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MINI MED SCHOOL

Talk 2: The role of genetic testing in medicine

DREW SMITH, BSC, UBC MD CLASS OF 2024

a place of mind
THE UNIVERSITY OF BRITISH COLUMBIA
Faculty of Medicine

University of Victoria

let's talk science

TERRITORIAL ACKNOWLEDGEMENT

I would like to begin by acknowledging that I am joining you from the traditi̓onal, ancestral, and unceded territory of the lək̓ʷəŋən (Lekwungen) speaking peoples, including the Songhees, Esquimalt, and W̱SÁNEĆ peoples whose historical relationships with the land continue to this day.

DISCLOSURE

I am a medical student. These talks do not constitute for or substitute medical advice.

Genetic testing is a complex topic with a great deal of nuances. I will try to present the information in a simple manner, which requires glossing over many details.

Please consult with your healthcare provider if you have questions about genetic testing for yourself.

OUTLINE

- SCREENING TESTING
  - Prenatal Screening
  - Newborn Screening
- CASCADE TESTING
- CARRIER TESTING
- DIAGNOSTIC TESTING

Which of the following genetic diseases is not regularly screened for during pregnancy?

A. Down Syndrome
B. Trisomy 18
C. Trisomy 13
D. Cystic Fibrosis

Which of the following genetic diseases is not regularly screened for during pregnancy?

~~A. Down Syndrome~~

~~B. Trisomy 18~~

~~C. Trisomy 13~~

D. Cystic Fibrosis

Which of the following is a metabolic disorder screened for in newborns?

A. Congenital Adrenal Hyperplasia
B. Phenylketonuria
C. Congenital Hypothyroidism
D. Sickle Cell Disease

Which of the following is a metabolic disorder screened for in newborns?

~~A. Congenital Adrenal Hyperplasia~~

B. Phenylketonuria

~~C. Congenital Hypothyroidism~~

~~D. Sickle Cell Disease~~

Which of the following is an example of a dominant genetic condition?

A. Huntington Disease
B. Cystic Fibrosis
C. Tay-Sachs Disease
D. Phenylketonuria

Which of the following is an example of a dominant genetic condition?

A. Huntington Disease

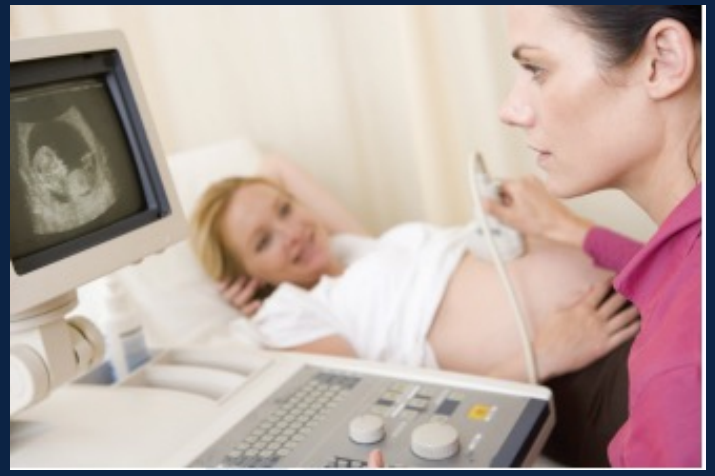
~~B. Cystic Fibrosis~~

~~C. Tay-Sachs Disease~~

~~D. Phenylketonuria~~

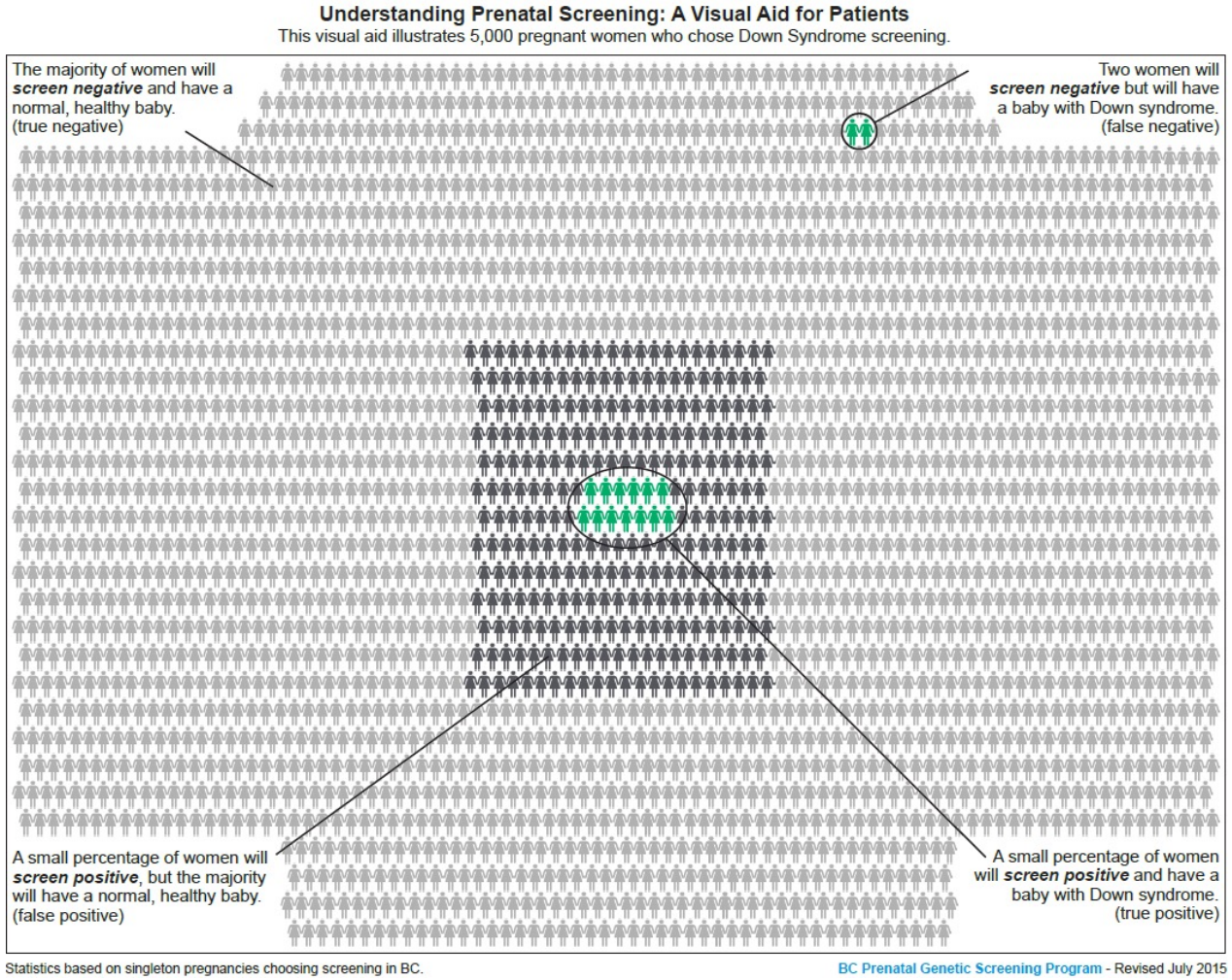
SCREENING TESTING

- PRENATAL SCREENING (will include follow-up diagnostic testing)
- NEWBORN SCREENING (will briefly mention follow-up diagnostic testing)



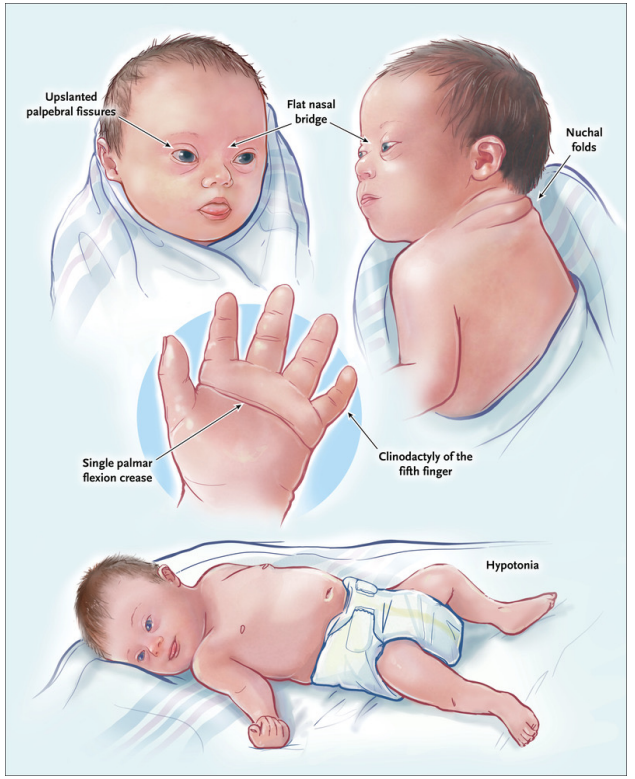
SCREENING TESTING

- Testing done in order to identify individuals in the population who have an increased risk of a condition
- Positive result ≠ diagnosis, will usually lead to diagnostic testing
- Negative result means the risk is quite low, no further testing typically

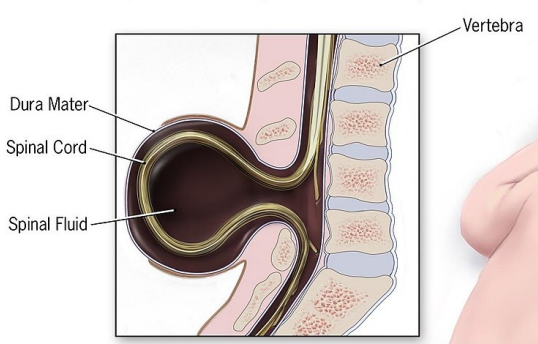


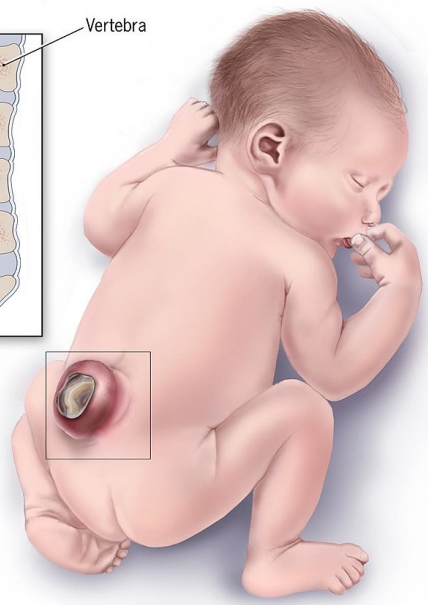
PRENATAL SCREENING

- Tests offered to pregnant women to determine if there is an increased risk of the fetus having Trisomy 21 (Down Syndrome), Trisomy 18, or a Neural Tube Defect (NTD)



Spina Bifida (Open Defect)

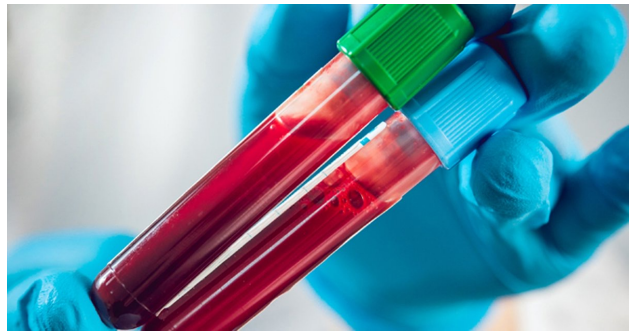


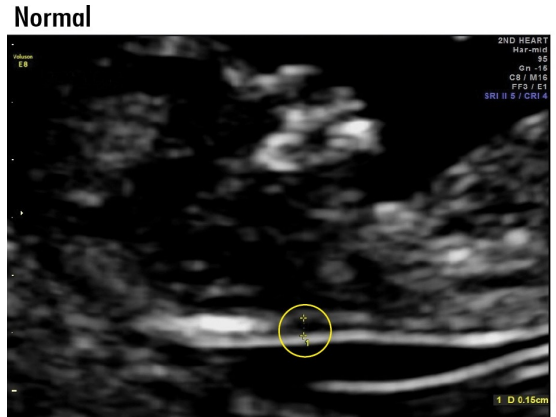


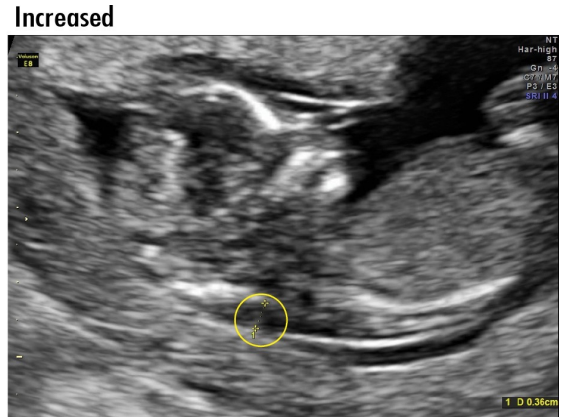
AGE RELATED RISK OF ANOMALIES IN FETUS AT BIRTH			
Mother's Age	Chance of Trisomy 21 (Down Syndrome)	Chance of Trisomy 18	Chance of Neural Tube Defect
25	1 in 2,500	1 in 25,000	1 in 1,000 for all ages
30	1 in 840	1 in 8,400	
35	1 in 356	1 in 3,560	
38	1 in 166	1 in 1,066	
40	1 in 94	1 in 940	

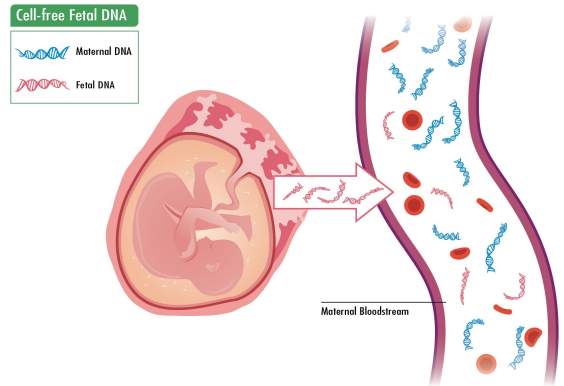
PRENATAL SCREENING

- Tests typically offered include:
  - Quad: blood test for AFP, uE3, hCG, inhibin A (2nd trimester)
  - Serum Integrated Prenatal Screening (SIPS): Quad + PAPP-A (1st + 2nd trimester)
  - Integrated Prenatal Screening (IPS): SIPS + nuchal translucency ultrasound (11-14 weeks for ultrasound)
- If one of these tests comes back positive for Down Syndrome or Trisomy 18, or there are certain risk factors → Non-Invasive Prenatal Screening (NIPT; 10+ weeks)
  - NIPT: collect and examine cell-free fetal DNA from mother's blood



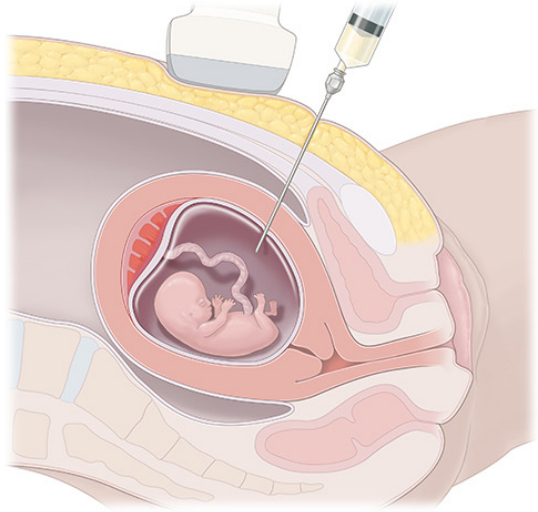


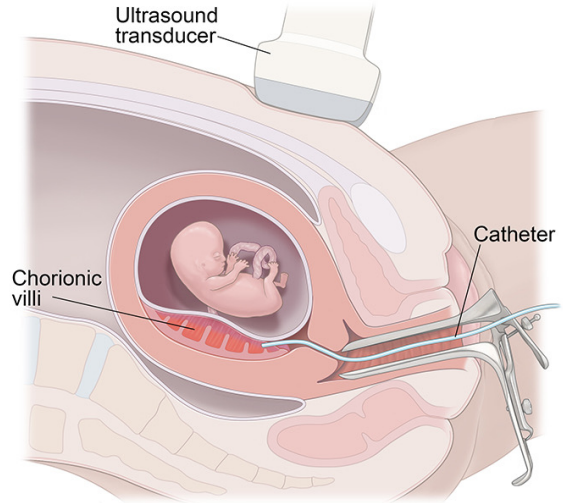




PRENATAL DIAGNOSTIC TESTING

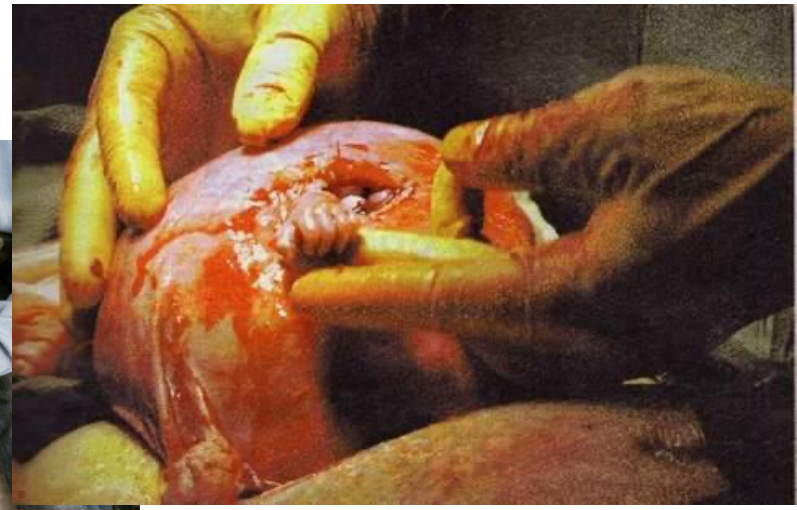
- If Quad, SIPS, or IPS are positive for a NTD → detailed ultrasound to confirm if there is a NTD
- If NIPT is positive for Down Syndrome or Trisomy 18, or there are certain risk factors → amniocentesis (15+ weeks) or chorionic villus sampling (11-13 weeks) to analyze fetal DNA and confirm Down Syndrome or Trisomy 18





WHAT NEXT?

- A medical geneticist or genetic counsellor will explain the options and help decide
- There are a few options:
  - Continue with the pregnancy and prepare for having a child with one of the conditions
  - End the pregnancy
  - Make an adoption plan

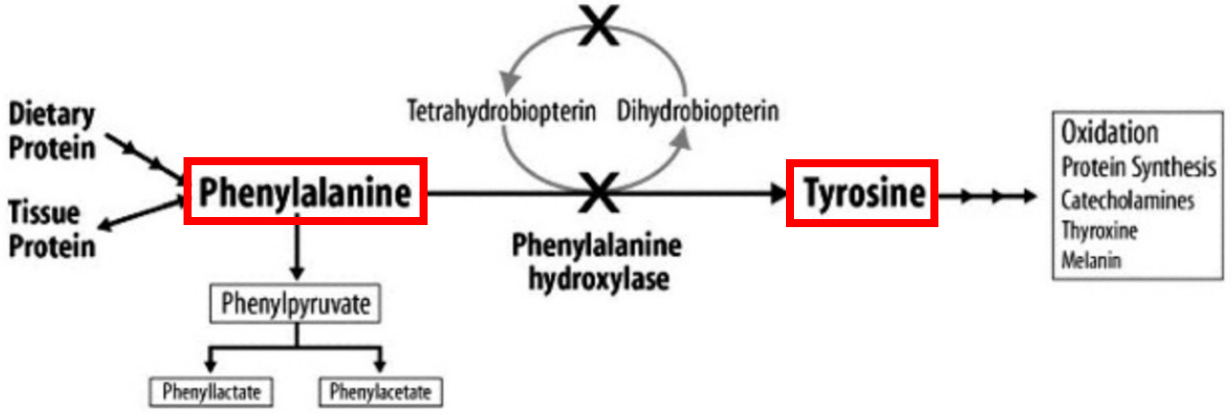


NEWBORN SCREENING

- Blood collected 24 to 48 hours after birth from heel prick
- Multiple drops are put on a blood spot card
- Blood is analyzed to screen for 24 rare but treatable disorders
- There are four main categories of disorders:
  - Metabolic disorders
  - Endocrine disorders
  - Blood disorders
  - Cystic Fibrosis

METABOLIC DISORDERS

- The body is unable to process certain molecules, leading to toxic accumulation of specific molecules and/or deficiency of important molecules
- If untreated can lead to various symptoms and eventually serious issues such as neurodevelopmental disorders or coma and death
- There are 15 disorders screened for
- E.g. Phenylketonuria (PKU): phenylalanine cannot be processed → too much phenylalanine and not enough tyrosine

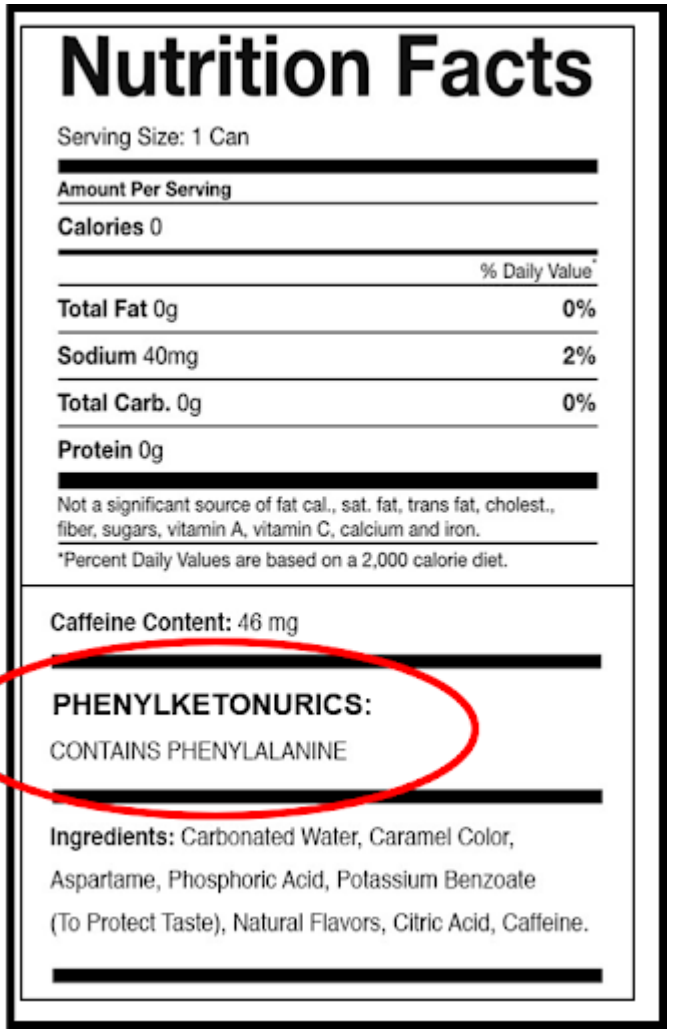


METABOLIC DISORDER TESTING

- Screening analyzes levels or characteristics of various molecules associated with each disorder
  - E.g. phenylalanine levels are measured for PKU
- Any positive results leads to further analysis of specific molecules in the blood and/or urine to confirm disorder
  - E.g. phenylalanine and tyrosine levels are measured
- Genetic analysis of specific genes may also be used to confirm disorder
  - E.g. analysis of PAH gene can also confirm PKU

METABOLIC DISORDER TREATMENT

- Mostly dietary changes in order to avoid build up of toxins
  - E.g. low phenylalanine diet in those with PKU
- Sometimes require supplementation or special formula
- In some cases require medications
- Early treatment can lead to reduced complications or no issues at all



Nutrition Facts

Serving Size: 1 Can

Amount Per Serving

Calories 0

	% Daily Value*
Total Fat 0g	**0%**
Sodium 40mg	**2%**
Total Carb. 0g	**0%**
Protein 0g	

Not a significant source of fat cal., sat. fat, trans fat, cholest., fiber, sugars, vitamin A, vitamin C, calcium and iron.

*Percent Daily Values are based on a 2,000 calorie diet.

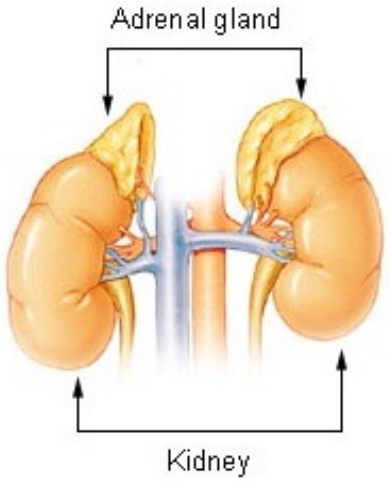
Caffeine Content: 46 mg

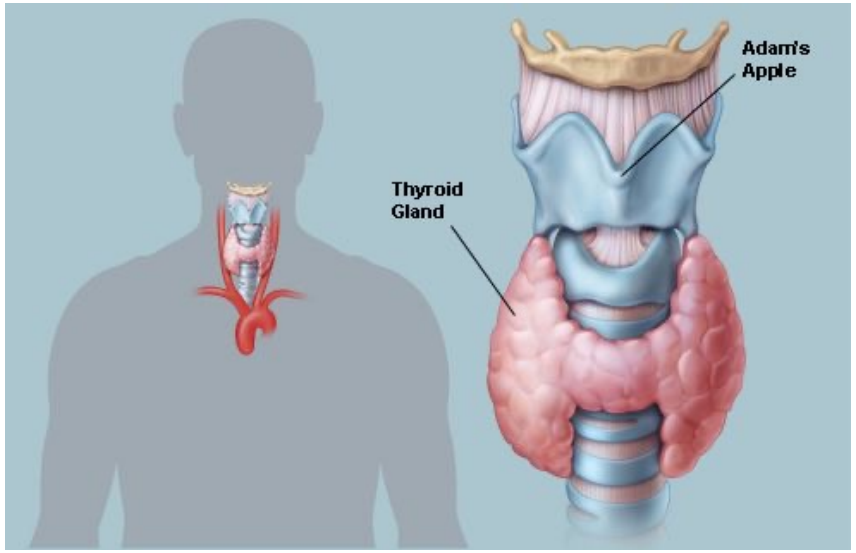
PHENYLKETONURICS:
CONTAINS PHENYLALANINE

Ingredients: Carbonated Water, Caramel Color, Aspartame, Phosphoric Acid, Potassium Benzoate (To Protect Taste), Natural Flavors, Citric Acid, Caffeine.

ENDOCRINE DISORDERS

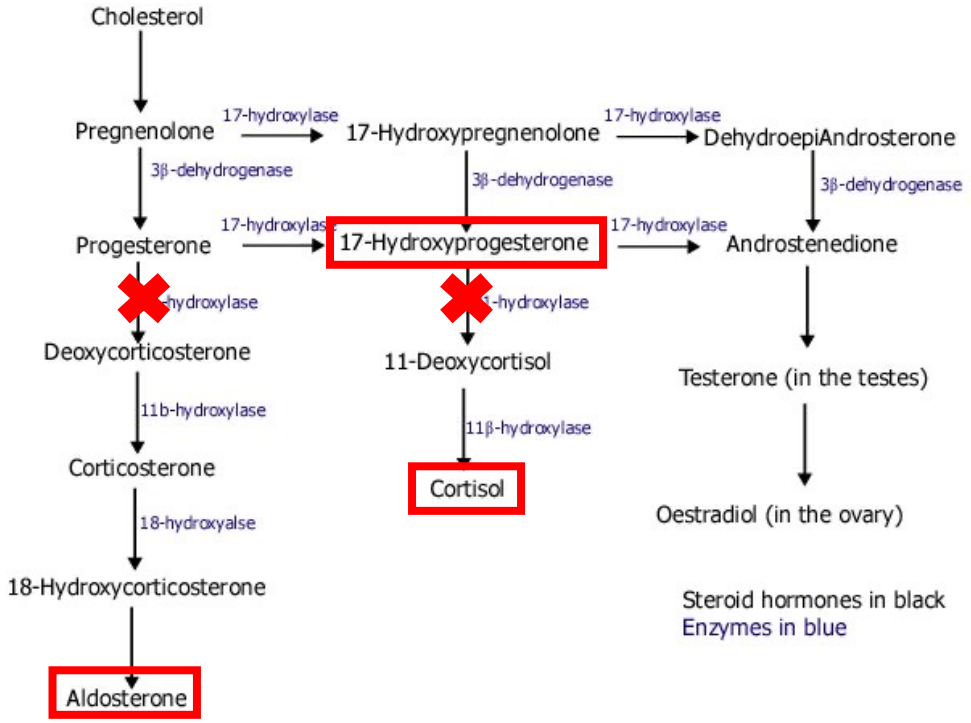
- Two conditions that result in low levels of certain hormones
- Congenital Adrenal Hyperplasia (CAH): not enough cortisol and aldosterone → salt-losing crisis and possibly death
- Congenital Hypothyroidism (CH): not enough thyroid hormone → intellectual disability and failure to thrive

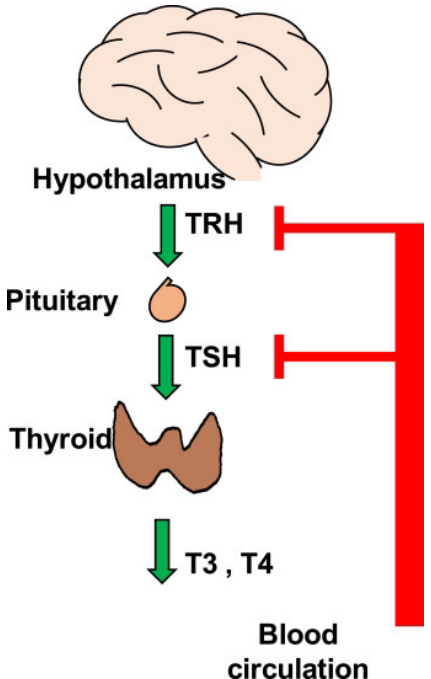




ENDOCRINE DISORDER TESTING

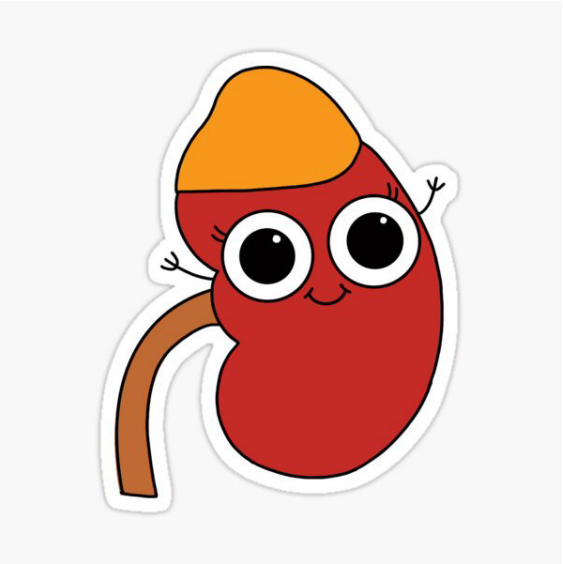
- CAH: measure level of 17-OHP as a screen, confirm by measuring levels of other adrenal hormones and analysis of CYP21A2 gene
- CH: measure thyroid stimulating hormone (TSH) as a screen, confirm with repeat TSH level and level of thyroid hormone

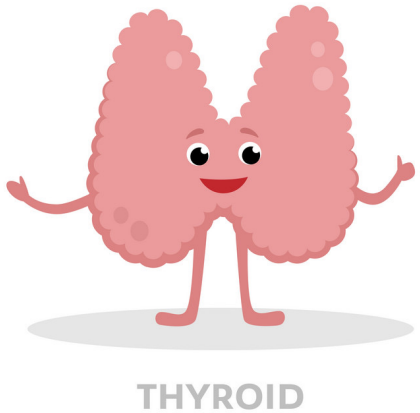




ENDOCRINE DISORDER TREATMENT

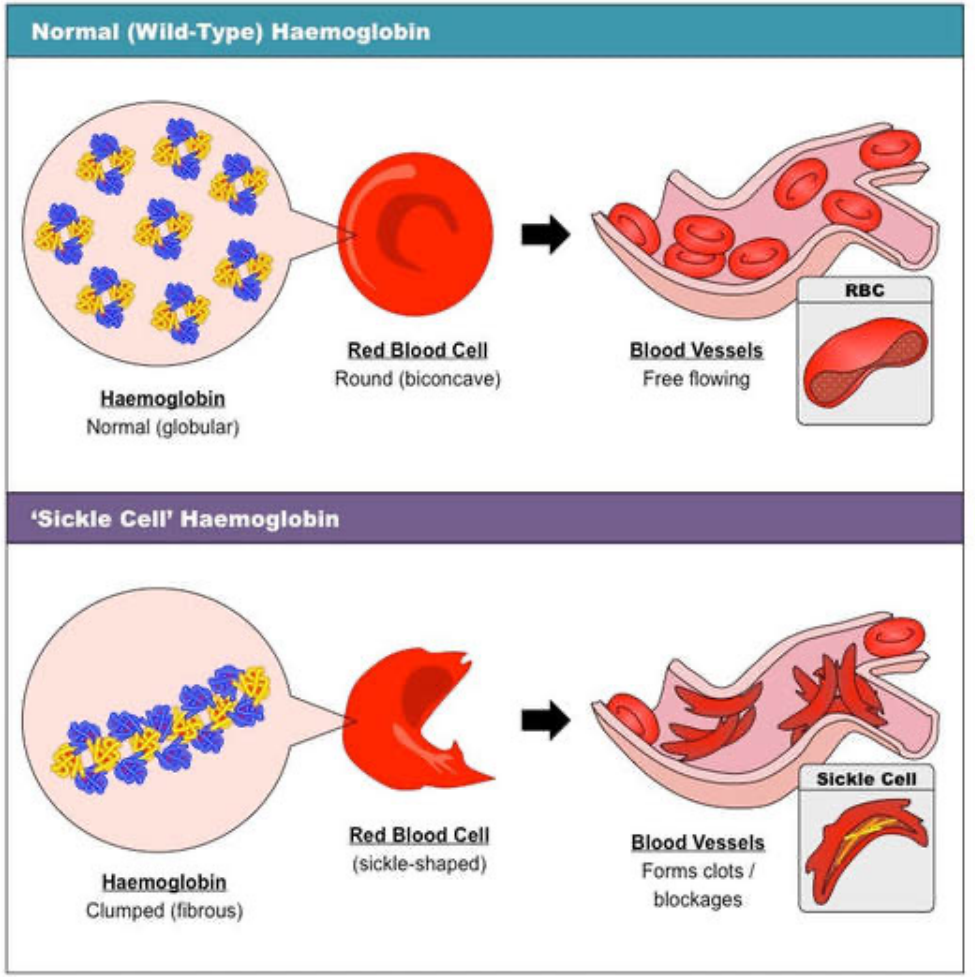
- In both cases treatment involves replacement of deficient hormones
- With early treatment, prognosis is very good and individuals can lead fairly normal lives albeit with regular monitoring of hormone levels





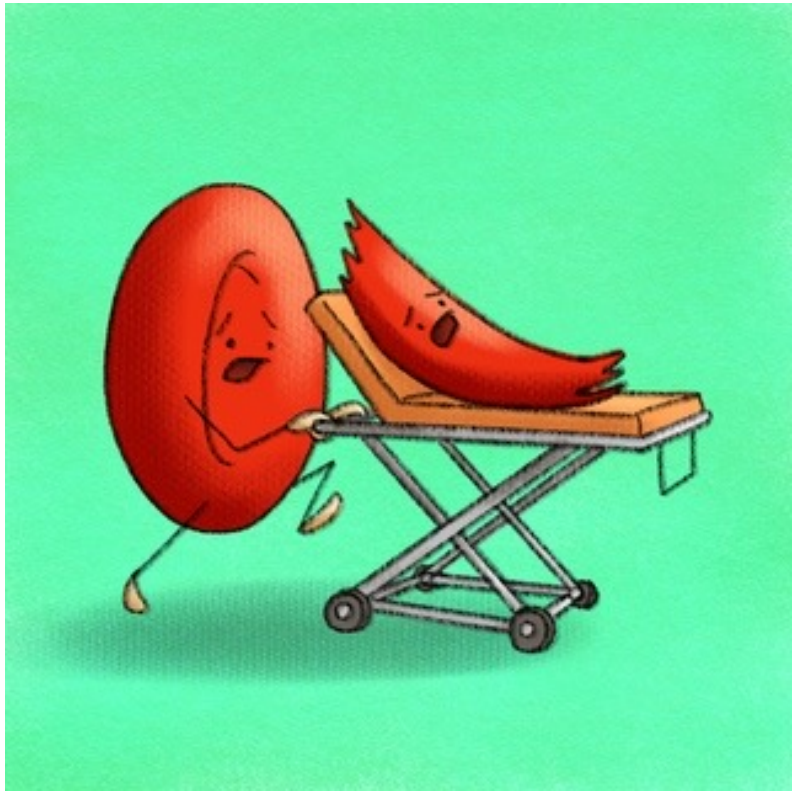
BLOOD DISORDERS

- Hemoglobin, the part of red blood cells that carries oxygen, is changed and/or there is a reduced amount
- Sickle cell disease and other hemoglobin disorders → various symptoms and issues such as anemia, pain crises, tissue ischemia and organ dysfunction, increased susceptibility to infections, etc.



BLOOD DISORDER TESTING

- Various methods used to screen for and confirm sickle cell disease or another hemoglobin disorder by analyzing hemoglobin
- Analysis of the genes that produce hemoglobin may also be used to help confirm a diagnosis
- Testing can also find carriers of hemoglobin disorders (more on this later) who are typically healthy

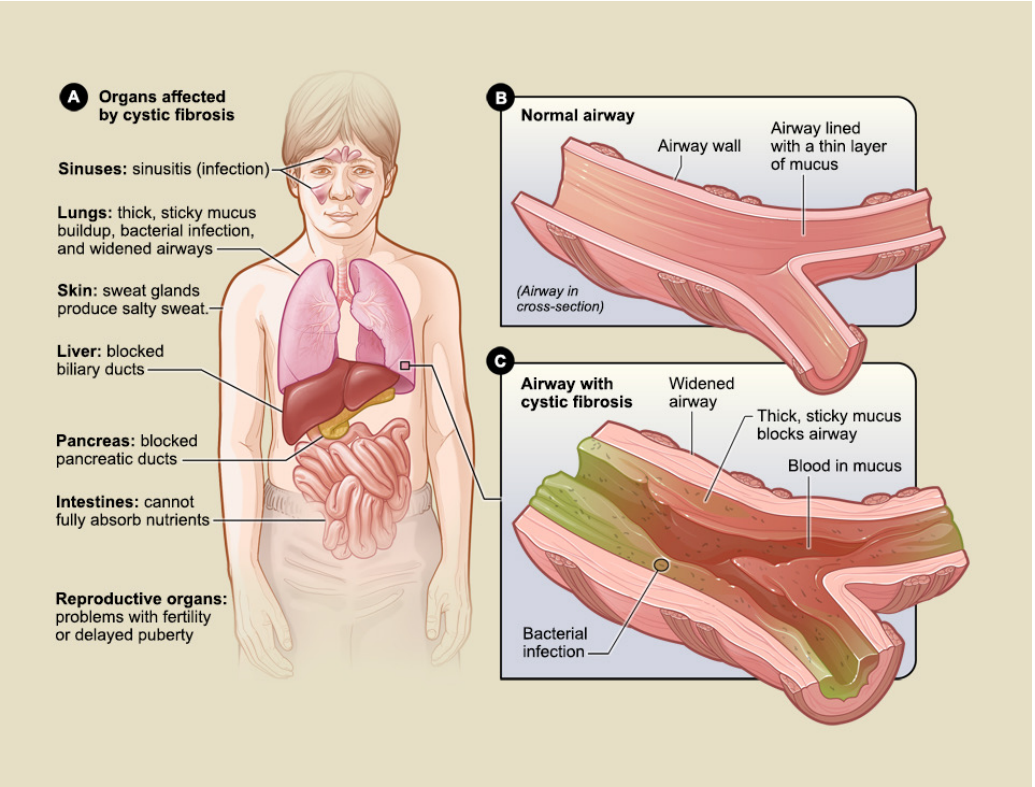


BLOOD DISORDER TREATMENT

- Symptom management through medications and in some cases blood transfusions
- Prophylactic antibiotics and immunizations
- Early management improves prognosis by avoiding complications such as organ dysfunction and infections
- Only way to treat has been a bone marrow transplant, however new treatments are emerging such as gene therapy

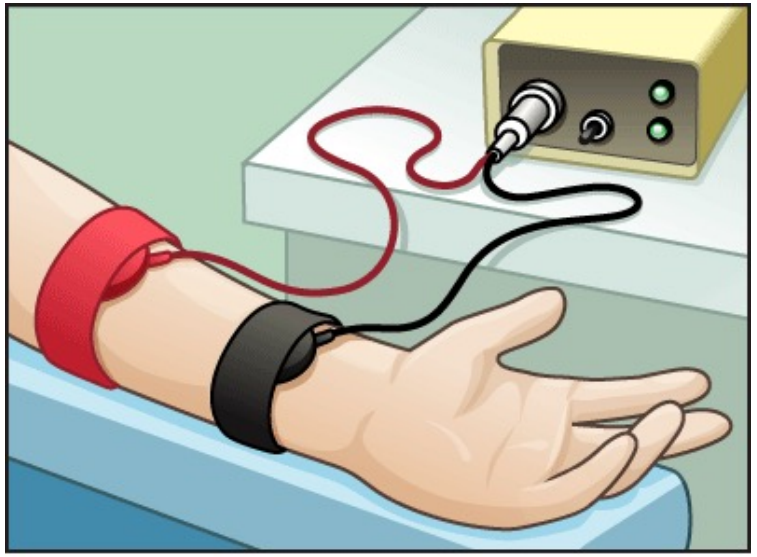
CYSTIC FIBROSIS

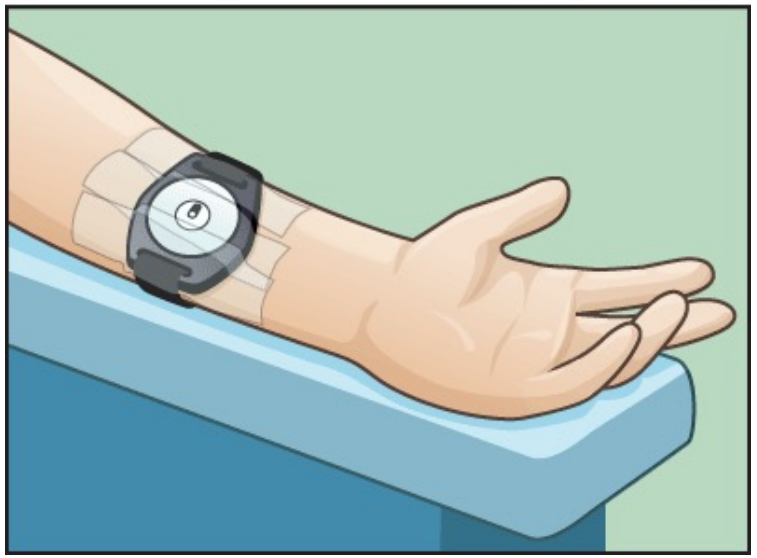
- Life-limiting disease caused by mutation of the CFTR gene
- Causes mucus to build up in the lungs and other organs
- Leads to breathing difficulty, recurrent chest infections, and problems with digesting food



CYSTIC FIBROSIS TESTING

- Screening involves testing the blood for immunoreactive trypsinogen (IRT) and DNA testing of the CFTR gene
- Results of these two tests may lead to the need for another blood spot card at 21 days old to re-test IRT levels
- Diagnostic test is a sweat test, where the level of salt in the sweat is measured





CYSTIC FIBROSIS TREATMENT

- Breathing exercises and physical therapy to help clear mucus in lungs
- Antibiotics to prevent or treat lung infections
- Pancreatic enzyme supplementation to help with digestion
- Newer gene therapy medications!
- Many other medications…
- Early management can greatly benefit infants
- Depending on severity of disease, lung transplant may be required

BREAK TIME FOR 10 MIN!

FILL OUT OUR RESEARCH SURVEY IF YOU HAVEN'T ALREADY!

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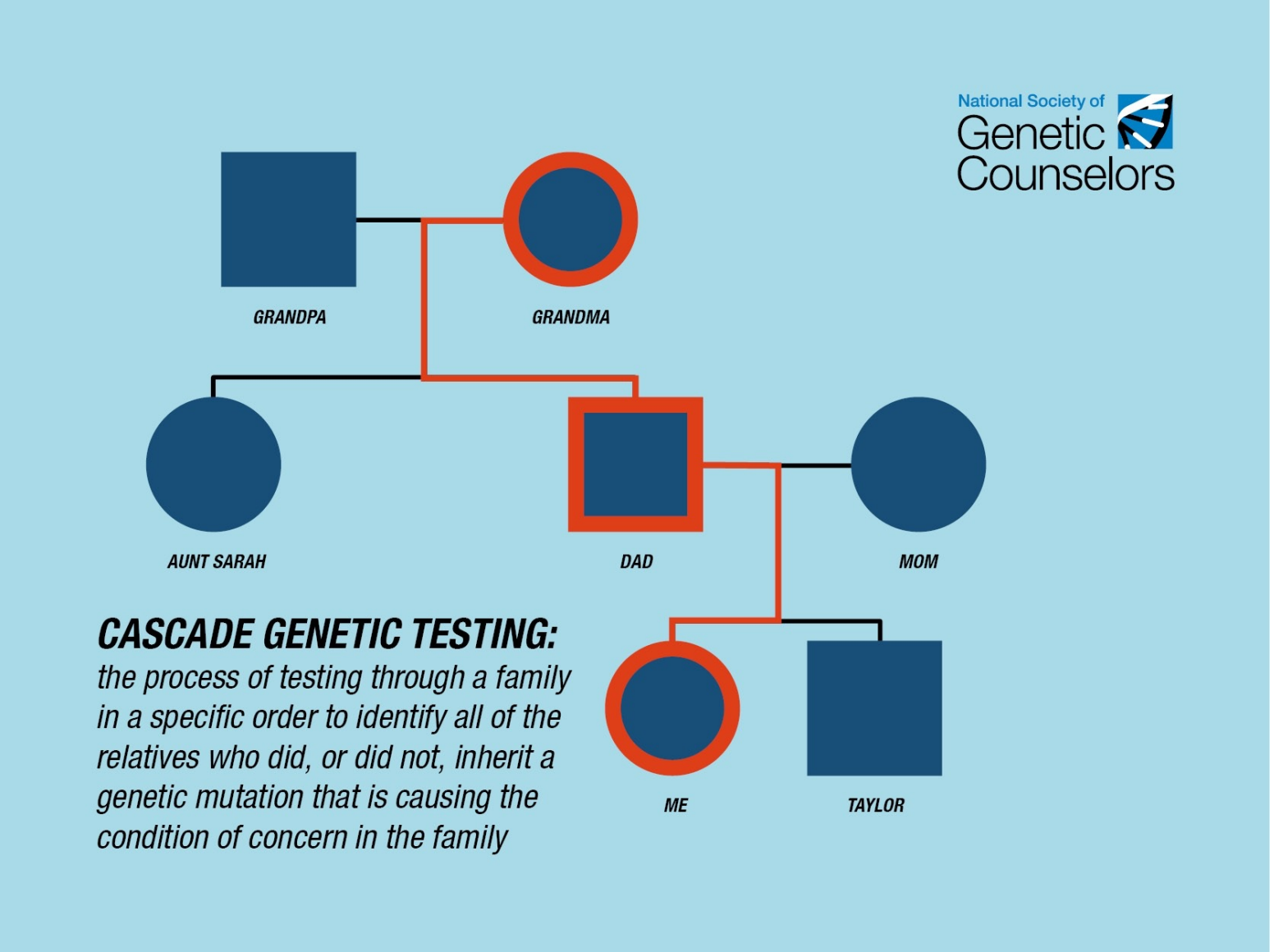
CASCADE TESTING

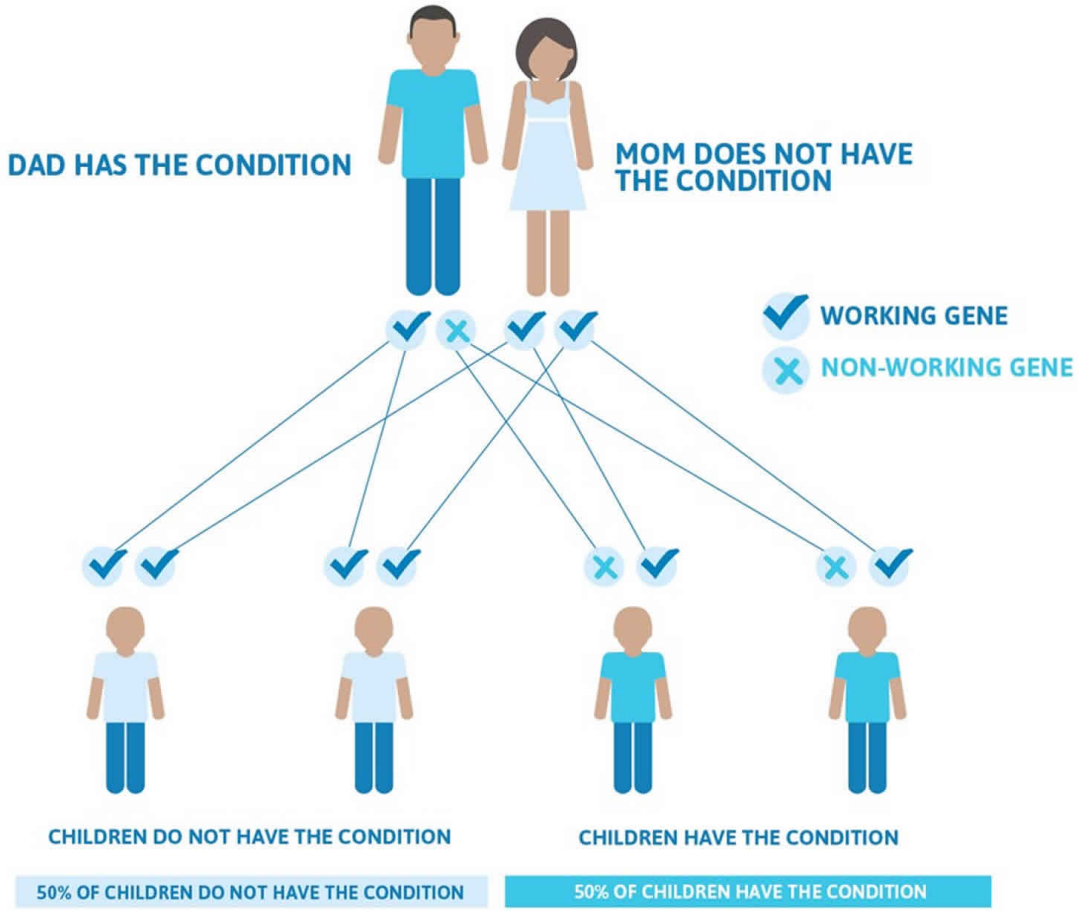
CARRIER TESTING

CASCADE TESTING



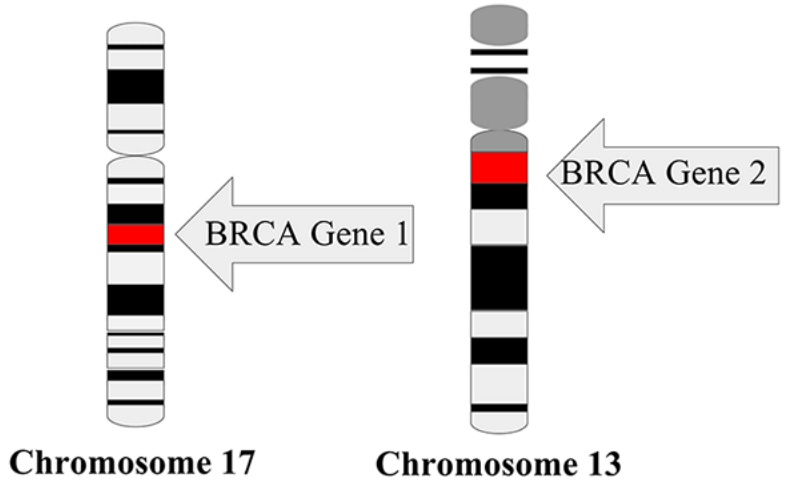
CASCADE TESTING

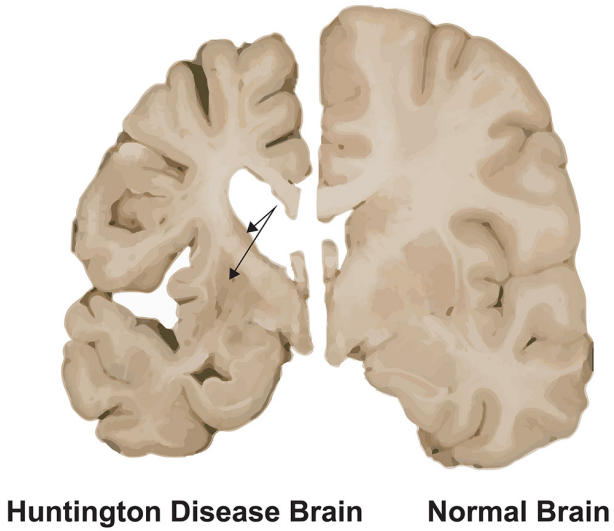
- Typically associated with dominant genetic conditions (only one mutated copy required to cause or increase likelihood of disease)



DOMINANT CONDITION EXAMPLES

- BRCA1/2: mutations that greatly increase likelihood of breast and ovarian cancer, as well as other cancers
- Huntington Disease: neurodegenerative disorder that causes problems with movement and cognition





Courtesy of Dr. Jean Paul Vonsattel
Columbia University

HOW CAN CASCADE TESTING HELP?

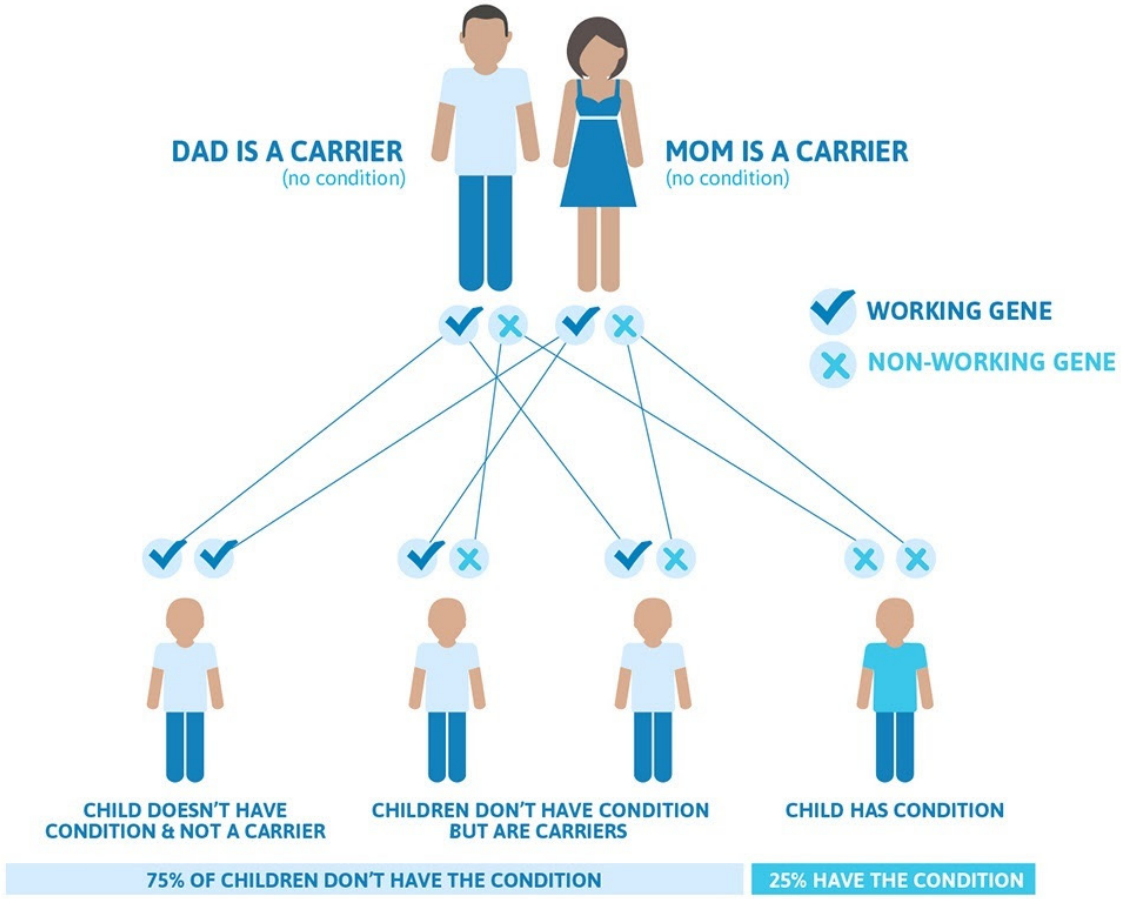
- Depends, but can help individual prepare in many ways
- BRCA1/2:
  - Enhance screening (screen earlier and/or more often, especially for breast and ovarian cancer)
  - Risk-reducing surgery (mastectomy and/or salpingo-oophorectomy)
- Huntington Disease: unfortunately, there is no cure or way to slow progression currently, but medications can be used to reduce symptoms

CARRIER TESTING

- Testing to determine if you carry a genetic mutation based on the presence of a family history of a genetic condition and/or when you belong to a group where a certain genetic condition is more common

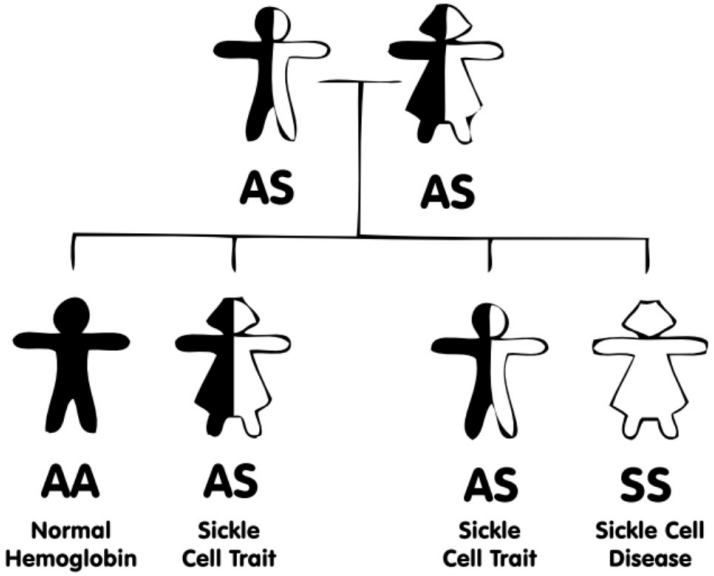
CARRIER TESTING

- Typically associated with recessive genetic conditions (two mutated copies required to cause disease)

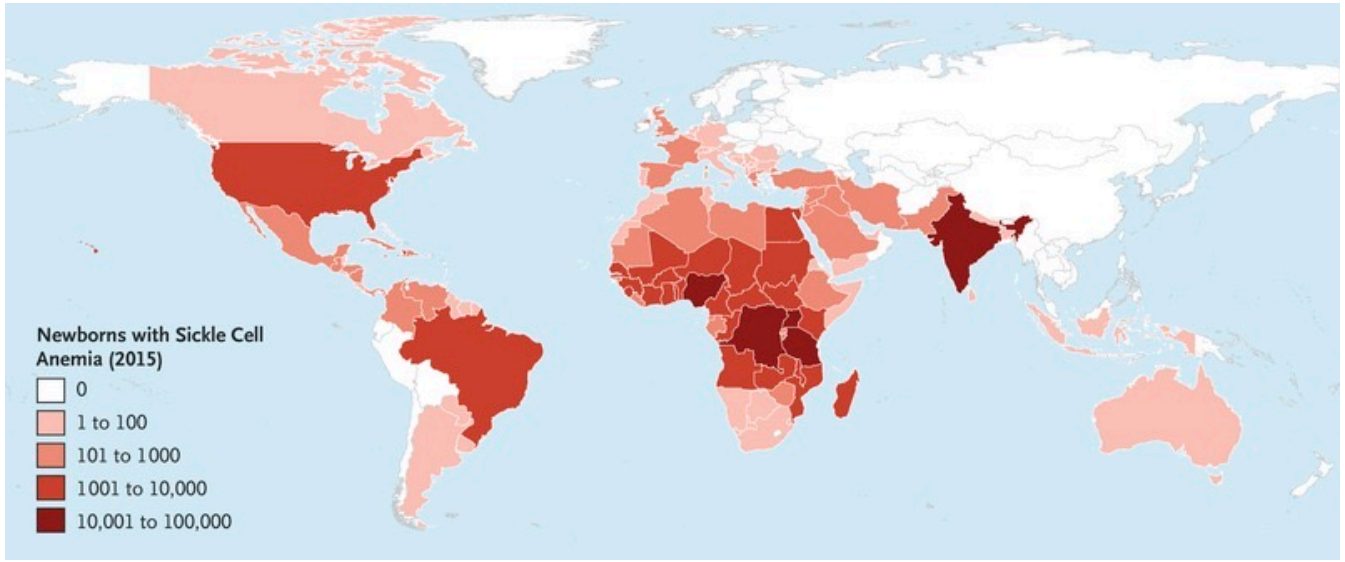


RECESSIVE CONDITION EXAMPLE

- Sickle Cell Disease

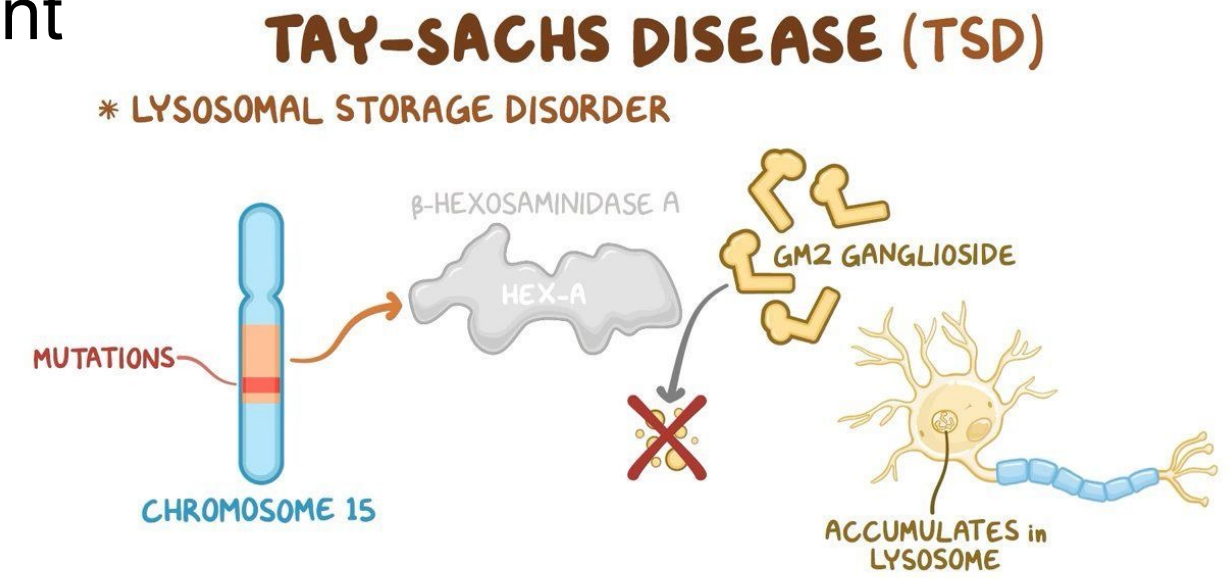


AS - Trait (Carrier)
AA - Usual (no sickle cell)
SS - Unusual (Sickle cell)



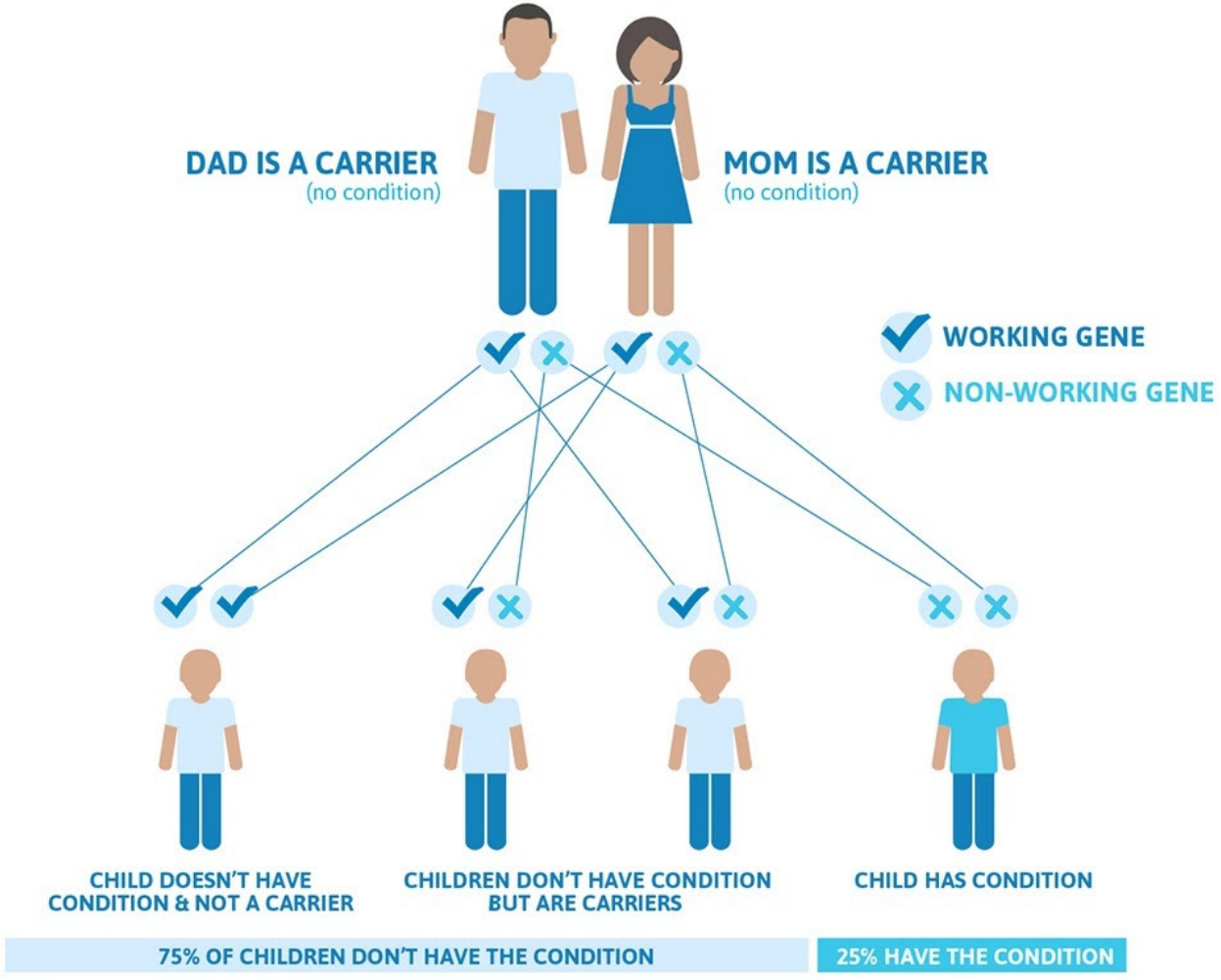
RECESSIVE CONDITION EXAMPLE

- Tay-Sachs Disease
- Problems breaking down fatty acids → fatty build-up in brain
- Seizures, intellectual disability, vision loss, early death
- More common in people of Ashkenazi Jewish, French-Canadian, and Cajun descent



HOW CAN CARRIER TESTING HELP?

- Family planning



Which type of genetic condition requires receiving a mutated version of a gene from both parents to get?

A. Dominant
B. Recessive

Which type of genetic condition requires receiving a mutated version of a gene from both parents to get?

~~A. Dominant~~

B. Recessive

DIAGNOSTIC TESTING

DIAGNOSTIC TESTING

- Testing of an individual in an attempt to confirm a genetic condition
- Many situations where you might expect a genetic condition:
  - Intellectual disability
  - Multiple malformations
  - Recurrent miscarriages
  - Infertility
  - Disease with a known genetic cause
  - Strong family history
  - Disease is more severe or has earlier onset than expected

DIAGNOSTIC TESTING CHALLENGES

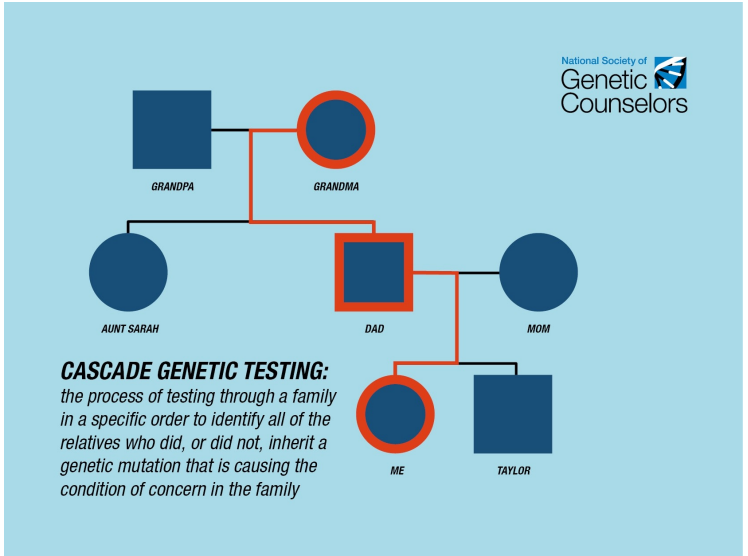
- Not all results are black and white
- Variant of Uncertain Significance (VUS)
  - Does not mean probably benign
  - Does not mean probably disease-causing
  - Means there is not enough information available to determine its role
- Art of medicine and the clinical context are important

DIAGNOSTIC TESTING CHALLENGES

- Variable expressivity, penetrance (e.g. Huntington Disease)
- Multifactorial (e.g. Neural Tube Defects)
- Wait time for results
- Limitations to access

HOW CAN DIAGNOSTIC TESTING HELP?

- Family planning
- Initiate or adjust treatment/management
- Instigate cascade testing
- Access to treatment/funding
- May just end an individual's search for the cause of their disease



DIRECT-TO-CONSUMER TESTING

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HELPFUL RESOURCES

- Your healthcare provider!

- Gene Therapy:
  - Cystic Fibrosis https://www.cff.org/gene-therapy-cystic-fibrosis
  - CRISPR https://medlineplus.gov/genetics/understanding/genomicresearch/genomeediting/
- Health Link BC https://www.healthlinkbc.ca/
- Perinatal Services BC http://www.perinatalservicesbc.ca/
- MedlinePlus https://medlineplus.gov/
- OMIM https://www.omim.org/
- National Human Genome Research Institute https://www.genome.gov/

- MedScape https://www.medscape.com/
- Mayo Clinic, Cleveland Clinic, etc. (.gov, .org)

FUTURE TALKS

- Sunday Dec 5: Diabetes

- Sunday Jan 16: Common medications and how they work
- Sunday Jan 23: Popular diets
- Sunday Jan 30: The biology of stress

- Sunday Feb 6: Stress management
- Sunday Feb 13: How to avoid a drug interaction
- Sunday Feb 20: Supplements

We hope to see you there!

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Thank you!

Any questions?