FINDING THE SWEET SPOT: DIABETES MELLITUS & HYPOGLYCEMIA IN MITOCHONDRIAL DISORDERS

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Mitochondrial Medicine Frontier Program
(thanks to Drs. Amy Goldstein & Marni Falk)

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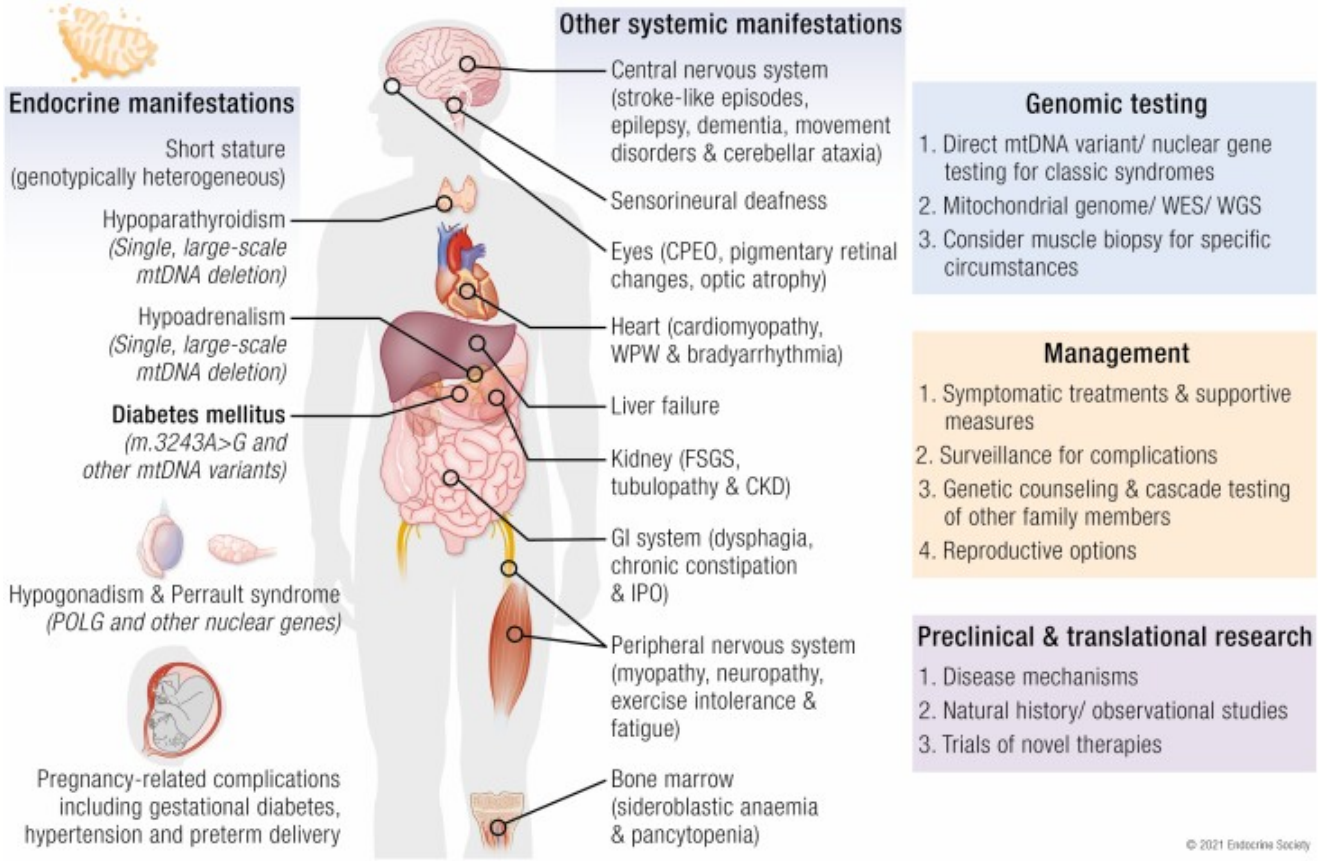
MITOCHONDRIAL DISORDERS IMPACT ENDOCRINE FUNCTION

- Multiple endocrine disorders have been associated with primary mitochondrial diseases.
- Certain sub-types have increased likelihood of endocrine disease.
- *Today's goal:* focus on blood sugar problems and related disorders.



Ng *et al.*, NR Endo (PMID: 34644386)

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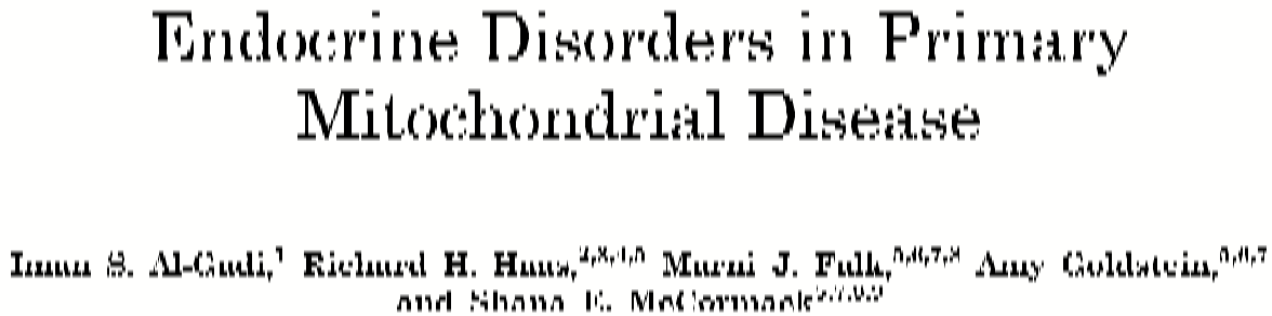
OUTLINE

- Diabetes mellitus & hypoglycemia
- Adrenal insufficiency
- Growth disorders
- *Not included here:* calcium homeostasis & bone health, thyroid disease, excess weight gain, hypogonadism (see resources)

PREVALENT & TREATABLE



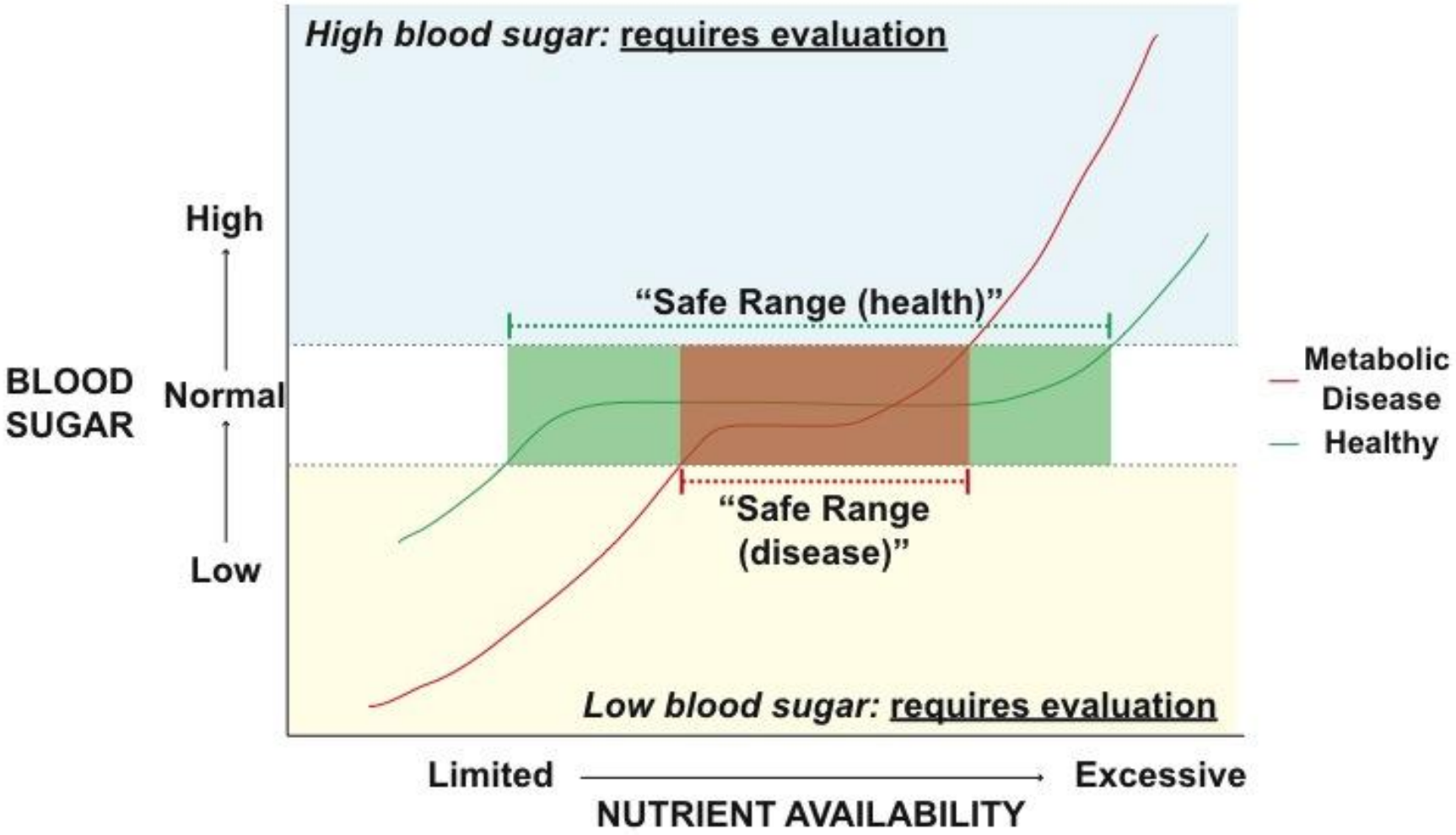
Endocrine Disorders in Primary Mitochondrial Disease

Inma S. Al-Gadi,[1] Richard H. Haas,[2,3,4,5] Marni J. Falk,[5,6,7,8] Amy Goldstein,[5,6,7] and Shana E. McCormack[5,7,8,9]

- North American Mitochondrial Disease Consortium
- N=404 (molecular diagnosis)
- *Common endocrine diagnoses:* atypical growth & sexual maturation (47%), diabetes mellitus (13%), hypothyroidism (6%)
- *Other endocrine diagnoses:* hypoglycemia, adrenal insufficiency, hypoparathyroidism, impaired bone health

Al-Gadi *et al.*, *JES* 2018 (PMID: 29594260)

GLUCOSE HOMEOSTASIS



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MITOCHONDRIAL DIABETES: SYMPTOMS

Emergencies: diabetic ketoacidosis, hyperosmolar hyperglycemia

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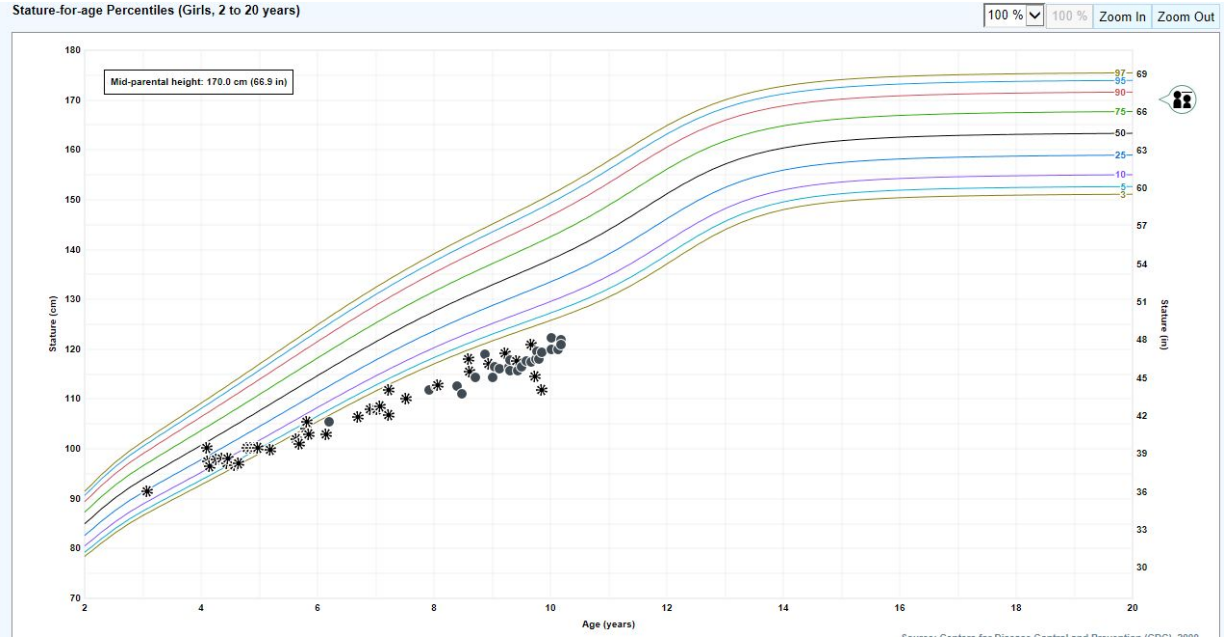
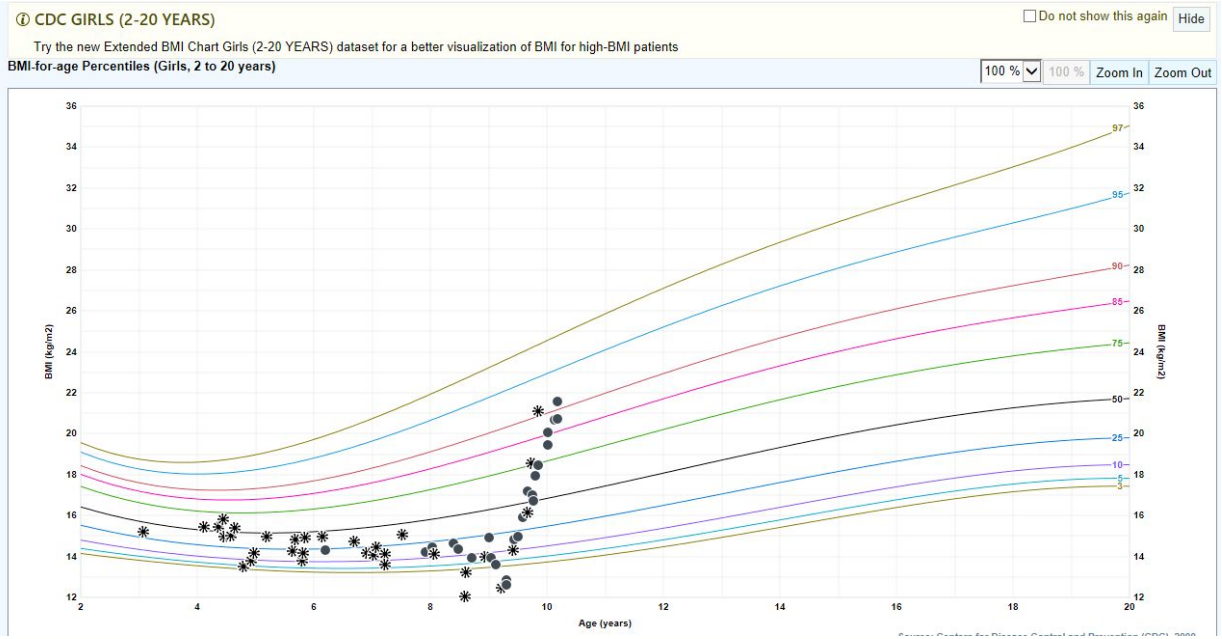
SLMDMS, CASE #1 (FEMALE)

Height



BMI



Endocrinopathies: 4 yo: hypoparathyroidism; 8 yo: short stature; **10 yo: mitochondrial DM**
Also has: ataxia, fine motor impairment, ptosis, SNHL, pancreatic insufficiency, pancreatitis, renal insufficiency, heart block

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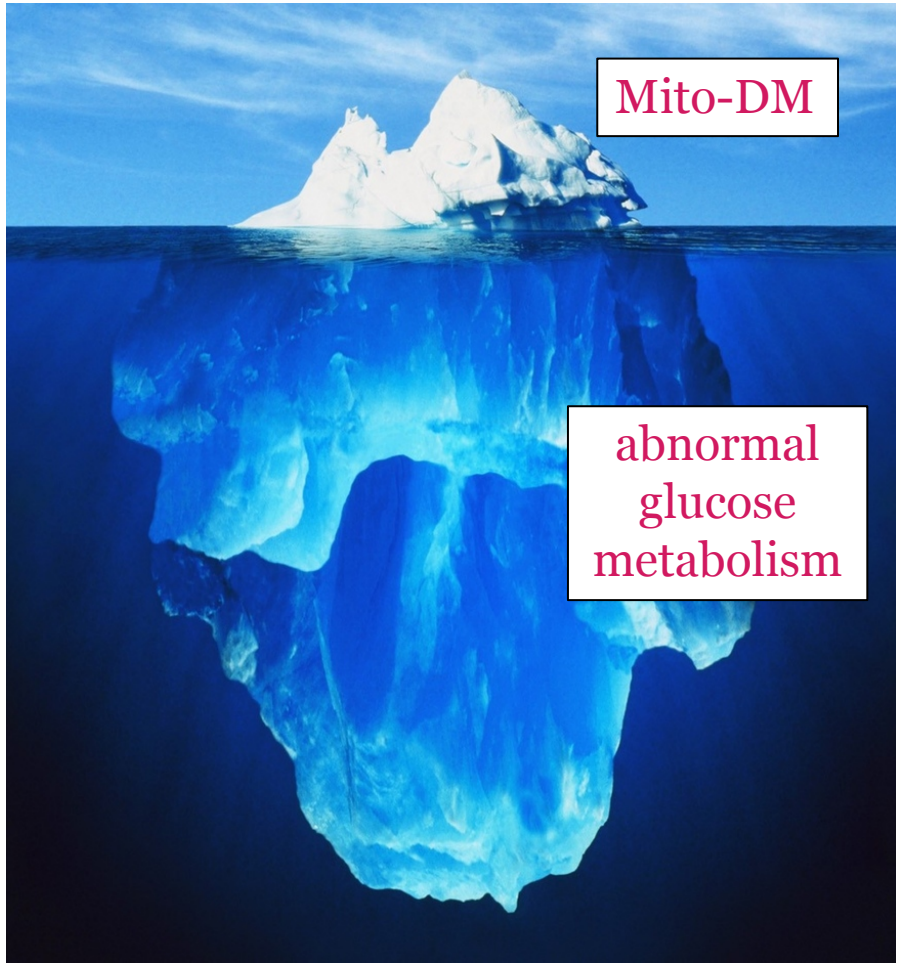
MITOCHONDRIAL DIABETES: BEYOND "TYPE 1" & "TYPE 2"

- Diabetes: 37.3 million US individuals (CDC)
- Pre-diabetes: 96 million US adults (CDC)
- CDC: Type 1 (autoimmune, 5%), Type 2 (heterogeneous, weight-related, 90%), gestational, **"other"**
- **Current framework does not work well!**
- Abnormal glucose metabolism is common in mitochondrial disease.



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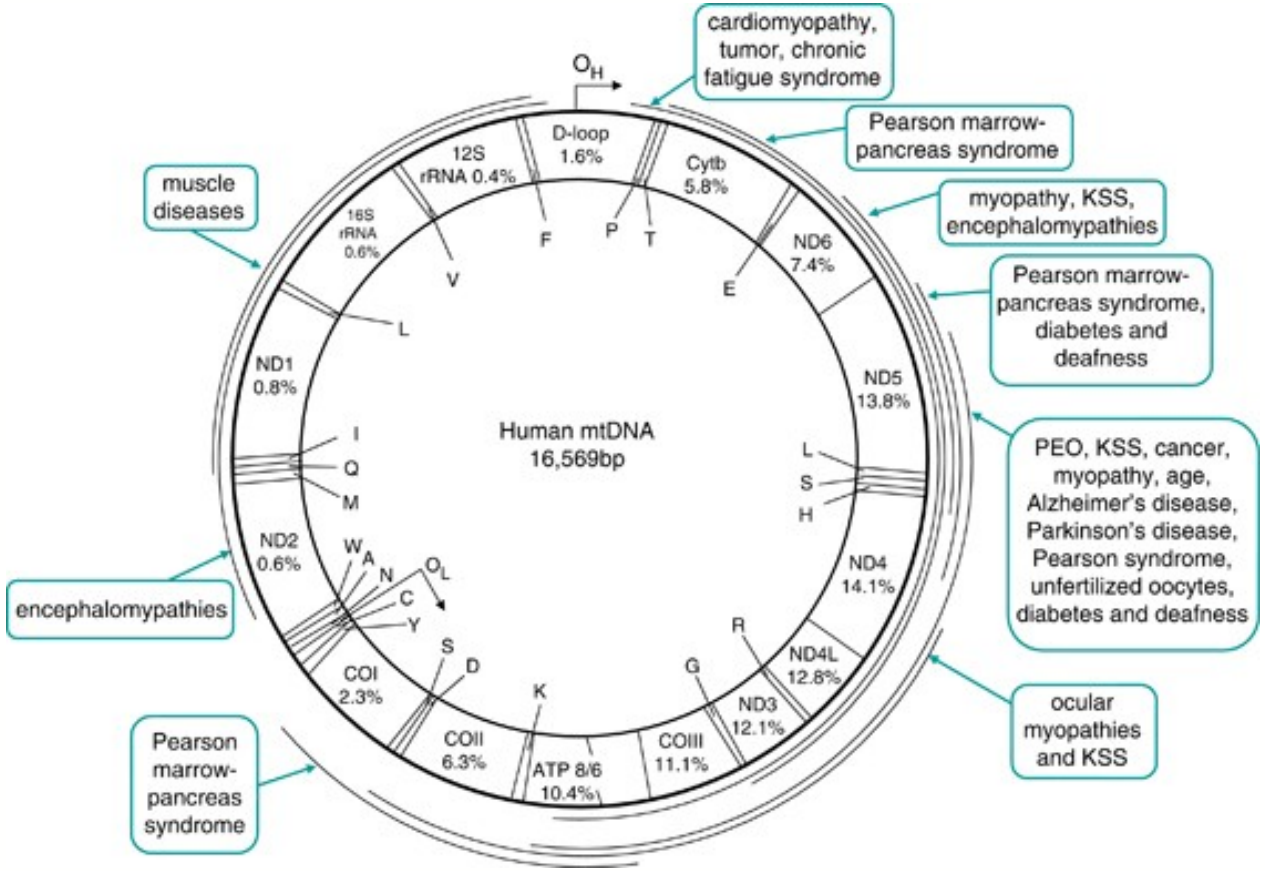
MITOCHONDRIAL DIABETES: CASE

- 6yo, excess urination and thirst
- Random blood sugar: 629 mg/dL (200 mg/dL+, consistent with DM)
- HbA1c 9.6% (reference, <5.7%)
- No ketones, no anti-pancreatic auto-antibodies
- Started insulin
- *Also:* ptosis, decreased tone, high lactate, retinal dystrophy, ECG with heart block
- Diagnosis: mtDNA deletion (KSS)



Amy Goldstein (CHOP MMFP); Chen *et al.*, *J Hum Genet* 2011 (PMID: 21866113)

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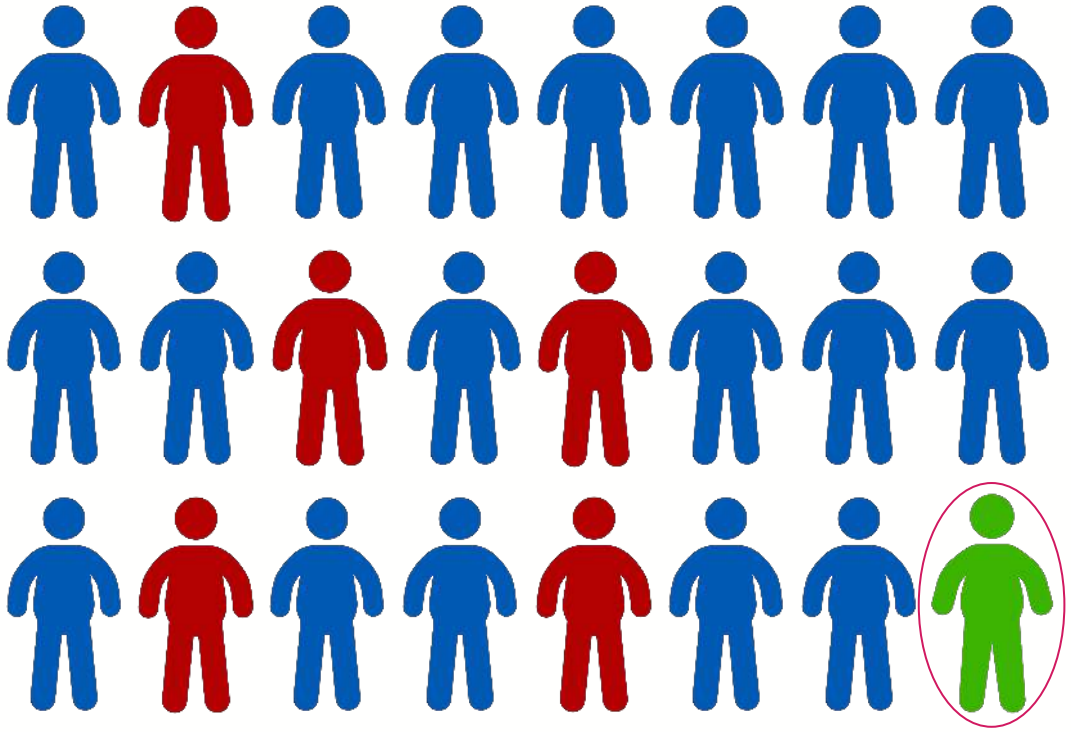
MITOCHONDRIAL DIABETES: BEYOND "TYPE 1" & "TYPE 2"

- By some estimates, up to 5% of "typical" DM is mitochondrial (e.g., A3243G; A8296G; T14577C).
- DM is common in mtDNA deletions (e.g., KSS).
- DM occurs in nuclear mutations as well (e.g., *POLG*, *RRM2B*, *OPA1*).
- In children, DM has more acute onset, with **insulin deficiency** (e.g., DKA).
- In adults, DM has more insidious onset, more **insulin resistance**, still occurs at lower BMI, earlier age (~30's), and with more nephropathy/neuropathy (but less retinopathy) than "typical" T2D.



Karaa & Goldstein, *Pediatric Diabetes* 2015 (PMID: 25330715)

MITOCHONDRIAL DIABETES: TREATMENT

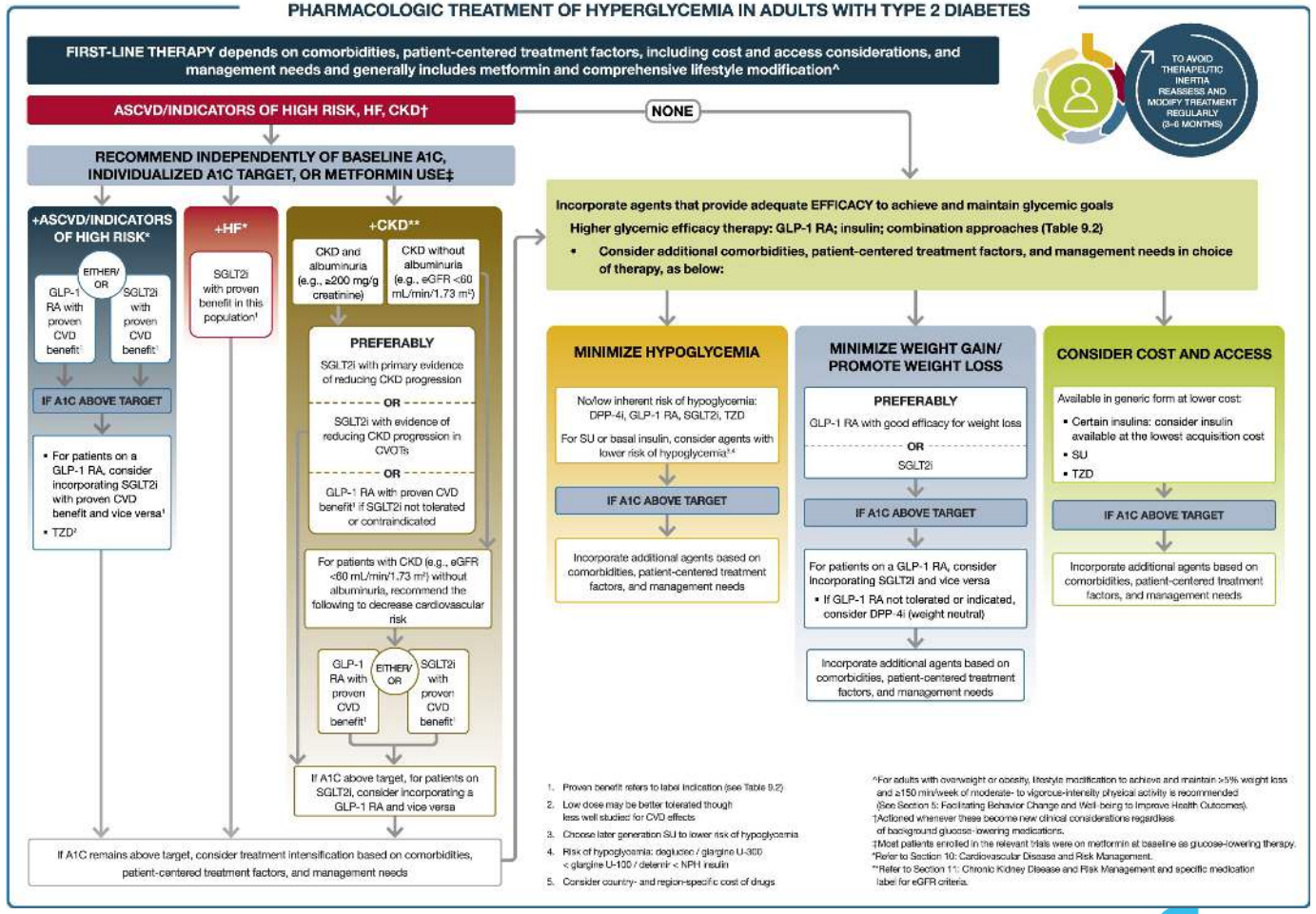
Reasons for insulin:
diabetic ketoacidosis, hyperglycemia causing dehydration or weight loss. Watch electrolytes!

Consider novel agents with appropriate risk/benefit balance and monitoring.

Avoid low's & ketones.

Use technology.

ADA 2023 Guidelines for Intensification



Yeung *et al., J Diabetes Complications* 2021 (PMID: 32331977)

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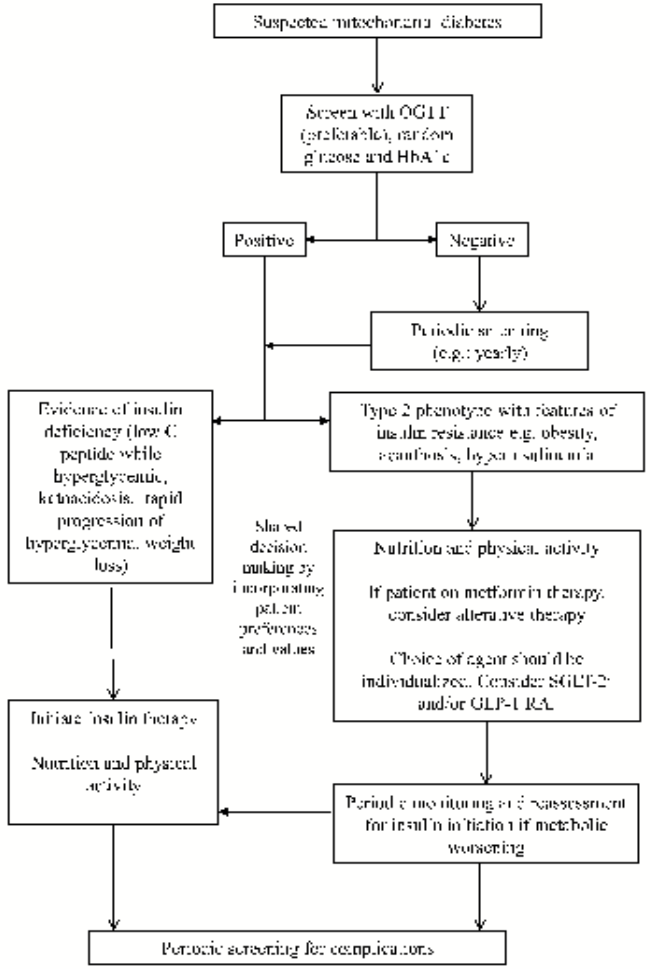
MITOCHONDRIAL DIABETES: TECHNOLOGIES

- Solutions exist for those with vision and mobility impairment.
- Novel forms of glucagon (e.g., premixed, intranasal) are valuable.
- Technologies exist to monitor blood sugar and deliver insulin (and transmit data).
- Automated insulin delivery systems are also available.

DM monitoring

MITOCHONDRIAL DIABETES: SUMMARY

- *Insulin secretion* requires mitochondrial ATP production.
- *Insulin resistance* (e.g., in muscle) can occur.
- **Educate** regarding symptoms.
- **Screen** annually.
- **Manage** based on physiology, including blood ketones.
- Select medications based on **comorbidities** and risk for off-target effects.
- Use **technology** (CGM, pumps) where possible.



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HYPOGLYCEMIA

- Symptoms: sweaty, shaky, pale, can proceed to seizure and unresponsiveness, **reversible with carbohydrate**.
- Look for **treatable causes** (e.g., malnutrition, cortisol deficiency, liver problems).
- Treat, reverse catabolism.
- Ideally, have an **emergency plan** and letter in place ***before*** illness.

Often (but not always):

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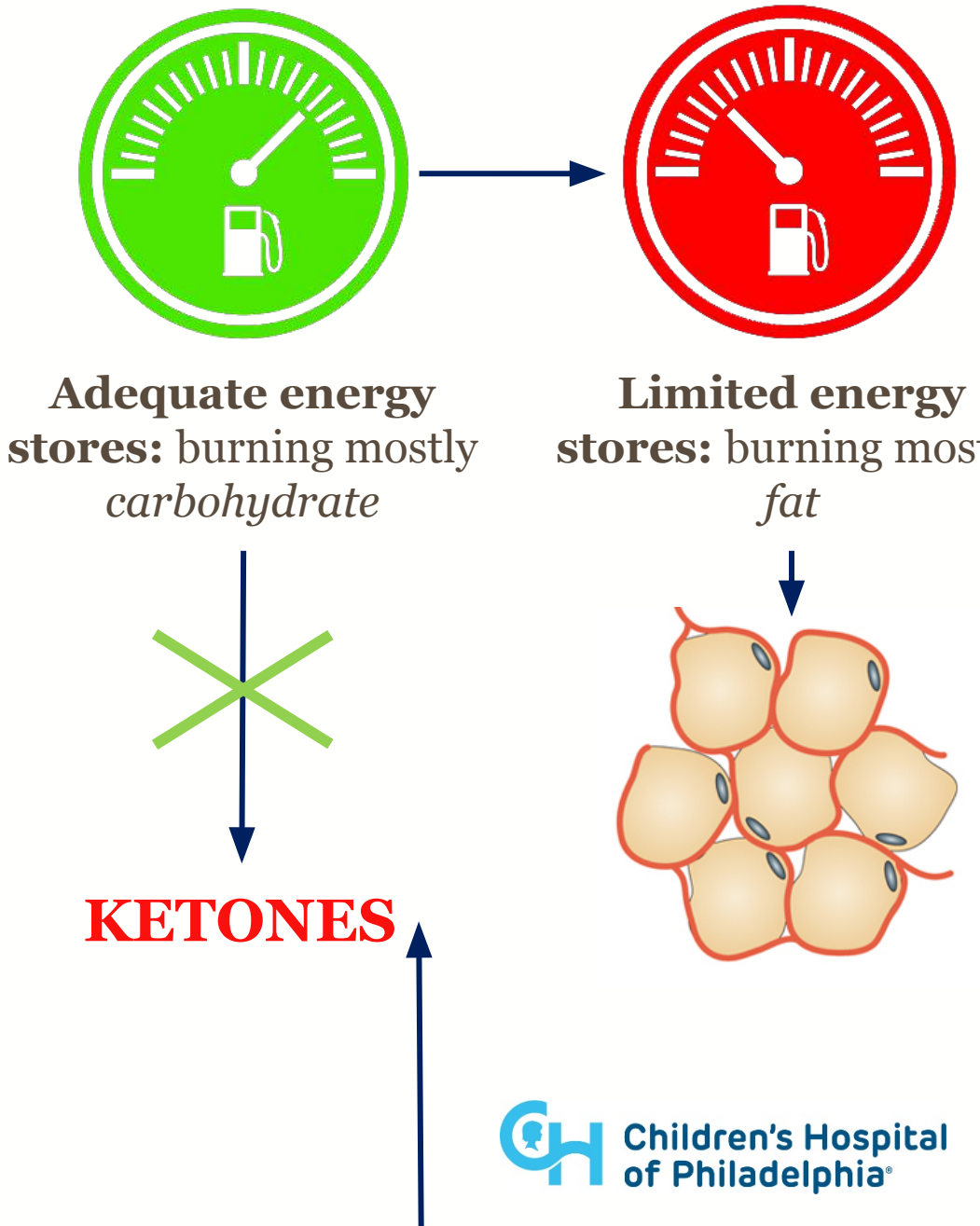
HYPOGLYCEMIA

- When evaluating, we divide into **ketotic** and **non-ketotic hypoglycemia**.
- Often, **"fasting"** hypoglycemia is **ketotic**.
- Often, **"reactive"** hypoglycemia is **non-ketotic**.
- Some individuals with metabolic disorders **cannot produce ketones**.



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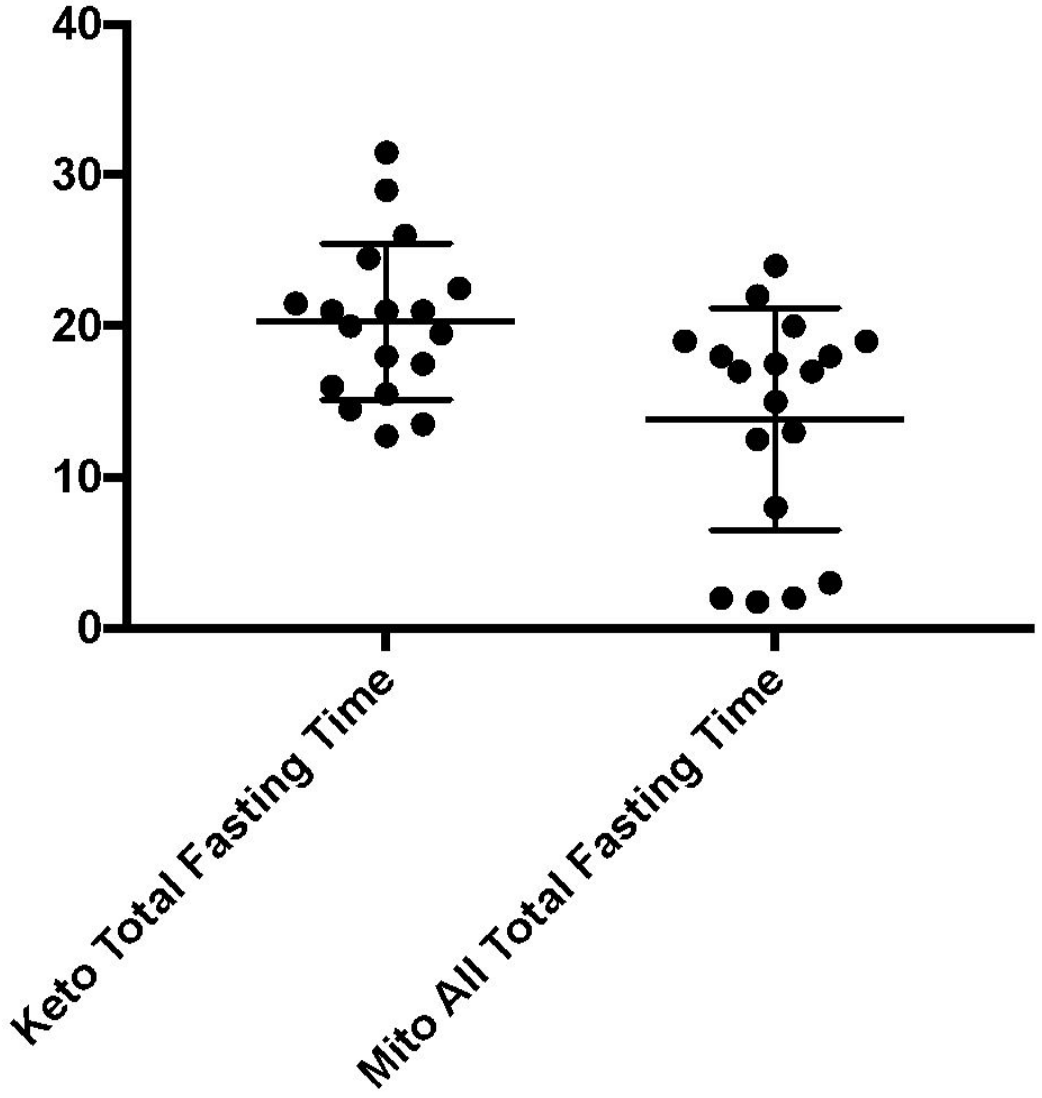
HYPOGLYCEMIA

- Inpatient diagnostic fasting studies (controlled monitoring).
- Compare mitochondrial disease (suspected, confirmed) to idiopathic ketotic hypoglycemia.
- Fasting time was shorter, and ketone production was less.



Patrick Hanley, CHOP/Nemours

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HYPOGLYCEMIA

- ***Initial evaluation:*** check blood sugar when symptomatic, check after longest usual fasting interval.
- Goal blood sugar at least 70 mg/dL (less than 50 mg/dL = emergency).
- **Check ketones** (blood, not urine)!
- Ketones <0.6 mmol/L = trace.
- ***Next steps:*** based on findings.
- ***Management:*** surveillance, rescue, support.
- **Watch out for NPO status!**

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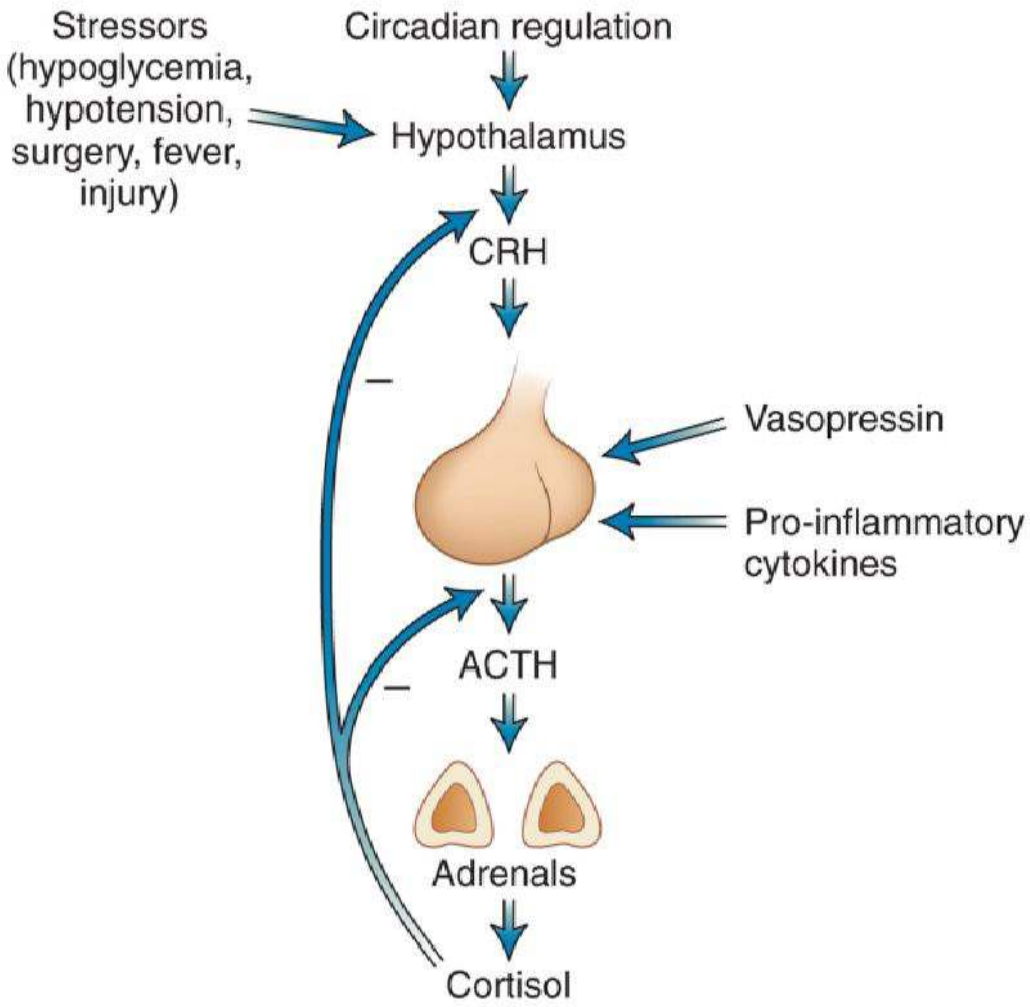
ADRENAL INSUFFICIENCY

- Mitochondria are critical for **steroid synthesis**.
- *Symptoms of adrenal insufficiency:* low blood sugar, low blood pressure, low sodium levels, especially with **critical illness**.



Williams, 12th edition

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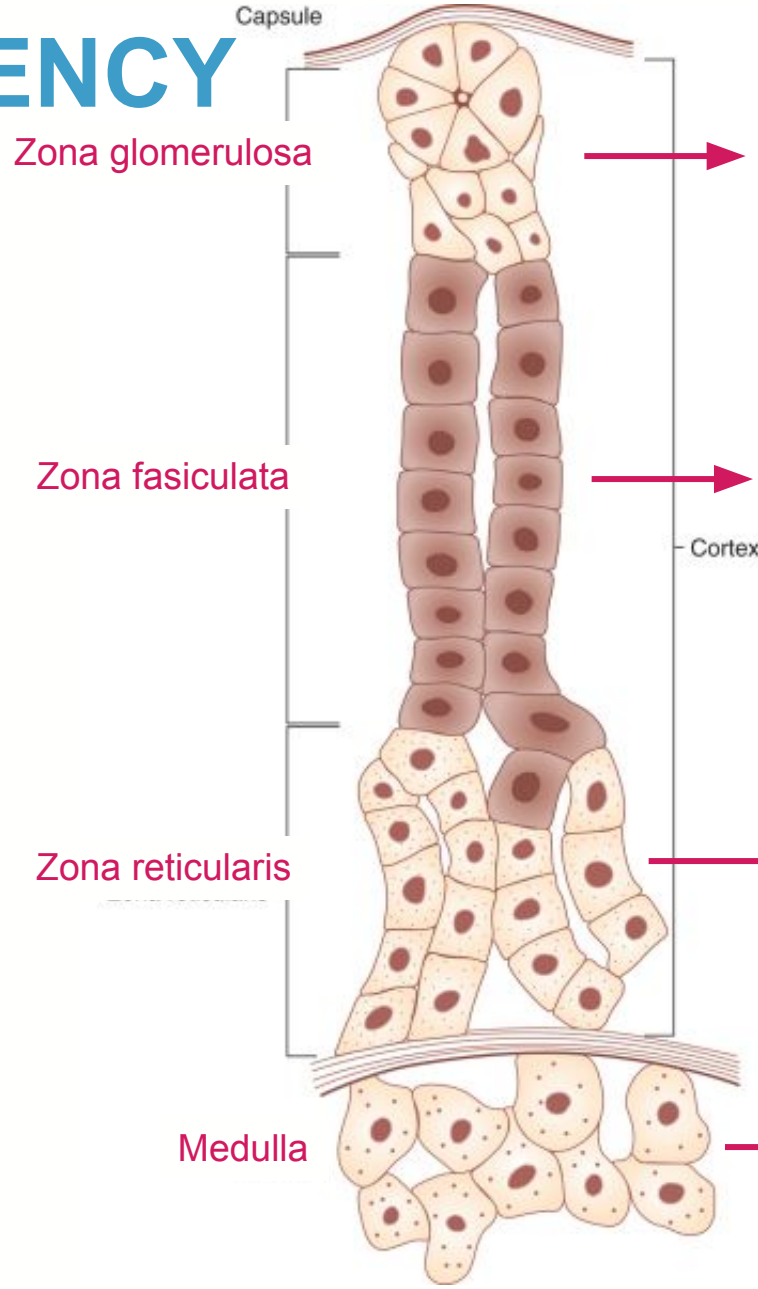
ADRENAL INSUFFICIENCY

- **Screening:** 8a ACTH, cortisol (PRA/aldosterone, DHEAS)
- **Provocative testing**
- **Decisions around replacement:** glucocorticoid/mineralocorticoid, formulation, daily, stress-dose
- **Adverse effects (iatrogenic Cushing's)**



Mineralocorticoids

Rx: fludrocortisone

Glucocorticoids

Rx: hydrocortisone, prednisone

Androgens

Catecholamines

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ADRENAL INSUFFICIENCY: WHO NEEDS TESTING?

- History of having received steroid medications (e.g., prednisone).
- Individuals with suggestive symptoms warrant testing.
- Empiric "stress steroids" are sometimes given in ICU settings.

Table 1. Descriptive statistics of clinical characteristics in pediatric intensive care unit (PICU) patients with and without mitochondrial disease.

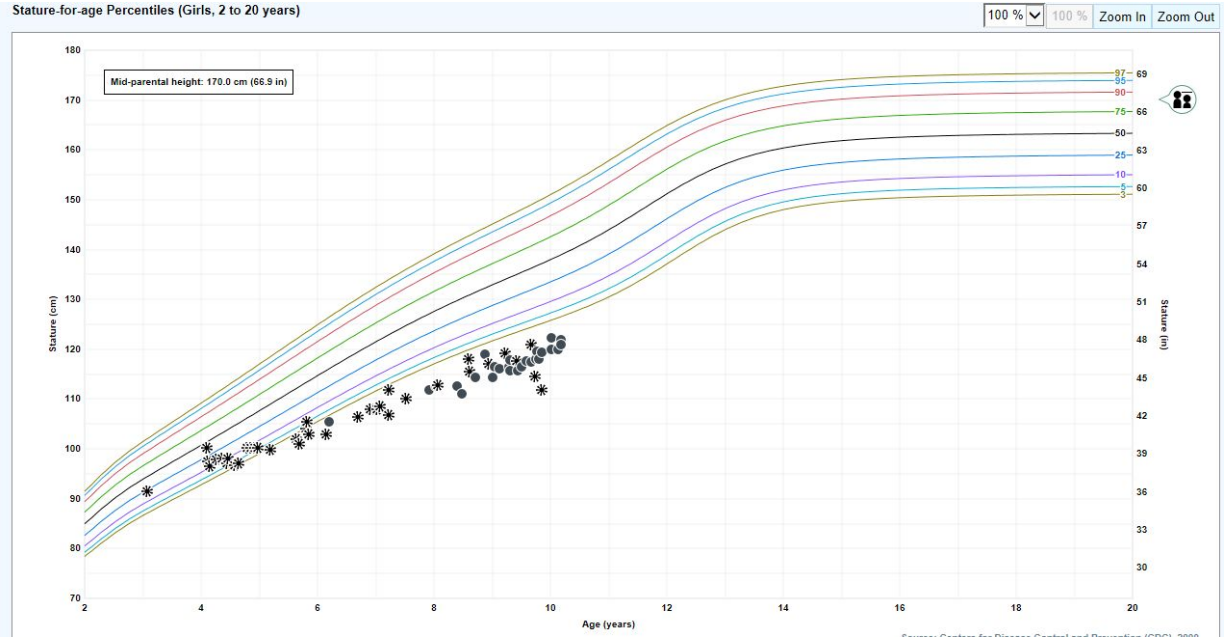
Factor	Mitochondrial disease	Other diagnoses
Age in years, median (IQR)	7.6 (9.0)	4.6 (11.6)
Length of stay in days, median (IQR)	2.9 (5.6)	1.7 (2.9)
Mortality, % deceased	5.2%	2.4%
PRISM score median (IQR)	3 (6)	2 (5)
PIM2 score (IQR)	−3.38 (1.88)	−4.74 (2.02)
Hours on ventilator, median (IQR)	71.5 (187.7)	14.0 (49.5)

IQR interquartile range.

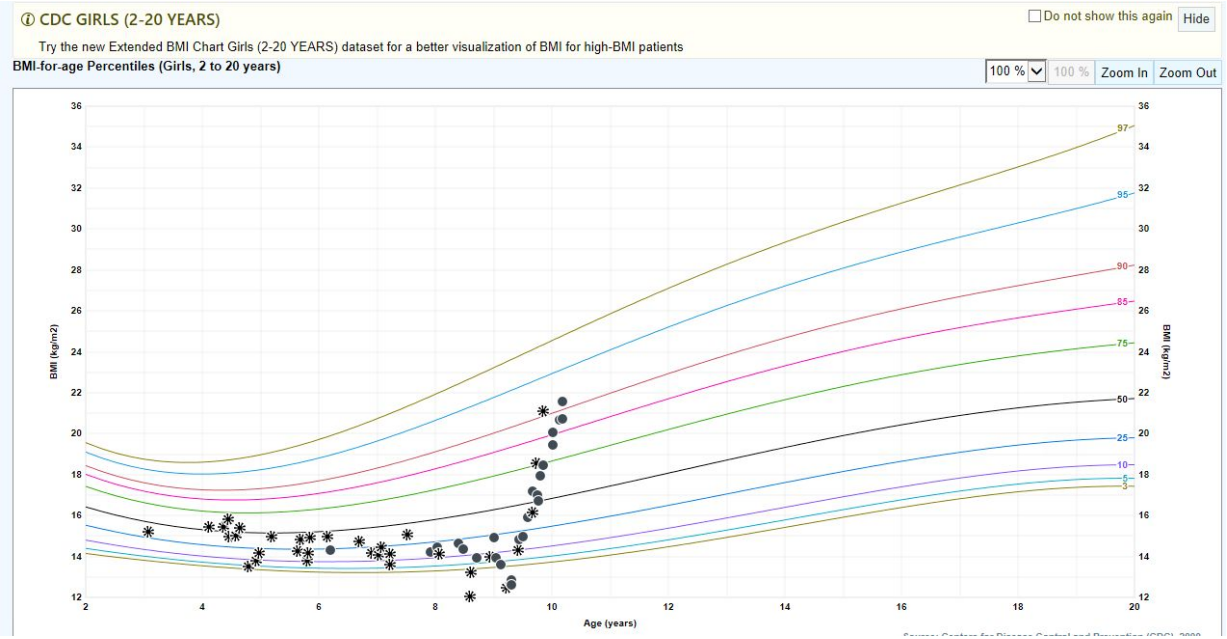
Ehinger *et al.*, *Ped Res* 2021 (PMID: 33627817)

SLMDMS, CASE #1 (FEMALE)

Height



BMI



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Also has: ataxia, fine motor impairment, ptosis, SNHL, pancreatic insufficiency, pancreatitis, renal insufficiency, heart block

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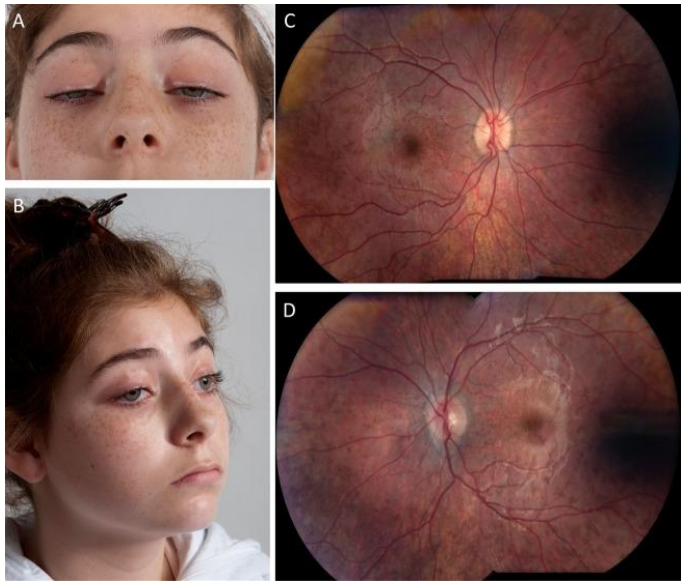
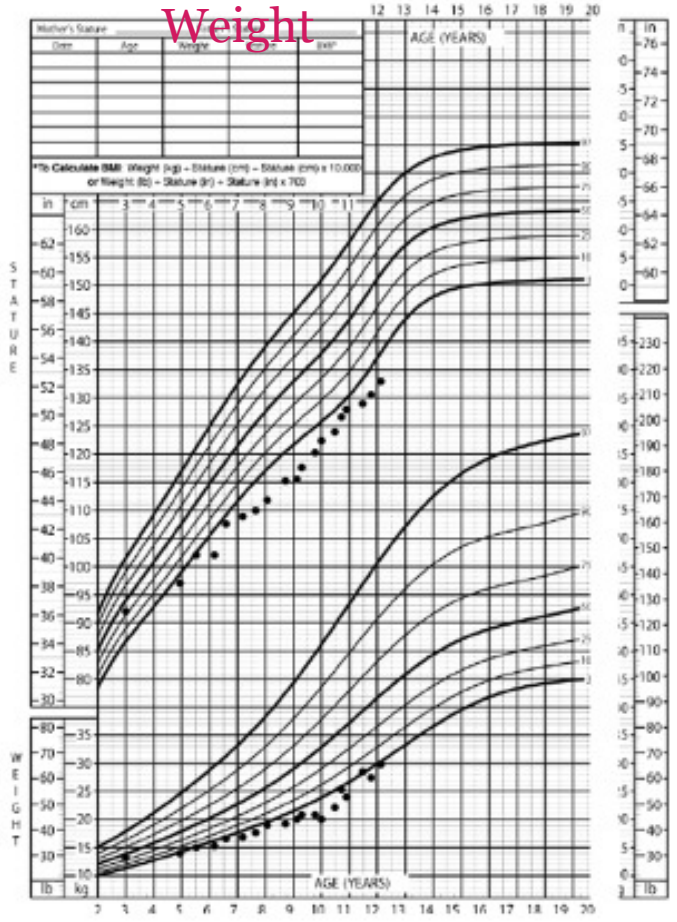
GROWTH REQUIRES ENERGY

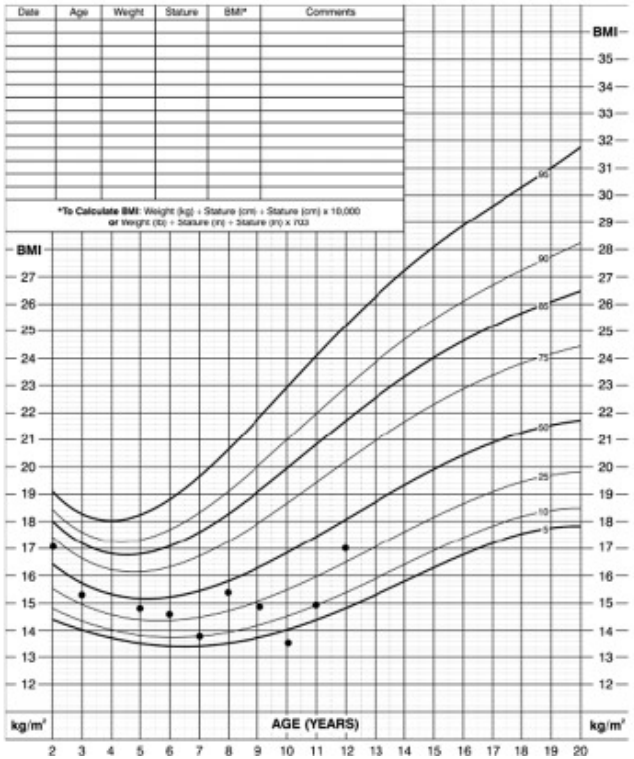
- Impaired growth can be the presentation of mitochondrial disease.
- *Example case:* 11yo, post-natal growth failure (also had fatigue, hypothyroidism, and eye findings).



Height & Weight



BMI



Holloman *et al.*, *BMJ Case Rep* 2013 (PMID: 23420719)

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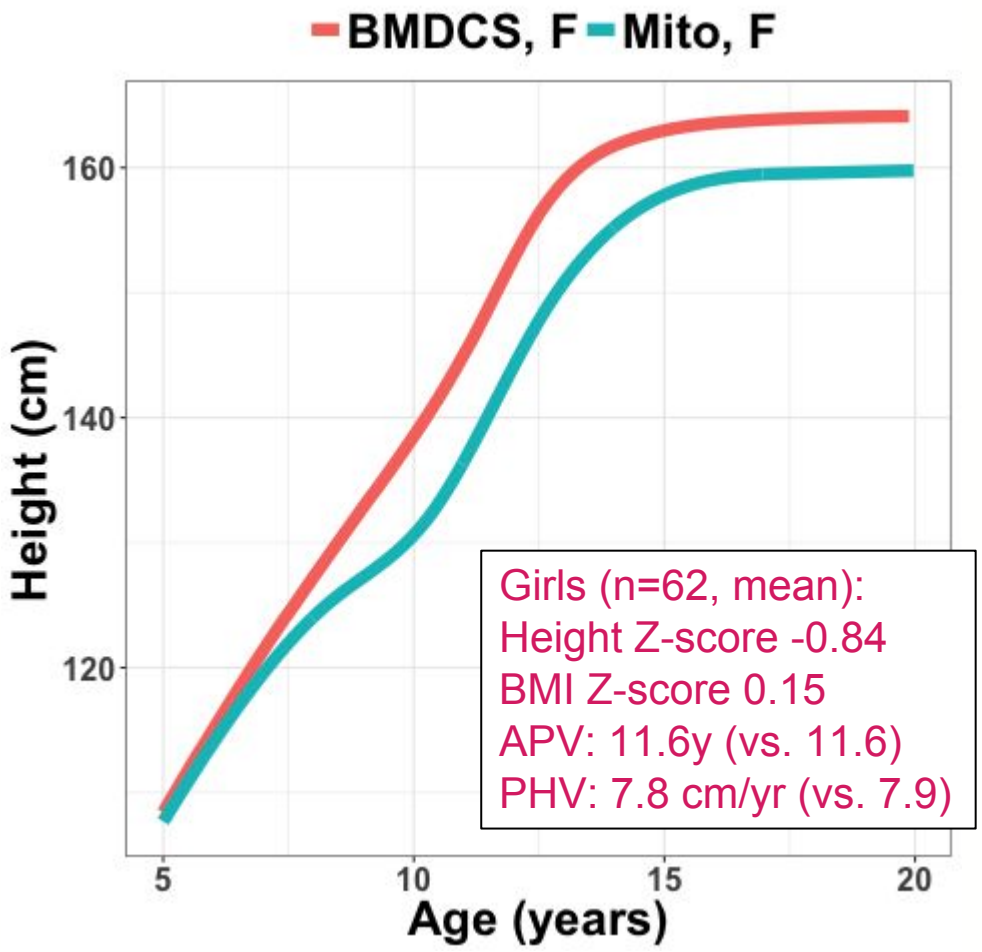
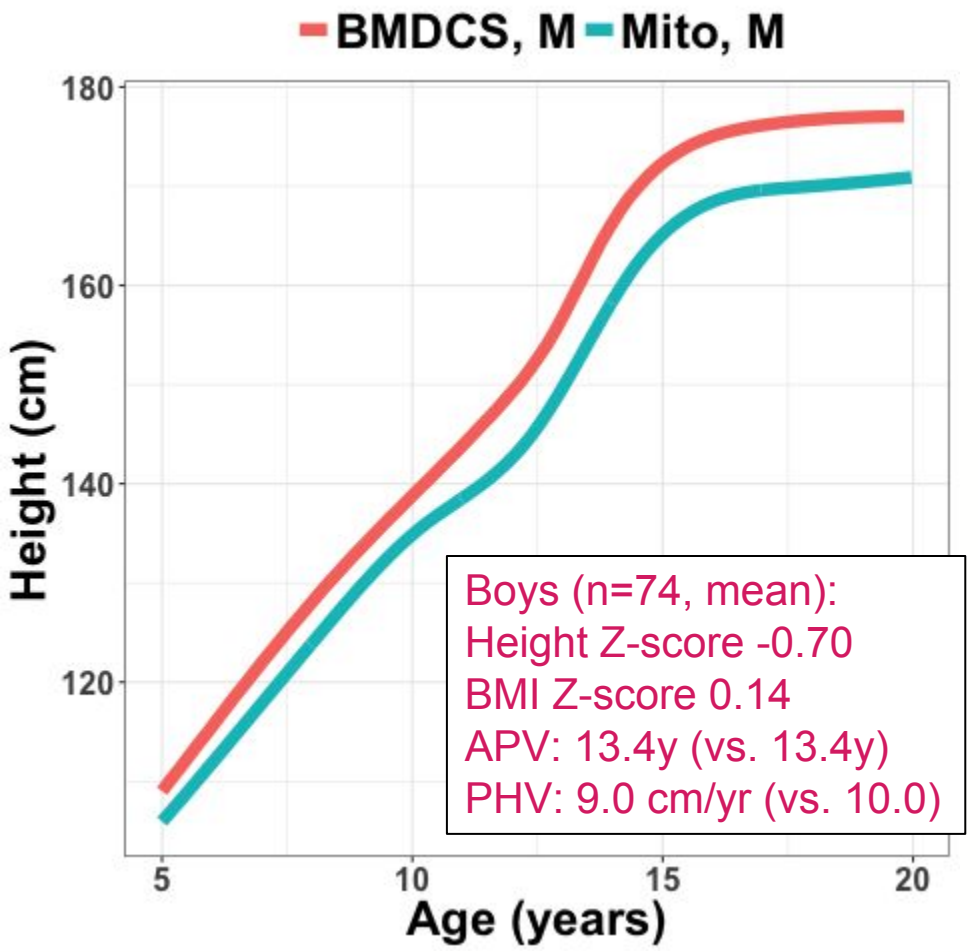
GROWTH TRAJECTORIES



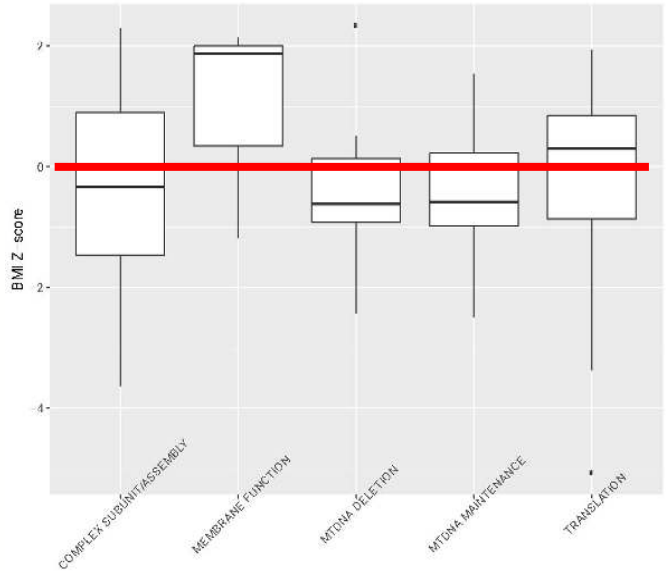


Short stature becomes more pronounced at puberty.

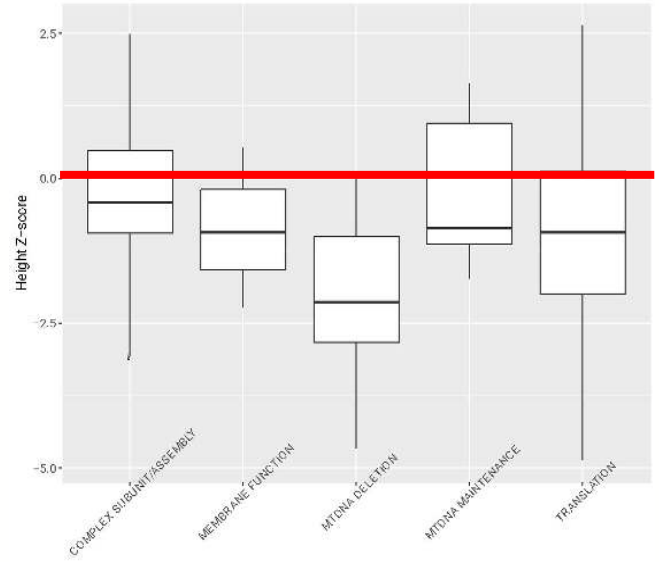
CAUSES OF IMPAIRED GROWTH

- Nutrition/GI disorders
- Other endocrine disorders, including hypothyroidism or sex steroid deficiency
- Growth hormone deficiency
- Stress/adaptation?

BMI Z-score



Height Z-score



Classes of mitochondrial disorders (CHOP MMFP):
1) Complex assembly; 2) Membrane Function; 3) mtDNA deletion; 4) mtDNA maintenance; 5) Translation

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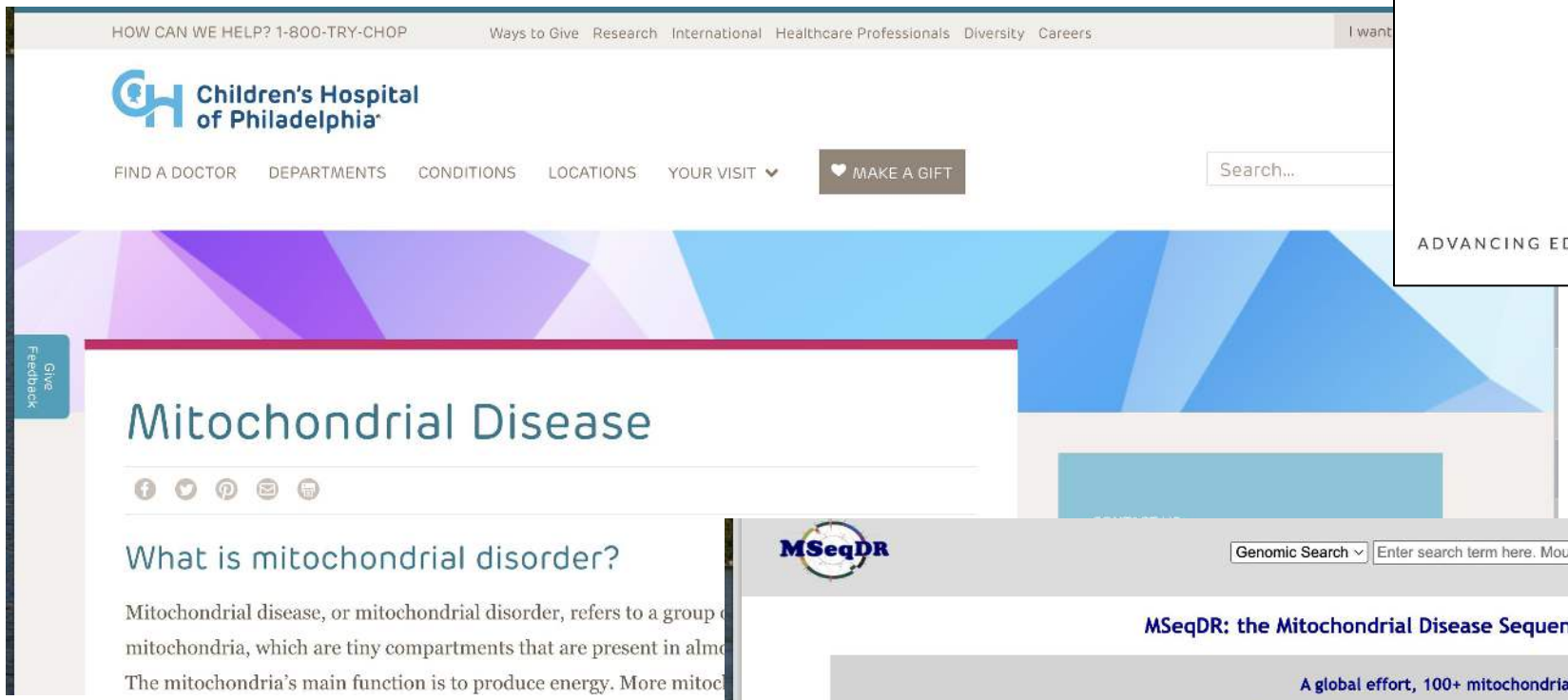
GROWTH HORMONE: DECISION TO TREAT?

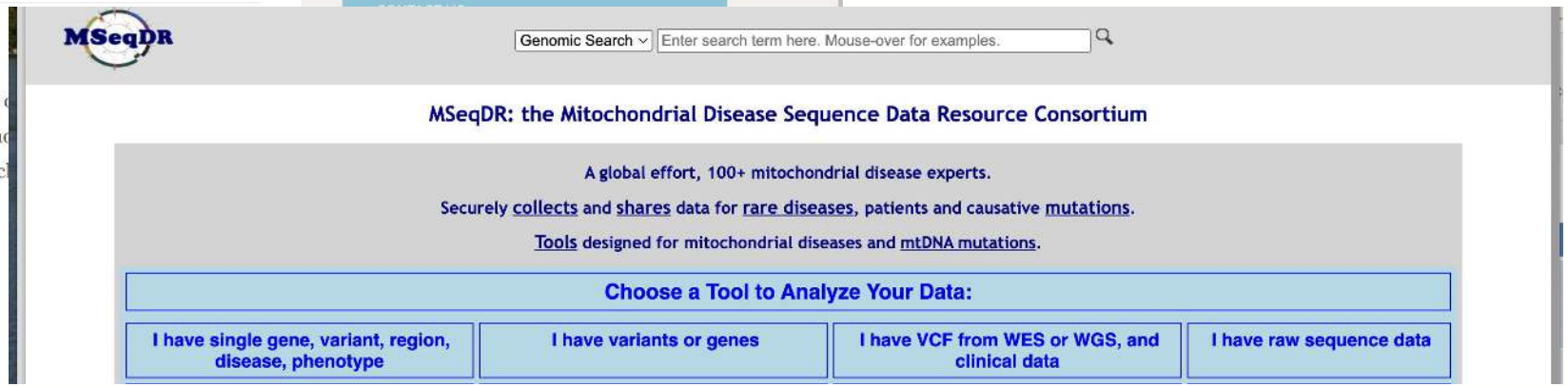
- **Symptoms:** short stature or decreased growth velocity, low blood sugar, fatigue, decreased muscle mass, impaired bone density
- **Assessment:** exclude/mitigate other causes, IGF1/IFBP3, consider GDF15, provocative testing
- **Management:** consider GH (adult vs. pediatric dosing)
- **Other considerations:** adverse effects of GH (stress, **DM**), patient-specific risk/benefit balance, manage expectations

SUMMARY

- Endocrine disorders are prevalent in individuals with mitochondrial disorders.
- Evidence-supported and symptom-directed patient screening is appropriate.
- Identify opportunities for effective interventions.

OTHER RESOURCES





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MANY THANKS!

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