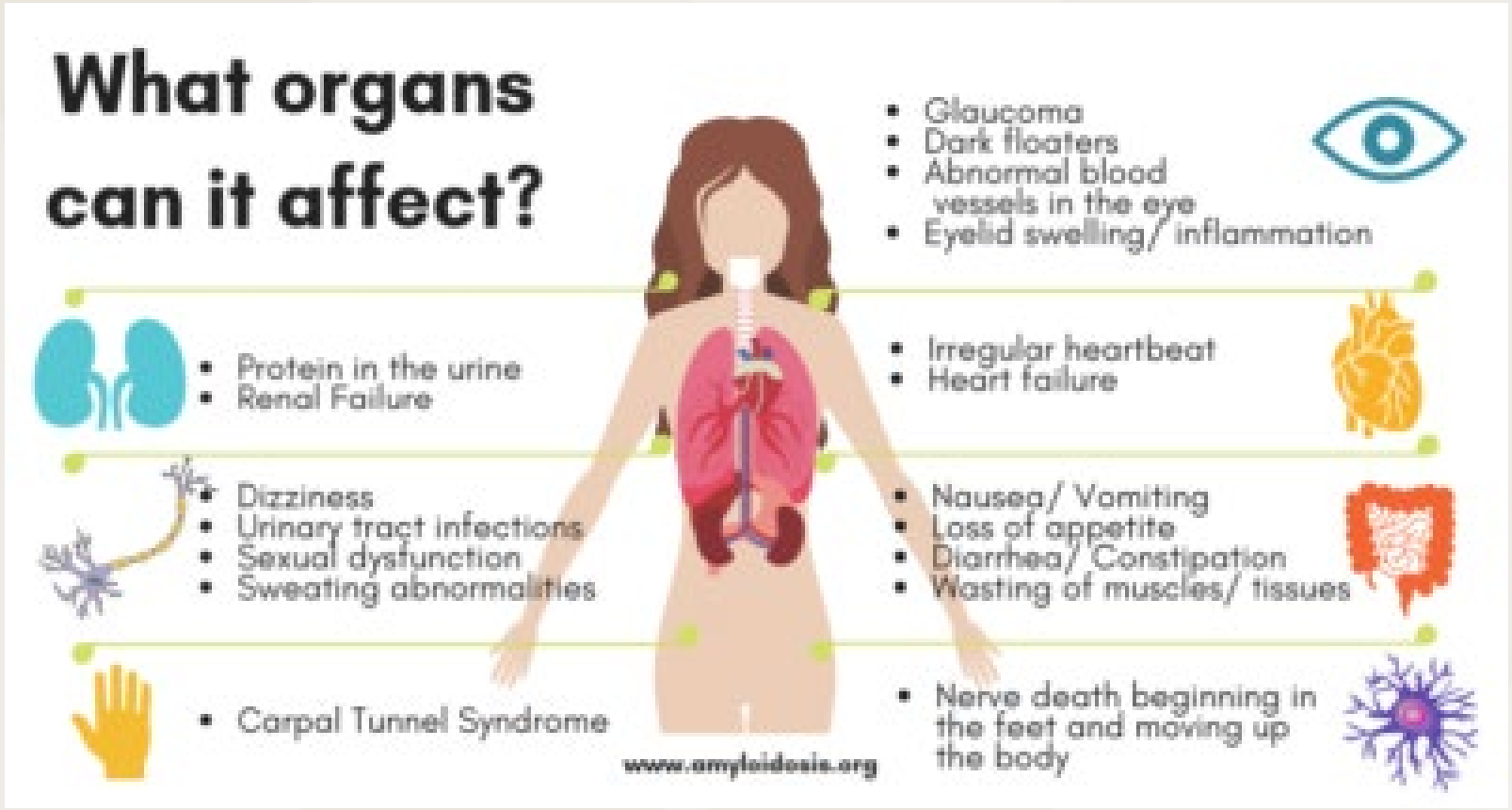


From: Semigran MJ. JACC 2016.

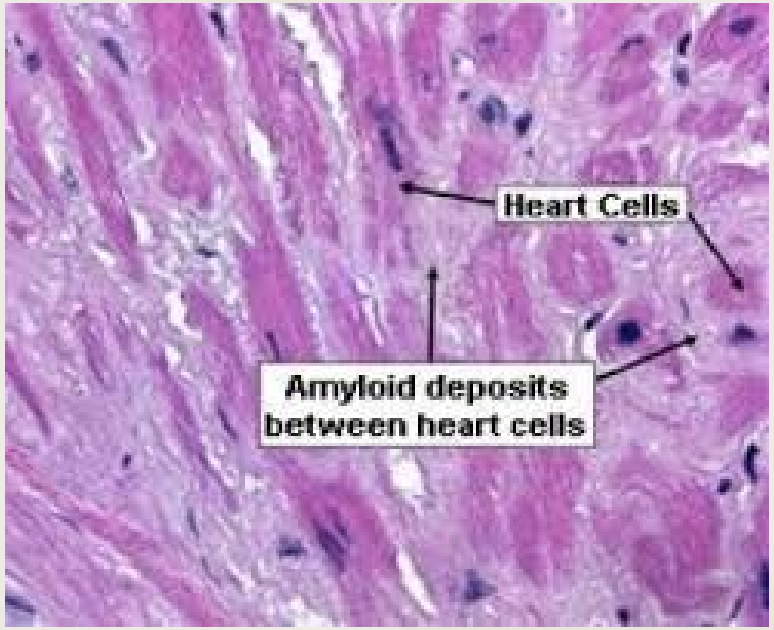
Transthyretin



Azevedo et al. 2013.



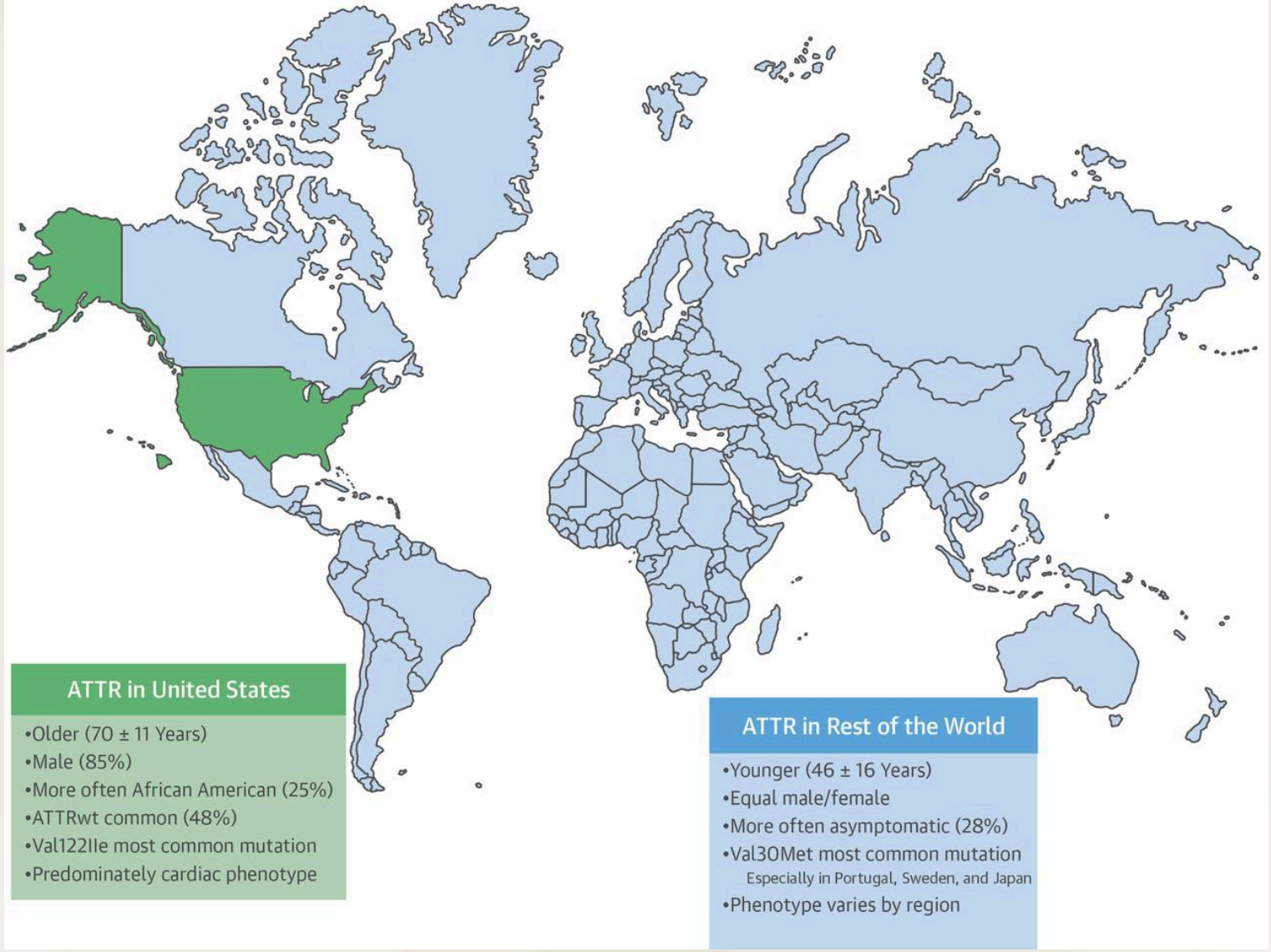
From amyloidosis foundation



https://www.acc.org/latest-in-cardiology/articles/2016/07/07/14/59/cardiac-amyloidosis

- Amyloid deposits with congo red staining and green birefringence can be seen in the heart, GI tract, kidneys, skin, nerves.
- In peripheral nerves often found in spinal roots and ganglia-sural nerve biopsy sensitivity <50%

Transthyretin Amyloid Outcomes Survey (THAOS)



ATTR in United States

- Older (70 ± 11 Years)
- Male (85%)
- More often African American (25%)
- ATTRwt common (48%)
- Val122Ile most common mutation
- Predominately cardiac phenotype

ATTR in Rest of the World

- Younger (46 ± 16 Years)
- Equal male/female
- More often asymptomatic (28%)
- Val30Met most common mutation
  Especially in Portugal, Sweden, and Japan
- Phenotype varies by region

VANDERBILT UNIVERSITY

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HEREDITARY NEUROPATHY & THE BENEFIT OF GENETIC TESTING

Emily Brown, MGC, CGC

Certified Genetic Counselor

Amyloidosis Center

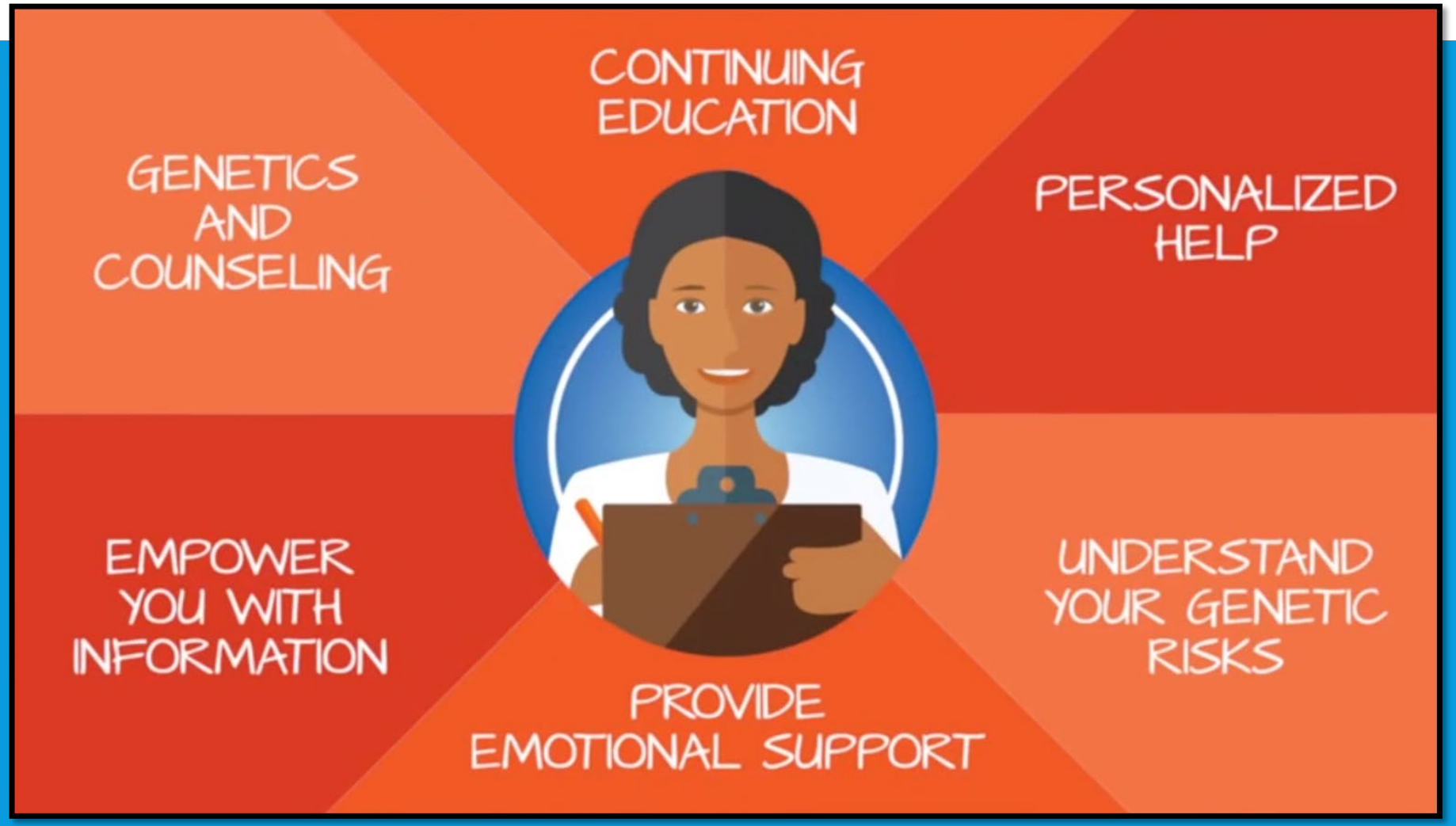
Johns Hopkins Hospital

DISCLOSURES

- I am an Advisory Board member for Alnylam Pharmaceuticals

GENETIC COUNSELING AND TESTING FOR HEREDITARY NEUROPATHIES

ROLE OF A GENETIC COUNSELOR



WHAT A GENETIC COUNSELOR *DOESN'T* DO

Clone people

Help expecting parents create designer babies

Slide curtesy of NSGC

WHY IS GENETIC COUNSELING IMPORTANT?

- Genetic testing is **MUCH** more than a simple blood test or cheek swab

- Familial implications
- Financial implications
- Mental health implications

WHEN SHOULD I SEE A GENETIC COUNSELOR

Pre-test Counseling

- Exploratory
- Know you want to proceed

Post-test Counseling

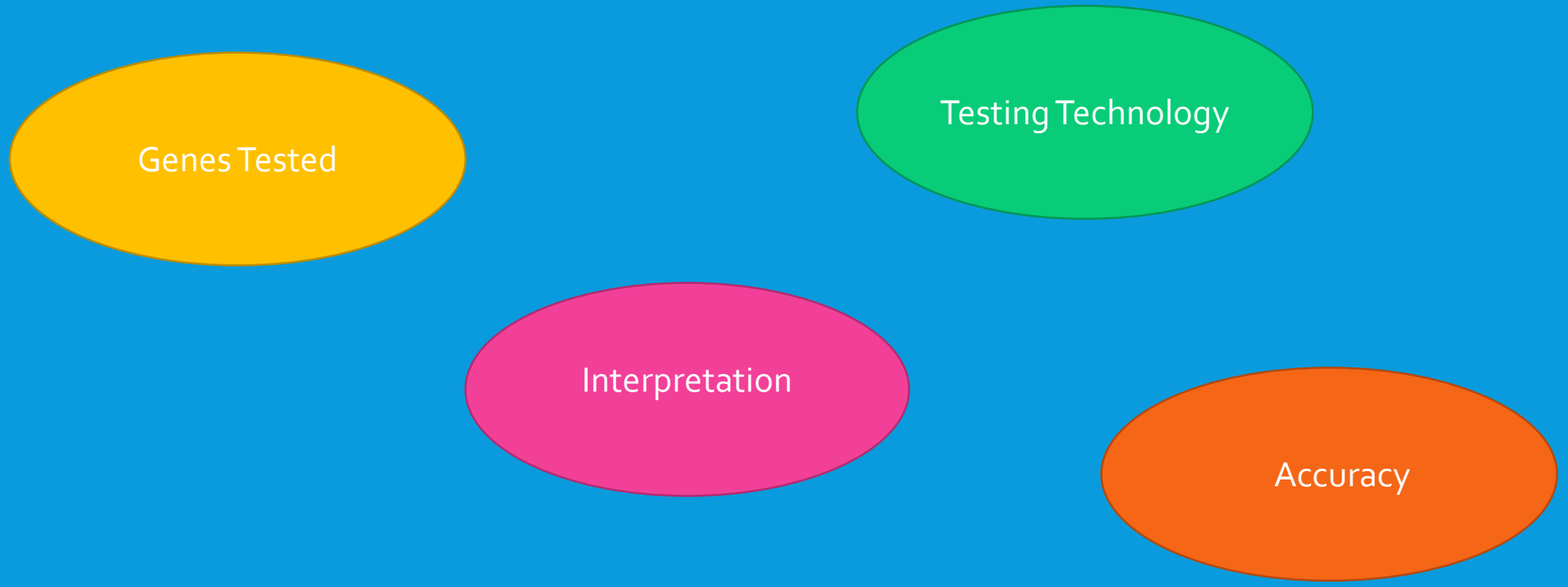
- Review results and medical management implications
- Family screening

Pre-conception

- Considering having a baby
- Prenatal genetic testing options

SELECTION AND INTERPRETATION OF GENETIC TESTS

- Not all genetic testing is created equal



DIRECT-TO-CONSUMER TESTING (DTC)

- 23andMe does look at a few neurological conditions
  - TTR amyloidosis
  - Parkinson's Disease
  - Carrier status:
    - Familial dysautonomia
    - Limb girdle muscular dystrophies
    - Agenesis of the Corpus Callosum with Peripheral Neuropathy

23andme.com

LIMITATIONS OF DTC

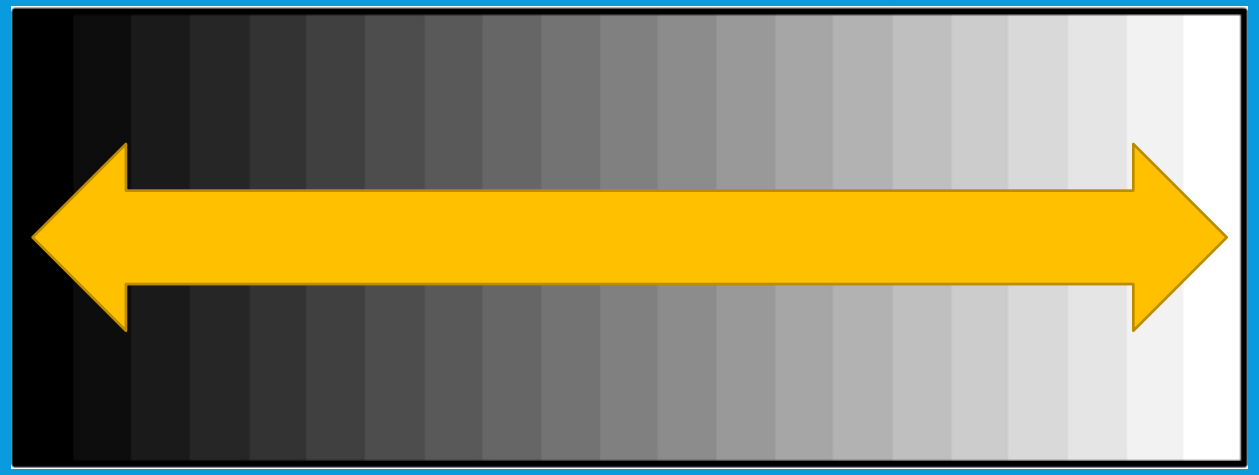
- Genotyping not full sequencing
  - Only identify a portion of patients with a mutation
  - Negative result is not a true negative

- *"The test is not intended to tell you anything about your current state of health, or to be used to make medical decisions, including whether or not you should take a medication, how much of a medication you should take, or determine any treatment."*

  -23andMe

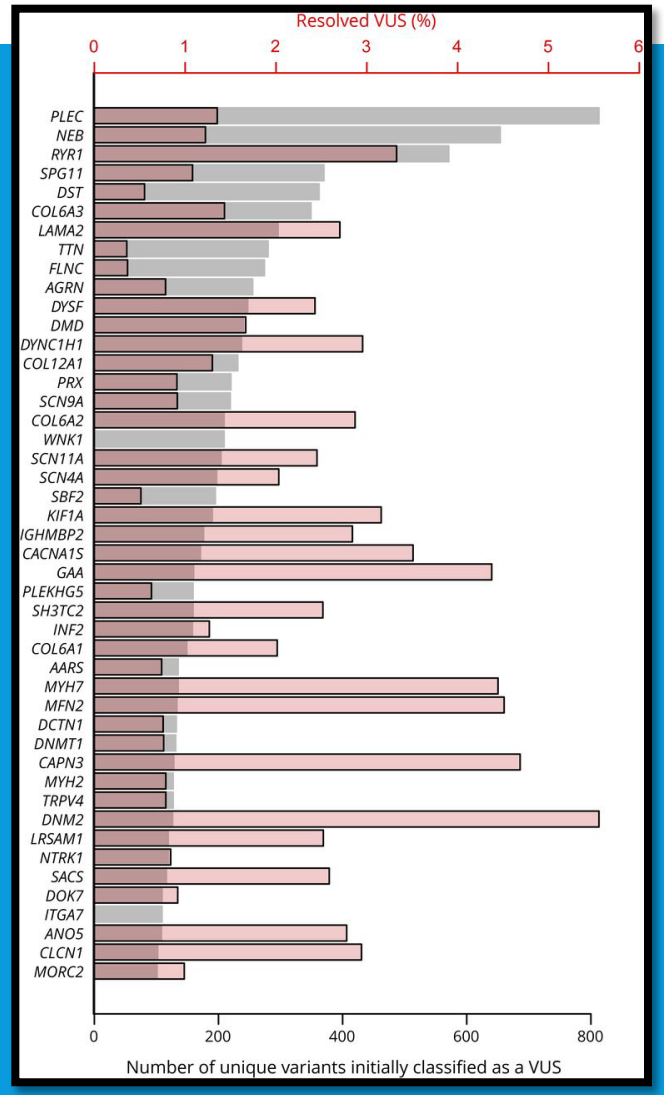
INTERPRETING RESULTS: IT'S A SPECTRUM, NOT BLACK AND WHITE

- Positive
- Negative
- Variant of Uncertain Significance



VARIANTS OF UNCERTAIN SIGNIFICANCE (VUS)

- Relatively common result
  - Likelihood increases as number of genes tested increases
- Can be difficult to interpret
- VUSes can be reclassified as further information is learned
- How do you handle uncertainty?



(Winder et al., 2020)

FINANCIAL IMPLICATIONS OF GENETIC TESTING

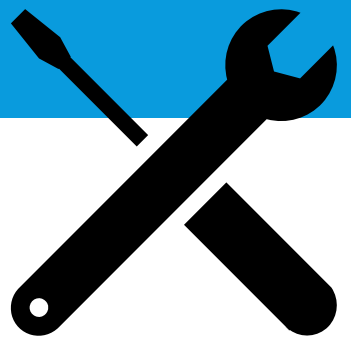
- Federal law (GINA) protects against health insurances and employer discrimination
  - Exceptions include: military, federal employees, employers with less than 15 employees
- Does not include protections for life insurance or long-term care insurance
  - These companies can use genetic information to determine an individual's coverage and rates
  - Consider updating or applying for life insurance or long-term care insurance prior to genetic testing (most applicable for familial testing)

GINA
GENETIC INFORMATION NONDISCRIMINATION ACT

PRIVACY IMPLICATIONS

- Most (if not all) DTC companies own the consumer data
  - sell data to interested third parties
- Most (if not all) clinical labs will NOT sell/disclose your data without your explicit consent
  - Labs will retain a copy of your results (often legally required)
  - Most clinical labs do participate with ClinVar, a federal program that enables research on genes and health. Anonymized variant information may be shared.

NUTS AND BOLTS



NUTS & BOLTS: GENETIC TESTING SAMPLES

- Accepted samples: blood, saliva, buccal swab
- Many labs will send kits to your house
- ~4 weeks turn around time

NUTS & BOLTS: INSURANCE COVERAGE

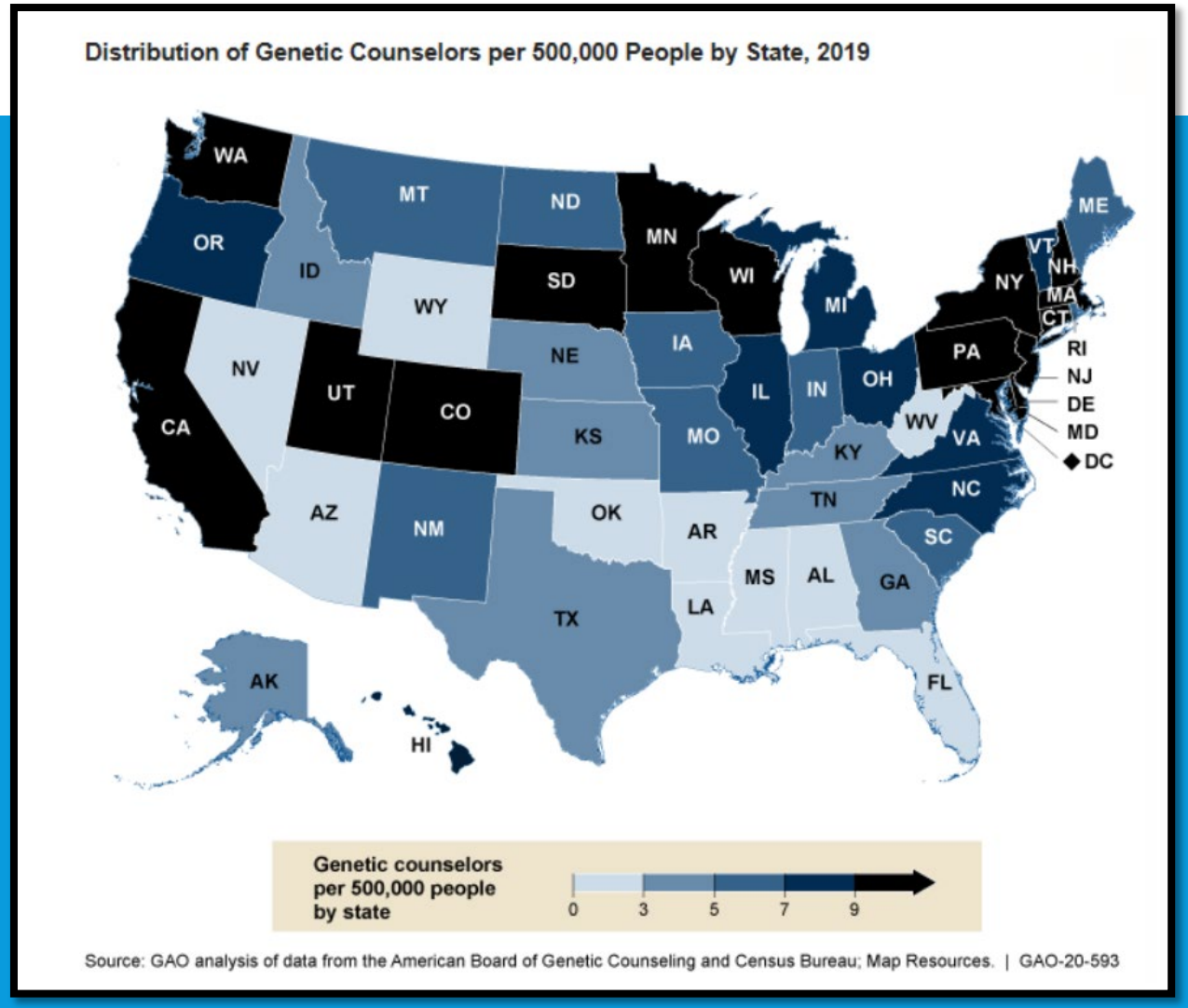
- Insurance coverage genetic counseling
  - Most private insurance companies cover genetic counseling
  - Billing (CPT) code: 96040
- Insurance coverage for genetic testing
  - Insurance dependent
    - Targeted familial testing vs full sequencing
    - Some labs will provide estimates up-front
    - Some insurances require genetic counseling
  - Reviewed during the genetic counseling appointment
  - Billing (CPT) code: lab dependent

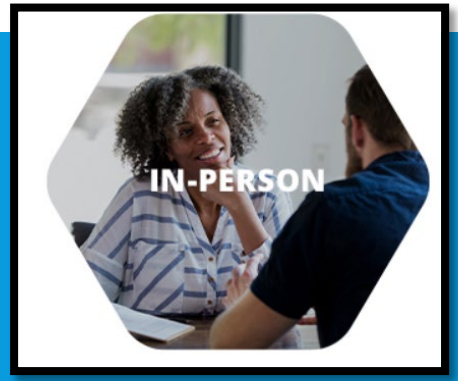
Pharmaceutical Sponsored Programs

- Alnylam Assist
- hATTR Compass

still need a healthcare provider to order the test

NUTS & BOLTS: FINDING A GENETIC COUNSELOR





Resources

- https://findageneticcounselor.nsgc.org/
- Telemedicine Companies
  - Informed DNA
  - Genome Medical

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Questions?

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