Not (Just) Your Mother's Genome

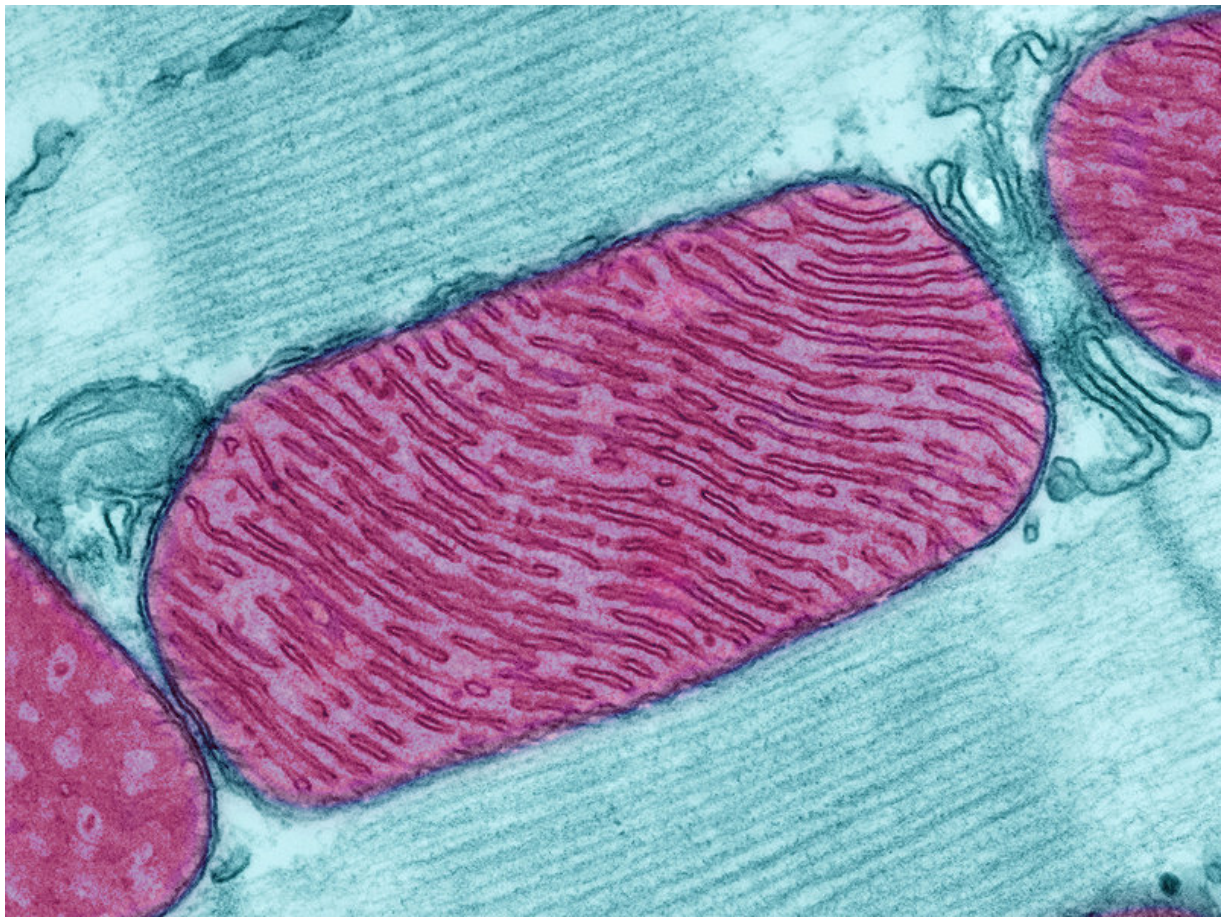
What you should know about genetic testing for mitochondrial disorders

GeneDx
an OPKO Health Company

Disclosures

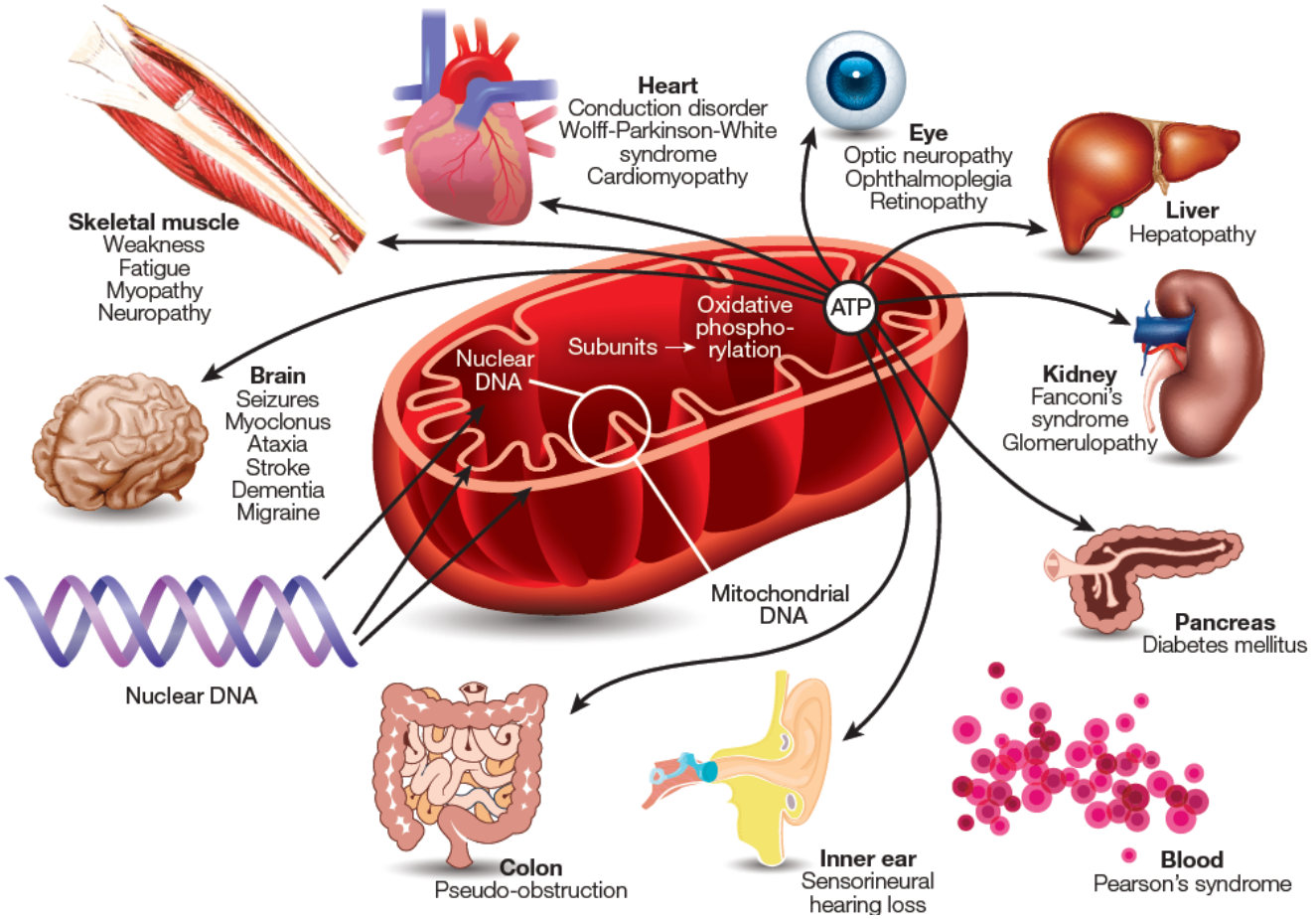
I am an employee of GeneDx, Inc., a wholly-owned subsidiary of OPKO Health, Inc.

What are Mitochondria?

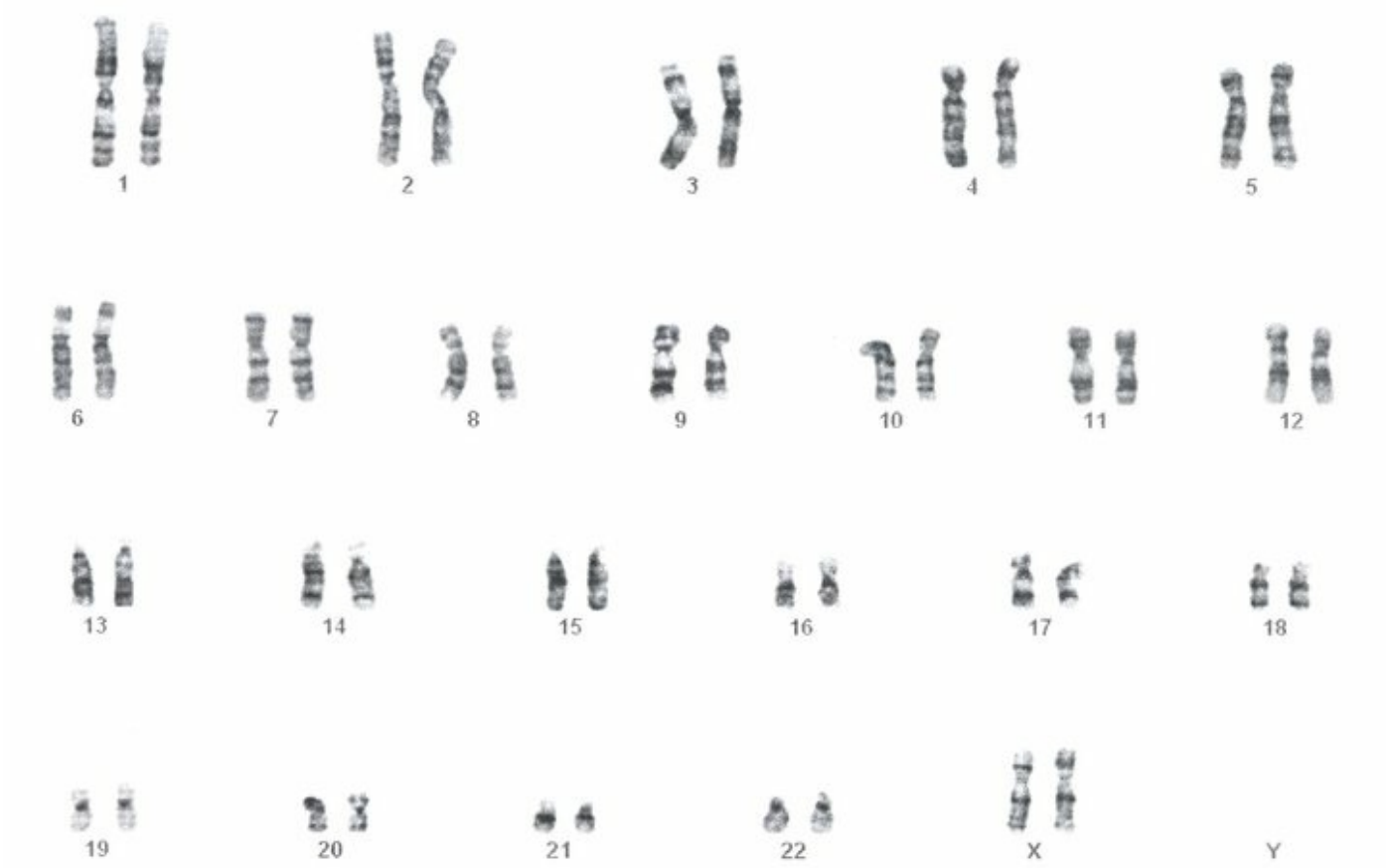


http://www.sciencesource.com/

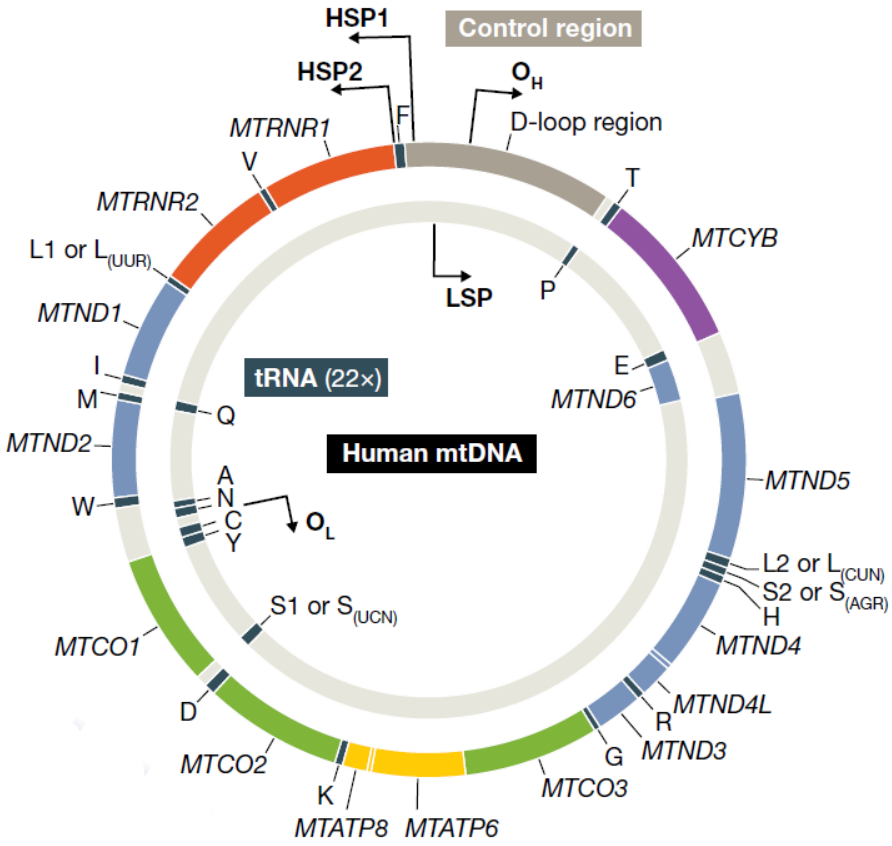
What are symptoms of Mitochondrial Disorders?

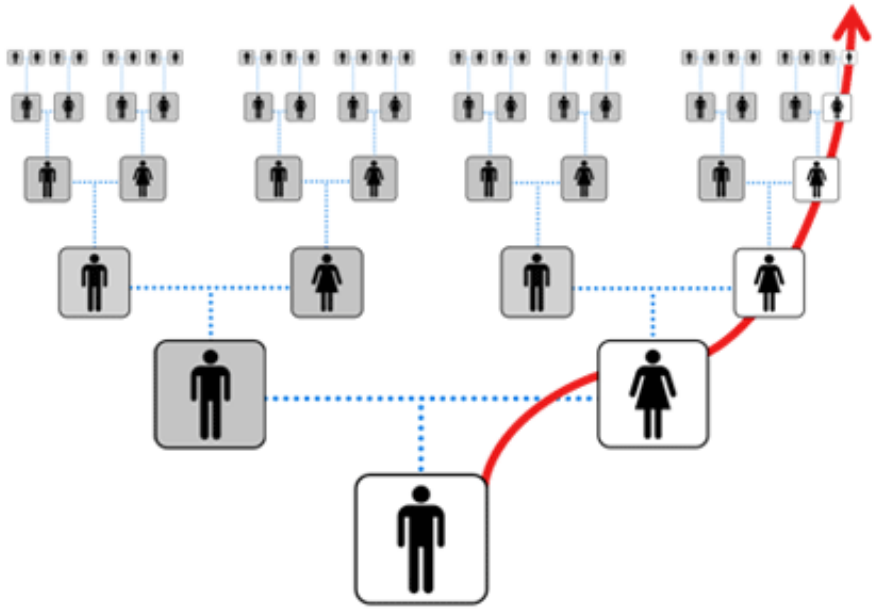


Genetics of Mitochondrial Disorders



Genetics of Mitochondrial Disorders

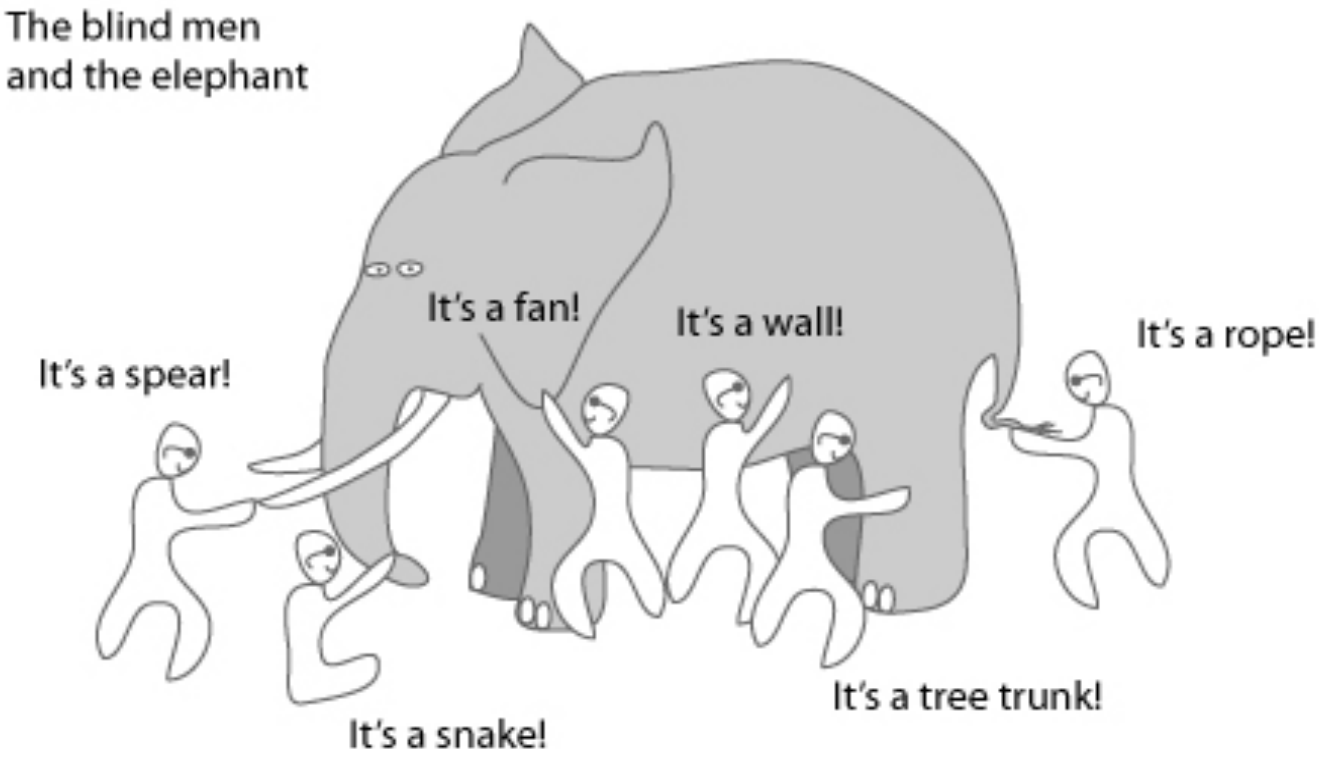




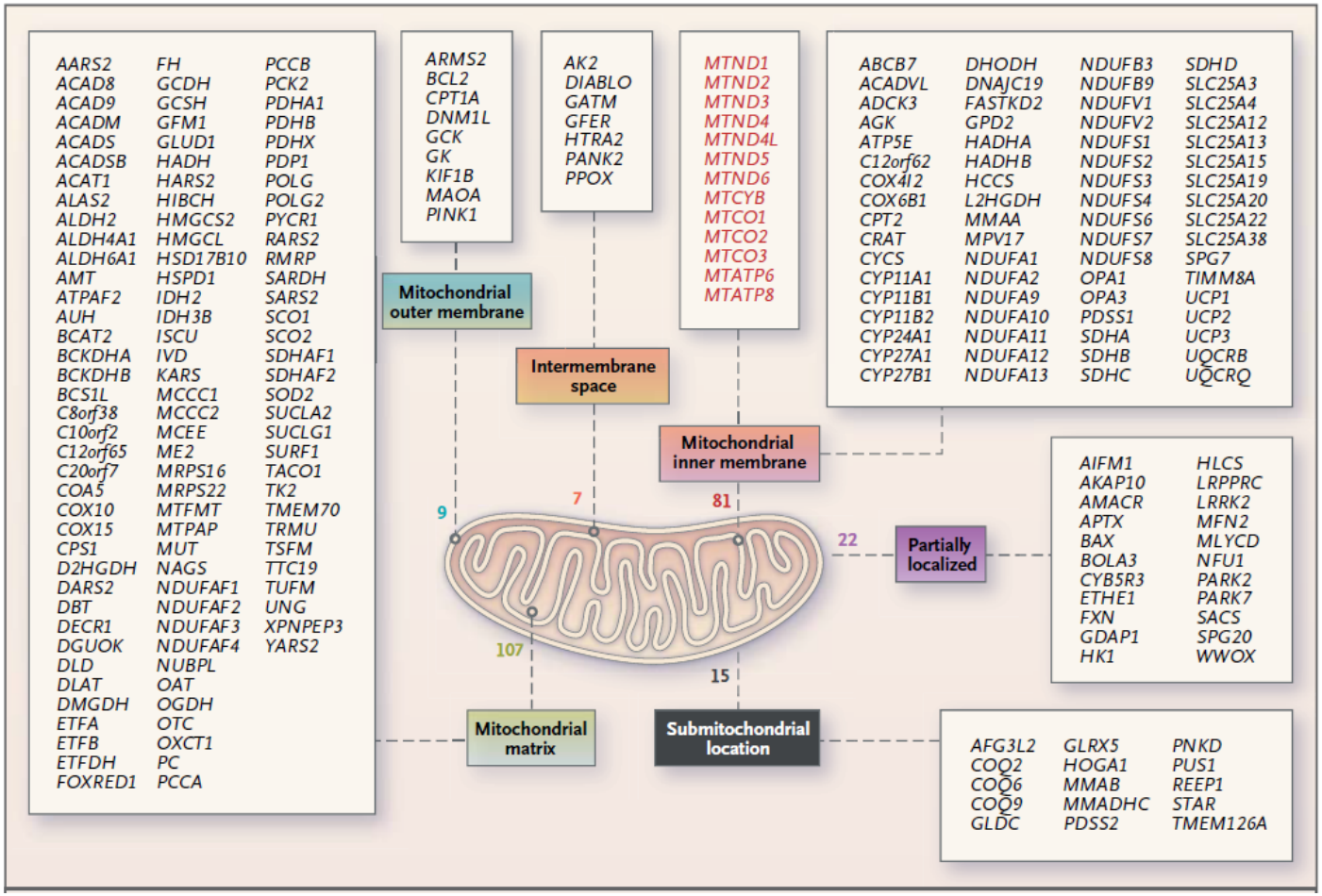
https://www.igenea.com/en/mitochondrial-dna

Chinnery et al. (2015) EMBO Mol Med 7 (12):1503-12 (PMID: 26612854)

How are Mitochondrial Disorders Diagnosed?



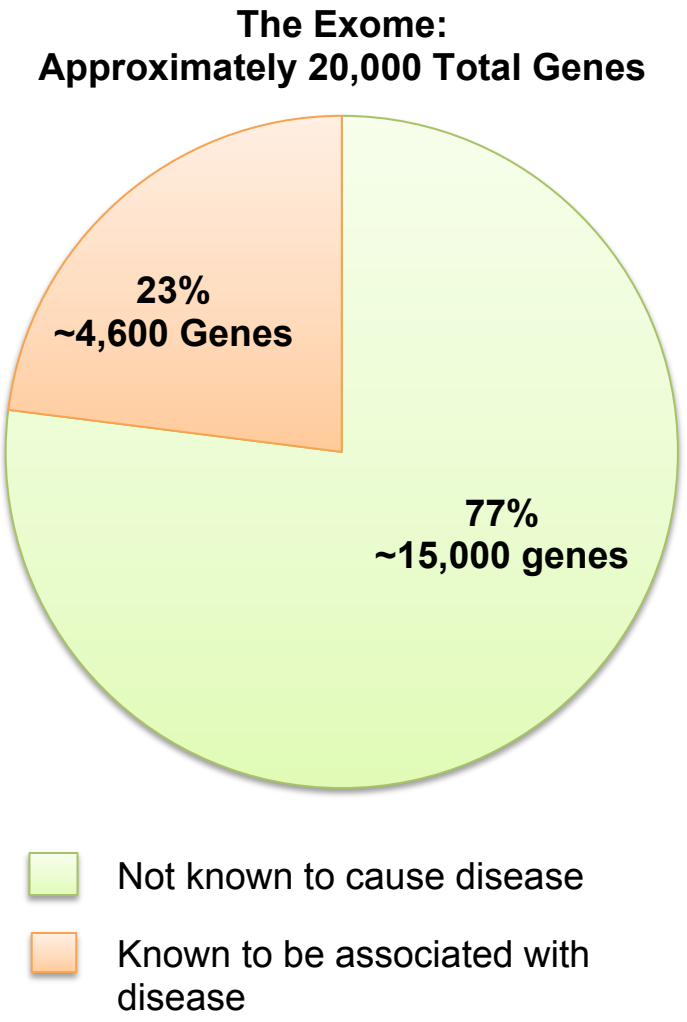
Genetic Testing for Mitochondrial Disorders – Panel Testing



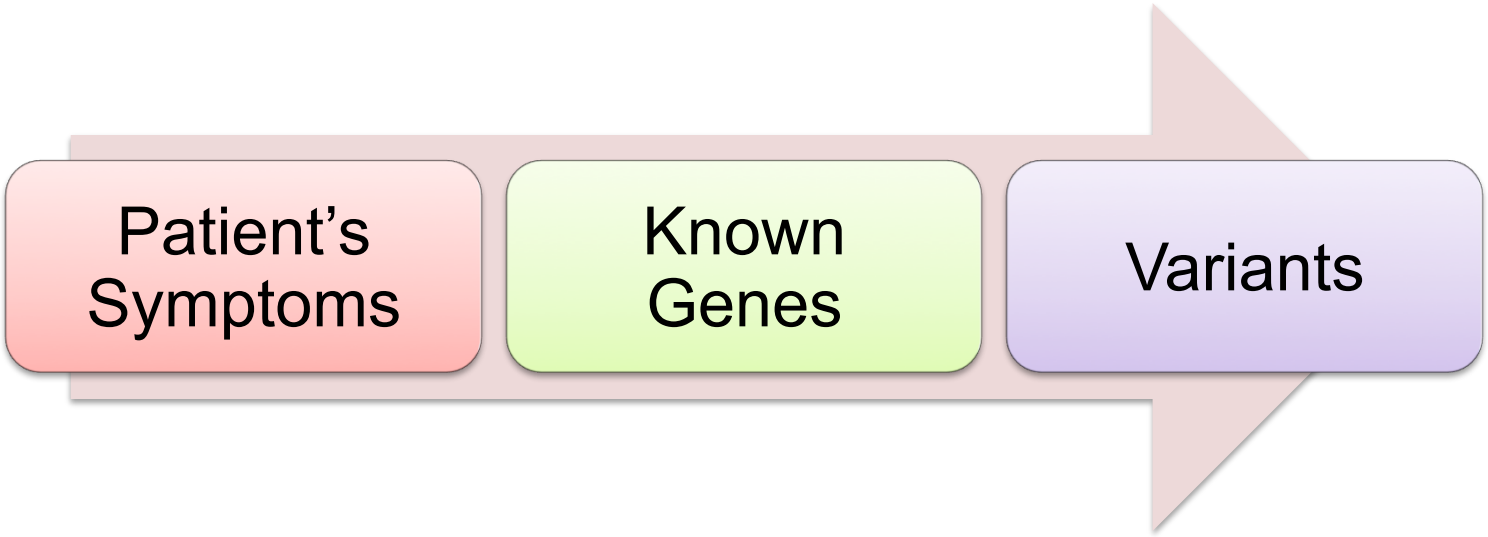
Koopman et al. (2012) N. Engl. J. Med. 366 (12):1132-41 (PMID: 22435372)

Genetic Testing for Mitochondrial Disorders - Whole Exome Sequencing

- **What is Whole Exome Sequencing**
  - Sequencing of the protein-coding regions of the human genome
  - Only genetic changes that seem like they're related to the patient's symptoms are reported



Analysis of Genetic Testing



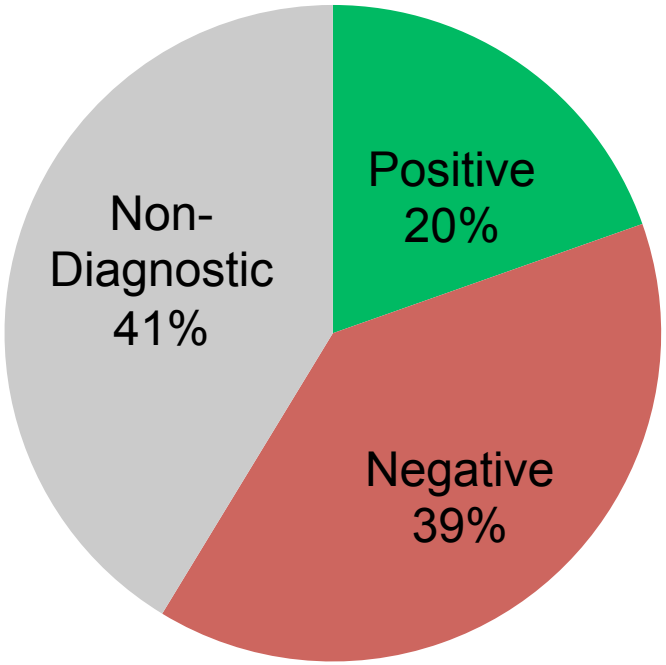
Variant Interpretation Guidelines

Which Test is Best for Mitochondrial Disorders?

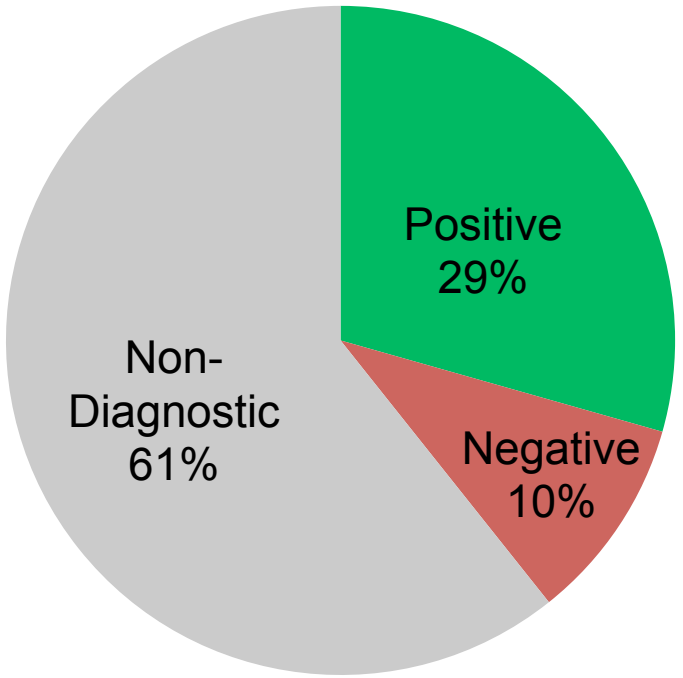
- There is no single best test for **all** patients who are suspected of having a mitochondrial disorder
  - It depends on specific symptoms that individual person has

Panel testing vs. Whole Exome Sequencing

Panel Testing



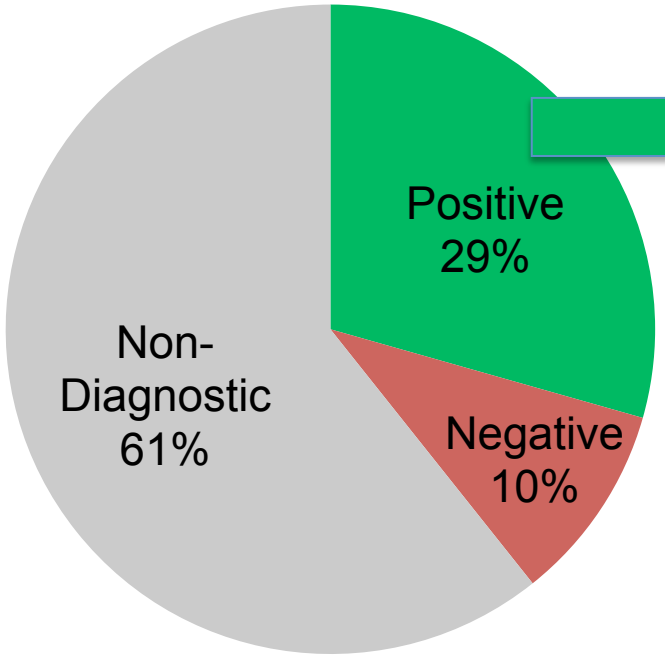
Whole Exome Sequencing



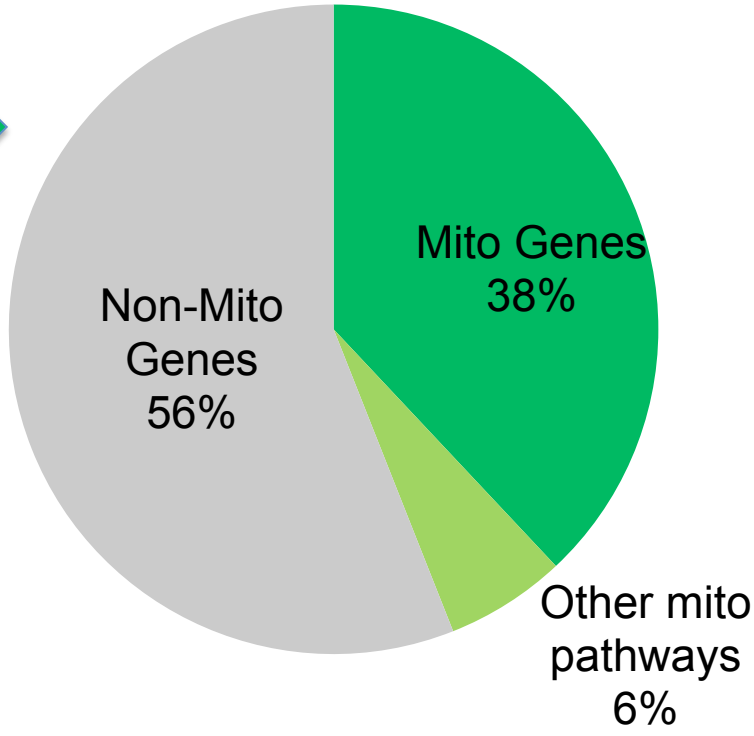
Bai R et al. WES and WMGS for Molecular Diagnosis of Mitochondrial Disorders: Lessons from 865 Cases [Abstract #119 and platform presentation]. Presented at the 2015 UMDF Symposium, June 18, 2015, Washington DC;

Whole Exome Sequencing Results

Whole Exome Sequencing

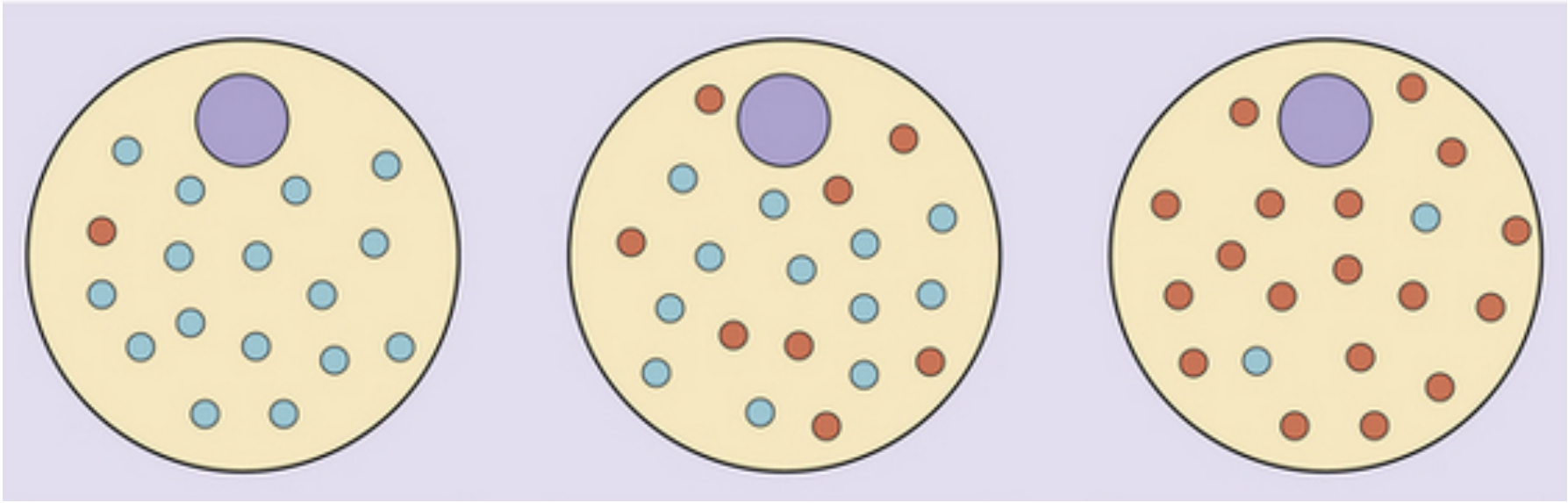


Positive WES Cases



3/2016 GeneDx internal data

Special Considerations with for Mitochondrial Genome Testing



Low Heteroplasmy

Intermediate Heteroplasmy

High Heteroplasmy

https://clinicalgate.com/mitochondrial-encephalopathies/

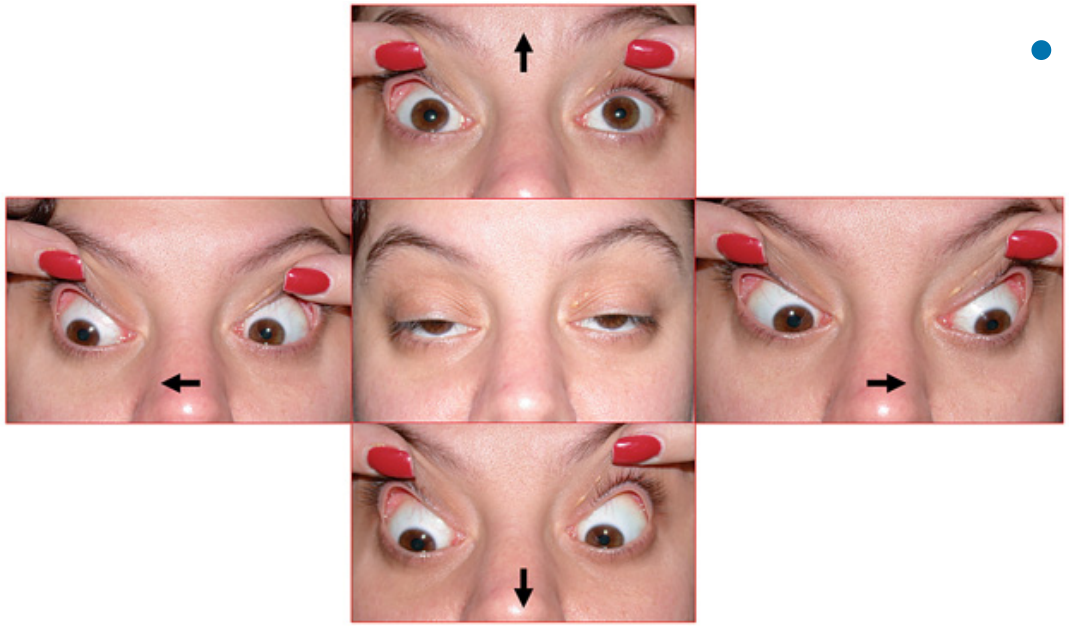
Mitochondrial Genome Heteroplasmy

- The proportion of mitochondrial genomes that have a variant
- Percentage can vary from tissue to tissue
- Percentage can vary with age
- Threshold effect
  - Variant must be present at a high enough level in a particular tissue in order to cause clinical symptoms
  - Threshold percentage can vary by variant

Sample Type and Mitochondrial Genome Testing

- Sample type
  - Heteroplasmy can vary from tissue to tissue
  - Best to send sample from an affected tissue
    - Most frequently this is muscle or liver
    - Very important for patients with specific symptoms

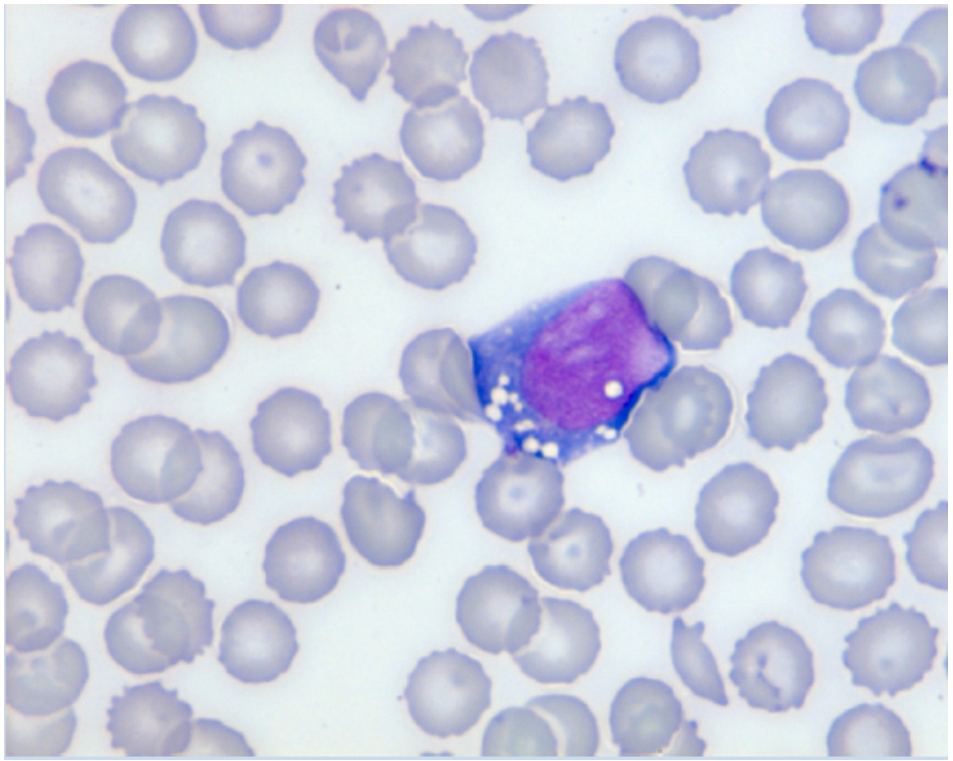
Chronic Progressive External Ophthalmoplegia



- CPEO is a symptom that is highly specific for a mitochondrial disorder
  - Approximately 50% of these patients harbor a large mtDNA deletion *that is confined to muscle*

http://www.reviewofophthalmology.com/article/how-to-spot-dangerous-ptosisthe-sequel

Pearson Syndrome



- Infantile onset sideroblastic anemia and pancreas dysfunction
  - Also associated

ınt in

blood.

Tumino et al. (2011) Am. J. Med. Genet. A 155A (12):3063-6 (PMID: 22012855)

Other sample types for Mitochondrial Genome Testing

- Oral rinse and buccal swabs
  - Similar to blood heteroplasmy for most patients
- Skin cells
  - Most skin cells are cultured and some mitochondrial genome variants are selected against when cultured making them more difficult to detect
- Urine epithelial cells
  - Similar to muscle heteroplasmy
  - However, DNA quality from urine is extremely poor, so it frequently does not yield results
- Hair follicles
  - Poor DNA quality
  - Heteroplasmy can vary greatly from follicle to follicle

Limitations of Genetic Testing

The scientific knowledge available about the function of all genes in the human genome is incomplete at this time

Testing may identify the presence of a variant in an affected individual, but we will not recognize it as the cause of their disease due to insufficient knowledge about the gene and its function

Not all types of genetic testing can detect all types of genetic variants known to cause disease (such as repeat expansions, variants not present in exons)

For mitochondrial genome variants, as heteroplasmy levels can vary from tissue to tissue, some variants may not be detected in the sample type submitted but still be present in other tissues

Acknowledgements

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