Mito Basics: Genetics, Testing and Financial

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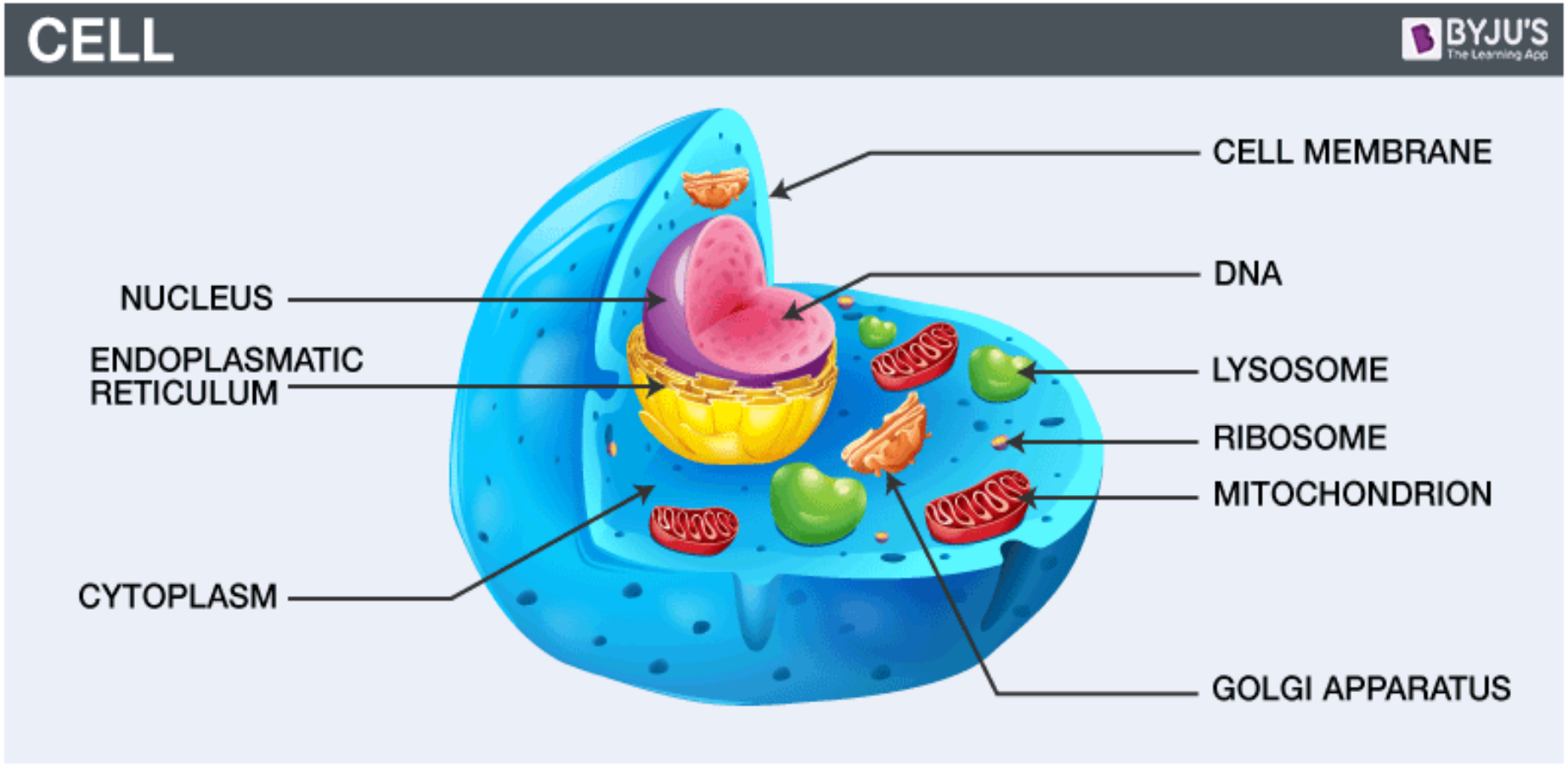
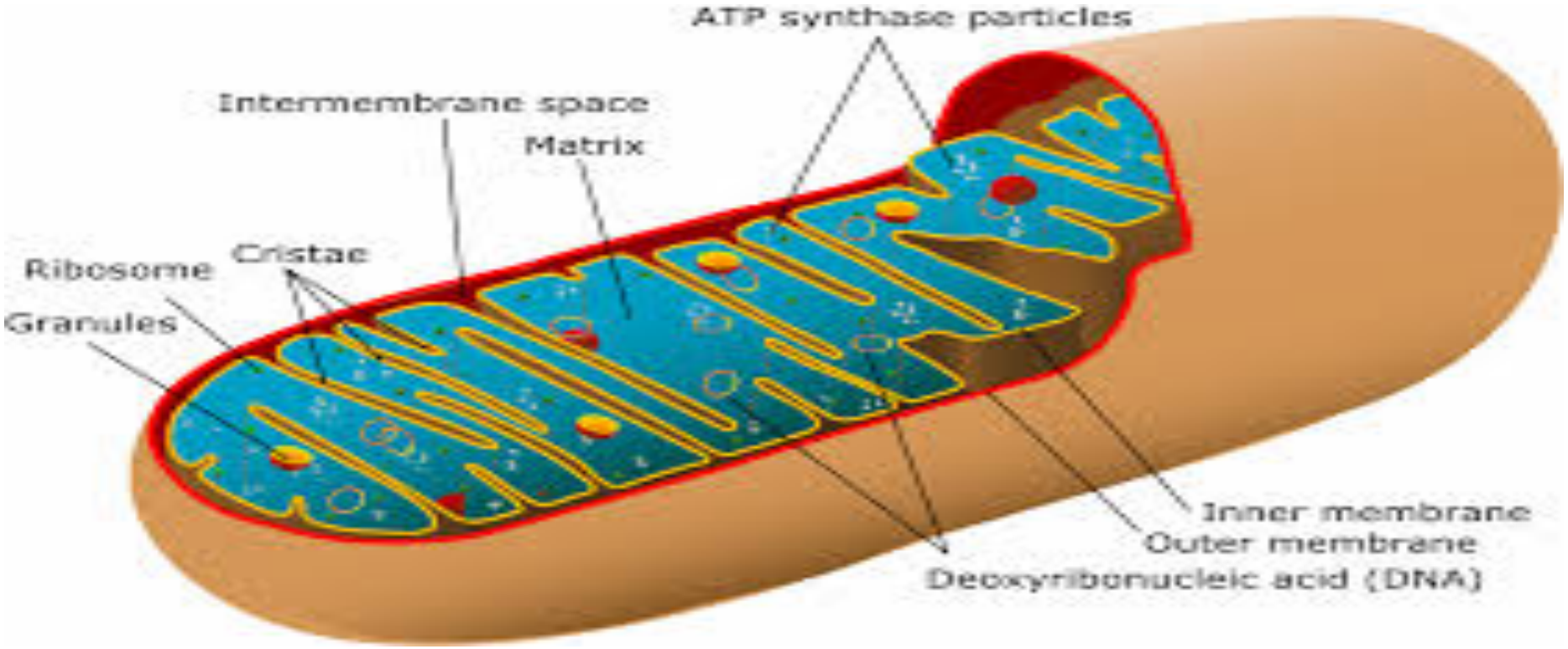
GENEDX

The Cell


CELL
BYJU'S
The Learning App
CELL MEMBRANE
DNA
NUCLEUS
ENDOPLASMATIC
RETICULUM
LYSOSOME
RIBOSOME
MITOCHONDRION
CYTOPLASM
GOLGI APPARATUS

Mitochondria: What are they and what do they do?



What are they?

- Mitochondria are intracellular organelles.
- Their job is to create the energy needed to run the cell.
- They transform food into ATP (The fuel that runs the cell) through a process called Oxidative Phosphoralization.

Mitochondrial Genetics

- mtDNA vs n DNA
  - Mitochondrial DNA (mtDNA) is the DNA separate from the nuclear DNA (nDNA) and found in each mitochondria.
  - mtDNA only has 37 genes; nuclear DNA contains over 20,000.
  - Each mitochondria has its own DNA loop and it can differ from other mitochondrial DNA in other mitochondria in the same cell. This is called heteroplasmy.
  - When a high enough percentage or "tipping point" of mitochondria have mutated DNA that is not functioning correctly that is expressed in symptoms or disease.
  - In simple terms, this means that your mitochondria are not working well enough to produce the energy in the form of ATP that is needed for the cell to function as it should.
    - Football team analogy.

mtDNA vs nDNA

- Nuclear DNA (nDNA) makes up the genes that everyone thinks about when they think of DNA.
- nDNA plays a big role in constructing and monitoring mitochondrial function.
- There are genes (like POLG) who's job it is to construct mitochondria and when there are mutations in those genes, they make poor or non functioning mitochondria.
- We currently know of about 1,500 nuclear genes that play a role in mito function (compare that to the 37 genes in mtDNA).

Mito Red Flag Symptoms

- Multi System involvement.
  - Brain, Heart, Muscle, Kidney, GI, etc.
  - Symptoms include:
    - Seizures
    - Muscle Weakness
    - Hearing Loss
    - Diabetes
    - Cardiomyopathy
    - GI Dysmotility (vomiting, etc)
    - Hypotonia
    - Exercise Intolerance
    - Short Stature/Failure to thrive
    - Vision issues

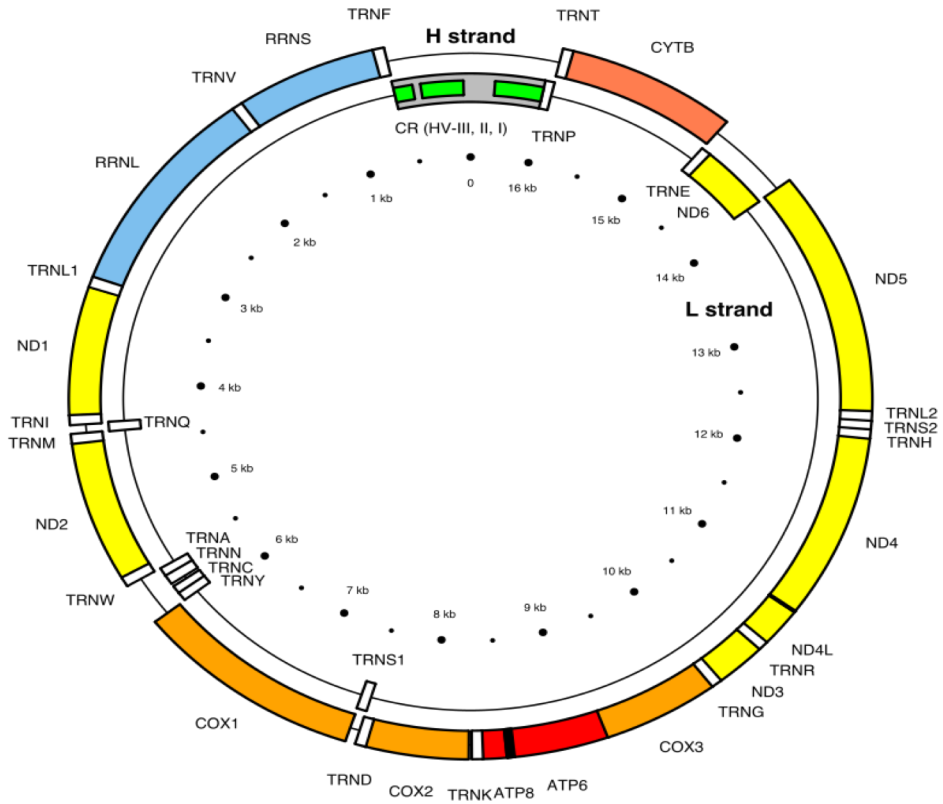
Testing

- Biochemical testing (initial workups)
  - Lactic Acid
  - Amino Acids
  - Pyruvate
  - CPK levels
  - Urine Organic Acids
  - Among Others

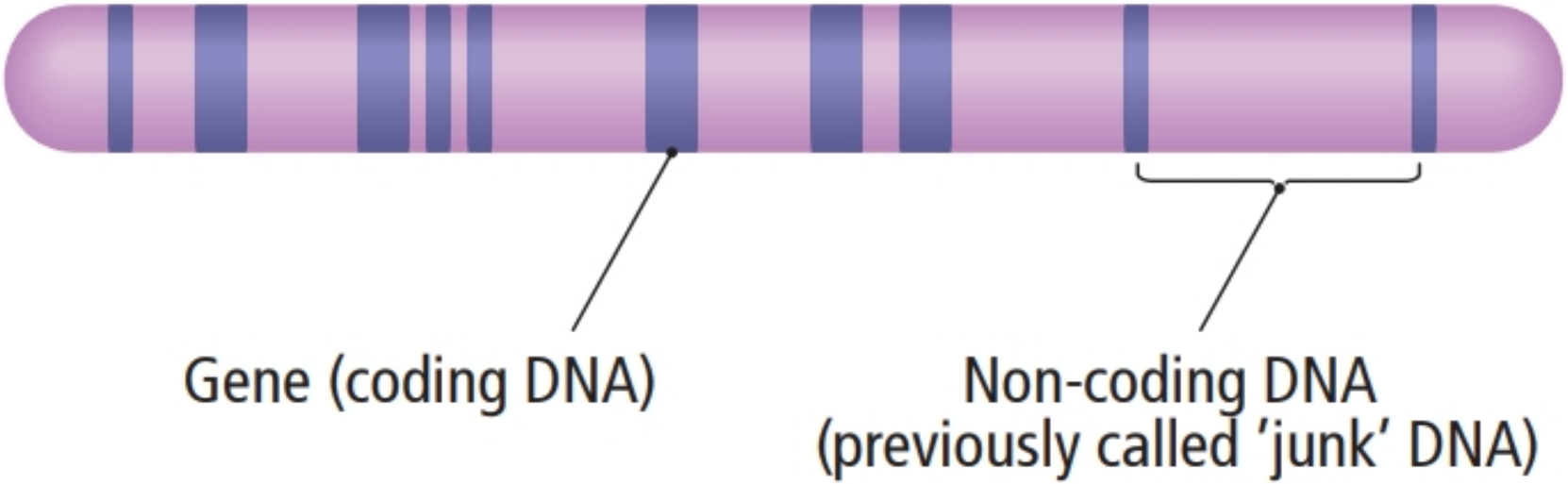
Testing

- Muscle Biopsy
  - Historically the way to identify mito disease.
  - Take a biopsy of muscle and look at it under a microscope
  - Do the mitochondrial look healthy or not?
  - “Ragged Red Fibers”
  - Oxphos (Oxidative Phosphoralation) Testing. Complex I-V. (Also known as Enzyme Testing)

Mitochondrial DNA



Nuclear DNA



Genetic Testing

- mtDNA
  - mtDNA (MELAS, MERRF, NARP, LHON, KSS/CPEO)
  - First discovered in 1988.
  - Point mutations (variants) and large deletions have been identified as causing these alphabet disorders.
  - Heteroplasmy
    - Different Heteroplasmy levels in different tissues. Affected tissues are assumed to have higher levels of heteroplasmy. Best to test affected tissues. Then why test blood/buccal swab/urine?
    - Now it is more comprehensive and cost effective to do whole mito genome with deletions rather than disease specific point mutations.

nDNA

- The DNA in your cells nucleus.
- About 1500 genes are known or thought to play a role in mito function.
- Different Genes do different things and thus cause different disorders.
- Some Diseases very well defined (text book cases)
- Mito is inherently difficult to pin down because of multiple systems involved and to varying levels. For instance, people in the same family with the same pathogenic variant can express different symptoms.

Genetic Testing

- Single Gene/Panels/WES/WGS
- No one does single gene testing anymore (with very few exceptions).
- NGS technological breakthrough
- Panels
  - Disease specific (Leigh's Disease Panel, Mitochondrial Encephalopathy Panel, etc)
  - More comprehensive/larger Panels (Mito Xpanded)

Genetic Testing

- Whole Exome Sequencing
  - Exome just means the coding region (Exons) of all of your genes (20,000+). This makes up only about 3% of your total DNA. What does "coding" mean?
  - Exons code for what we know the most about as it relates to disease.
  - Any Exome done should include mtDNA in suspected mito disease and preferably be a trio
  - This is currently the gold standard (most comprehensive, and less expensive in the long run)
  - Why not just do a panel?
  - Typical genetic work up is step by step.
    - CMA, FRAGX, Panel, WES/WGS
    - Insurance driven

Genetic Testing

- Whole Genome Sequencing
  - Future of genetic medicine is here!
  - Genome is all of your DNA, not just the coding regions. (100% not just 3%).
  - Genome includes exons, intronic regions and non coding regions.
  - We are discovering more and more about the function of the whole genome every day.
  - WGS is currently available but insurance will not currently cover it. Most insurances are reviewing their genome coverage policy.
  - Still considered "experimental." (that is a poor excuse, IMO)

Direct to Consumer Testing

- DTC testing is not a diagnostic test.
- No reputable Geneticist will use this data.
- "The SNP-chip genotyping method that most DTC genetic tests use is unreliable at testing for very rare disease-causing genetic variants. A recent study looking at *BRCA1* and *BRCA2* genes in UK Biobank participants found that 96% of disease-causing very rare variants identified by SNP-chip genotyping were false positives." **(British Medical Journal)**
- "I did 23 and Me and they didn't find anything…"
- Read the fine print. What are you agreeing to?
- Entertainment purposes only.

Why Testing is important

- Genetic Testing is important for a wide variety of reasons.
  - Possible therapies and Drug Trials.
    - Most trials require a molecular diagnosis to enroll in a study.
    - MitoAction has a list of active therapeutic trials on their website
    - Clincaltrials.gov
  - Family planning
  - Getting an answer.
    - Even if no treatment or cure, you will no longer need to keep looking. (Piece of mind and no more diagnostic odyssey)
    - Even if negative you will know more. WES/WGS data will always be there (Free Reanalysis).
    - New pathogenic genes discovered almost daily.

Insurance coverage/Financial aspects

- Private Insurance and Public Insurance
  - Private insurances are things like BCBS/Aetna/Cigna/UHC/Humana, etc.
  - Public Insurances are things like Medicare and Medicaid.
    - Managed Medicaid
    - Supplemental Medicare plans

Private Insurance

- Each private insurer has a genetic testing policy (some prohibit genetic testing).
- Prior Authorizations (Most private insurances and all Medicaid require a prior auth for this level of testing).
  - Make sure your doctor/staff knows that a PA is needed.
  - Some require the physician to do the PA themselves *UHC and BCBS (roadblocks)
  - Tight windows (48 hrs to 1 week).
  - What you need to know about getting a PA.
    - Coding is King! The ICD-10 codes much match and be specific (Unspecified is rarely good).
    - Letter of Medical Necessity (most reputable labs will have template letters to use).

Private insurance and Labs

- What you should ask about the lab doing the testing
  - Are you in network with my insurance?
  - Can you do the Prior Auth?
  - Do you limit my out of pocket responsibility?
  - Will I be balance billed if my insurance does not cover this?
  - Do you have self pay options?
  - Do you have Financial Assistance?
  - Do you have Charity Care?
  - Do you offer Genetic Counselling?
  - Will You appeal an insurance denial?

Public Insurances

- Medicare
  - Medicare will not cover most genetic tests. Know that going in. They only cover a limited number of inhereited cancer tests.
  - Your best options if you have Medicare is usually to ask for self pay option.
  - ABN

Medicaid

- Medicaid is state specific
  - Each state has it's own policy and they vary greatly.
  - Example NC v GA
  - Each state should have their genetic testing policy on line.
  - Find out if the lab being used is in network with that state's Medicaid.
  - Managed Medicaid (Wellcare, Amerigroup, etc).

Appeals

- If an insurance (Medicaid or private insurance) denies coverage for a test or service, you have the right to appeal.
- This is where letters of medical necessity, comprehensive medical records/clinical notes, proper coding and following procedure (PA, etc) comes into play
- Be aggressive. You are their customer.
- Georgia Appeal Statute: O.C.G.A. 33-20A-5 (3) (B) (ii) states: "Such hearing shall be conducted by a panel of not less than three persons, at least one member of which shall be a physician other than the medical director of the plan and at least one member of which shall be a health care provider competent by reason of training and licensure in the treatment or procedure which has been denied." What does this mean??
- Medicaid appeal is more difficult.
- Medicare appeals not worth the risk

Resources

- MitoAction
  - New Patient Kit
  - Mito 411
- UMDF
  - Mito U
  - Mito 101
- Mitochondrial Medicine Society
  - Higher level of science here, but still interesting and a valuable tool.

Questions?

- I would like to thank MitoAction for the opportunity to speak and for all of the wonderful work they do!
- If you would like to contact me directly, you can email me at dkeane@genedx.com or just call MitoAction and they can provide you my contact info.