Essentials in Endocrinology

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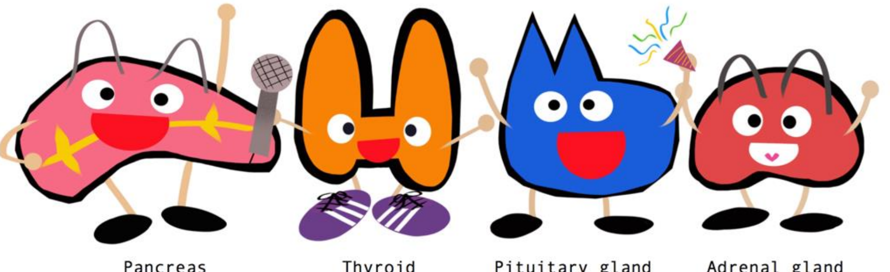


Key Long Case

- History
- Physical examination
- Laboratory investigation
  - Interpretation: Level 1 & 2
  - Clinical correlation
- Diagnosis
- Treatment
  - Specific
  - Supportive
- Advice

Level 2

Imaging

- Bone and joint radiography, Chest X-ray
- Skull X-ray
- CT brain, abdomen, thorax
- MRI brain
- Thyroid uptake and scan

Hormones

- Adrenal function test
- Parathyroid hormone
- Pituitary function test
- Thyroid function test
- Urinary metanephrine/normetanephrine
- Water deprivation test
- Reproductive hormones

Outlines

Pituitary

- Hypopituitarism (anterior/posterior)
- Hyperfunction (acromegaly, prolactinoma, TSHoma, etc.)

Adrenal

- Pheochromocytoma
- Primary aldosteronism

Adrenal & Pituitary

- Adrenal insufficiency
- Cushing's syndrome

Others

- Syndrome and related conditions

Terms

- **Adrenal insufficiency**
  - Primary
  - Central (or secondary, tertiary)
- **Cushing's syndrome**
  - Exogenous
  - Endogenous
    - ACTH-dependent (ACTH-secreting pituitary adenoma & ectopic ACTH)
    - ACTH-independent (adrenal)

Adrenal Insufficiency: Manifestations

- Chronic adrenal insufficiency
  - Non-specific symptoms, e.g., nausea/vomiting, weight loss, postural hypotension, etc.

- Some patients may present with **adrenal crisis**.
  - Decompensated stage of adrenal insufficiency
  - Always look for precipitating factors, e.g., infections, drug interactions, etc.
    - **OR** it can be the first manifestation of chronic adrenal insufficiency in some patients.

Symptoms and Signs

Symptoms

- Fatigue or anorexia
- GI symptoms
- Postural hypotension
- Salt craving*

Signs

- Weight loss
- Hyperpigmentation*
- Hypotension (SBP<110 mmHg)

*Only found in primary adrenal insufficiency

Laboratory Findings

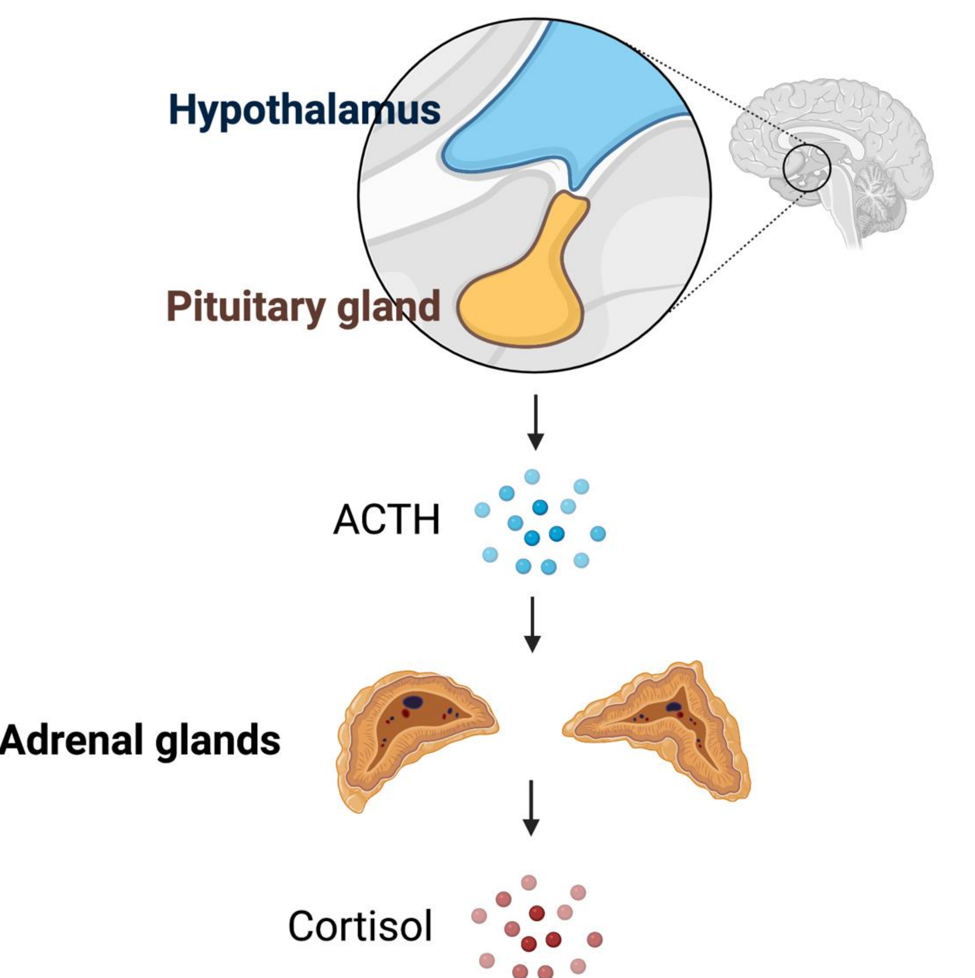
- Electrolyte disturbances: most common
  - Hyponatremia
  - Hyperkalemia (could be found in primary adrenal insufficiency)
  - Hypercalcemia
- Azotemia
- Anemia
- Eosinophilia

Adrenal Insufficiency

Chief complaints:

- Fatigue
- Nausea/vomiting
- Weight loss
- Postural hypotension
- Hyponatremia

Pathophysiology of Adrenal Insufficiency



Central adrenal insufficiency

- May be called secondary and tertiary adrenal insufficiency

Patients may have other hypothalamic/pituitary hormone deficits.

- e.g., TSH, FSH/LH, vasopressin

Primary adrenal insufficiency

Patients may have other adrenal hormone deficits.

- Mineralocorticoids (including aldosterone)
- Adrenal androgen

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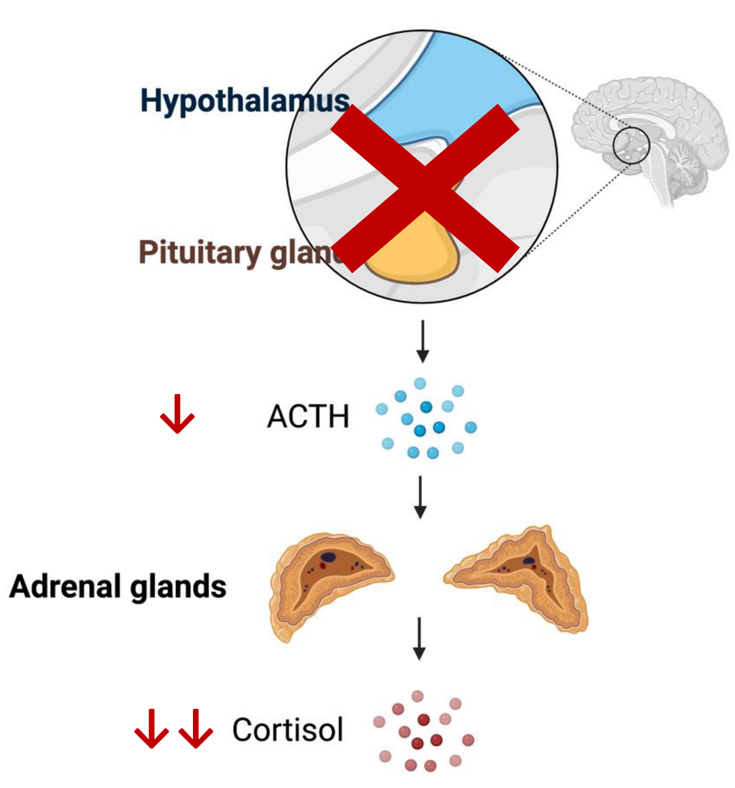
Central Adrenal Insufficiency



- Drug-induced
  - Glucocorticoids, opioids, and immune-checkpoint inhibitors
- Tumor
  - Hypothalamic/pituitary tumor
  - Metastatic tumor
  - Posttreatment (e.g., surgery/radiation)
- Hypophysitis
- Ischemia/hemorrhage
  - Pituitary apoplexy
  - Sheehan’s syndrome
- Infection
- Congenital

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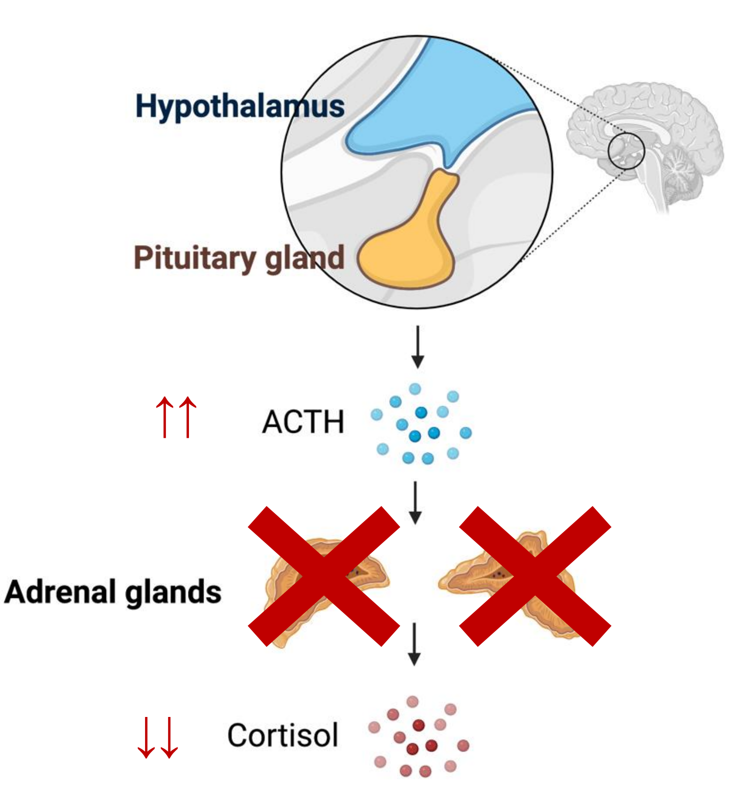
Primary Adrenal Insufficiency



- Infection
  - Common: Adrenal histoplasmosis, TB
- Adrenal hemorrhage
- Congenital (e.g., CAH, ALD)
- Drug
- Post surgery (bilateral adrenalectomy)

Patients may have other adrenal hormone deficiencies.

↓ Aldosterone.

↓ Adrenal androgen

CAH, congenital adrenal hyperplasia; ALD, adrenoleukodystropy

Image created with Biorender

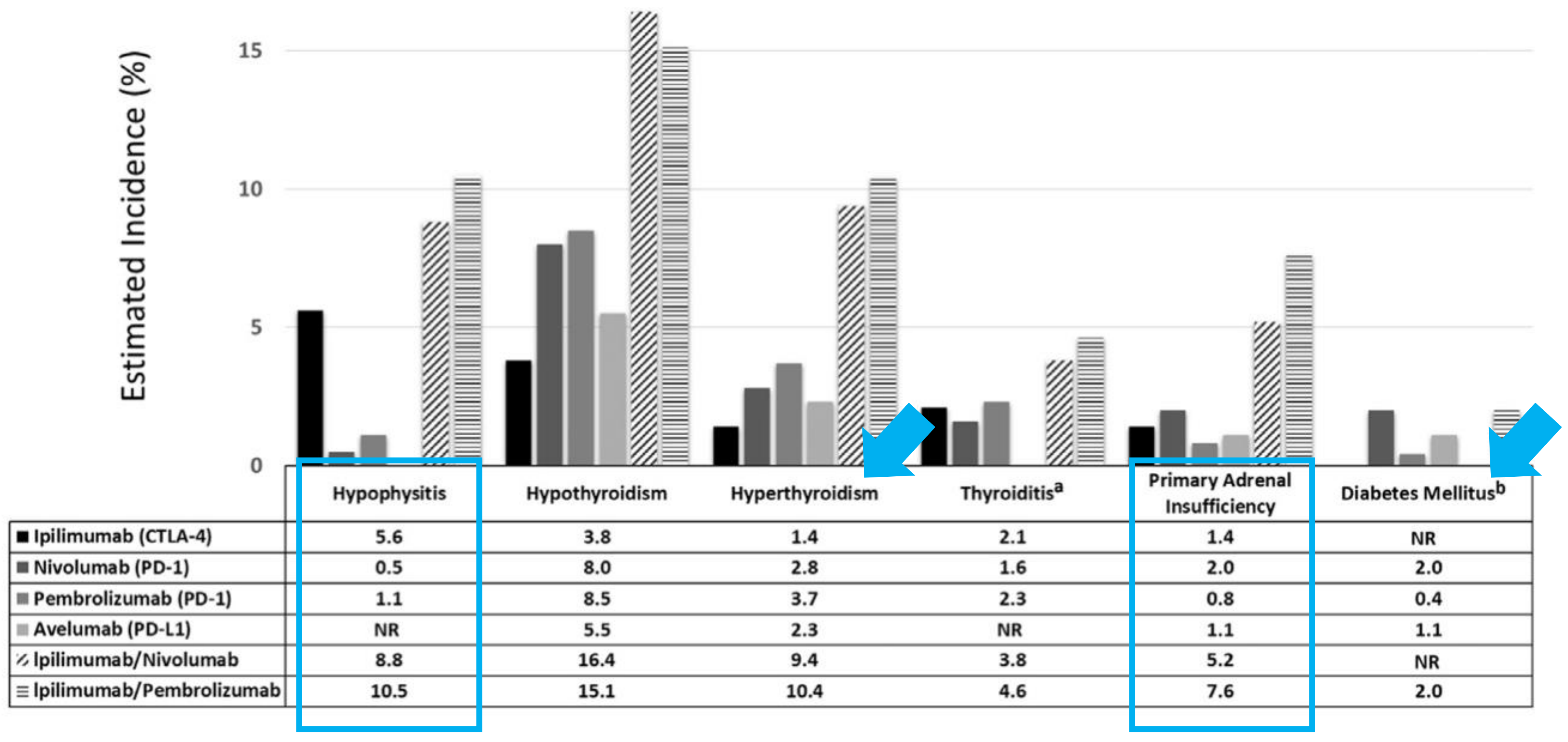
Immune Checkpoint Inhibitors

Drug	Target	Year of initial approval
Ipilimumab (Yervoy)	CTLA-4	2011
Nivolumab (Opdivo)	PD-1	2014
Pembrolizumab (Keytruda)	PD-1	2014
Atezolizumab (Tecentriq)	PD-L1	2016
Durvalumab (Imfinzi)	PD-L1	2017
Avelumab (Bavencio)	PD-L1	2017
Cemiplimab (Libtayo)	PD-1	2018

Abbreviations: CTLA-4 = cytotoxic T-lymphocyte antigen 4; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death protein 1 ligand.

Kotwal A et al. Endocr Pract 2024. PMID: 38554775.

Estimated Incidence (%) of Endocrinopathies



	Hypophysitis	Hypothyroidism	Hyperthyroidism	Thyroiditis[a]	Primary Adrenal Insufficiency	Diabetes Mellitus[b]
Ipilimumab (CTLA-4)	5.6	3.8	1.4	2.1	1.4	NR
Nivolumab (PD-1)	0.5	8.0	2.8	1.6	2.0	2.0
Pembrolizumab (PD-1)	1.1	8.5	3.7	2.3	0.8	0.4
Avelumab (PD-L1)	NR	5.5	2.3	NR	1.1	1.1
Ipilimumab/Nivolumab	8.8	16.4	9.4	3.8	5.2	NR
Ipilimumab/Pembrolizumab	10.5	15.1	10.4	4.6	7.6	2.0

Image from Kotwal A et al. Endocr Pract 2024. PMID: 38554775.

History Taking

- **Symptoms**
  - เบื่ออาหาร น้ำหนักลด ไข้ น้ำตาลต่ำ (หรือ น้ำตาลคุมได้ดีขึ้นในคนที่เป็นเบาหวานเดิมทั้งที่ใช้ยาเท่าเดิม หรือ มีอาการของ hypoglycemia ทั้งที่เดิมไม่เคยเป็น) ลุกนั่งเปลี่ยนท่าทางแล้วมีอาการหน้ามืดdฯลฯ
  - อาการบางอย่าง ช่วยบอก etiology ได้ เช่น salt craving (หิวเกลือ) หรือ ผิวคล้ำขึ้น
- **Etiology**
  - Central adrenal insufficiency
  - Primary adrenal insufficiency

Primary Adrenal Insufficiency (PAI)

- **Symptoms**dอาการหิวเกลือ (mineralocorticoid deficiency),dผิวคล้ำขึ้น (elevated ACTH)
- **Onset**
  - Childhood, e.g., CAH ถ้าจะออกสอบบอร์ดdน่าจะ 21-OH deficiency ที่เป็น classic salt-wasting form
  - Adrenoleukodystrophy (ALD): presenting symptoms in childhood = PAI, myelopathy in adults
- **Infection**
  - Non-HIV, non-DM มองหา adrenal histoplasmosis หรือ adrenal TB ด้วย!!!
  - HIV + low CD4 มองหา opportunistic infectiondอื่นๆ
- **Infiltration**
  - Metastatic cancer: CA metastasis ≠ PAIเพราะ adrenal gland ต้องเสียมากและสองข้างdจึงจะมีอาการของ primary AI
- **Adrenal hemorrhage**
  - มักมาด้วย acute onset + ปวดท้อง + มี risk factors
    - Risk factors: coagulopathy (on anticoagulants, antiphospholipid syndrome), trauma, sepsis
- **Autoimmune diseases**, e.g., autoimmune polyendocrine syndrome (APS)
  - APS 1: PAI + chronic mucocutaneous candidiasis + hypoparathyroidism

Central Adrenal Insufficiency

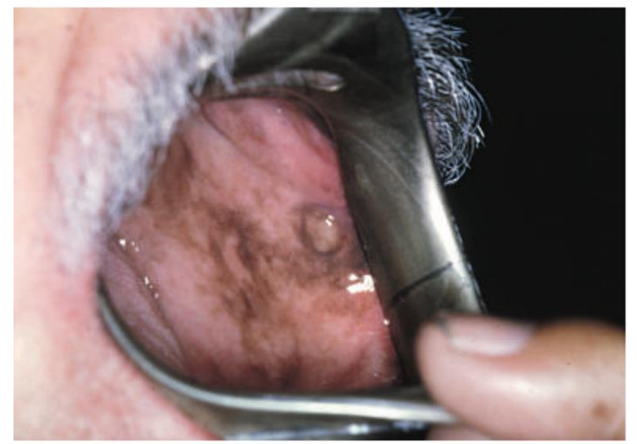
- **Drug-induced**
  - Glucocorticoids: dose, duration, Cushingoid feature, ประวัติน้ำหนักขึ้น หน้ากลมขึ้น เคยหยุดแล้วมีอาการอ่อนเพลีย
  - Immune checkpoint inhibitordถามประวัติมะเร็งdประวัติยาที่ใช้dและ onset

- **Hypothalamic and pituitary tumors**
  - Pituitary adenoma ถามเรื่อง mass symptoms, อาการ hormonal deficiency/functioning tumorsdของ hormone อื่นๆ, ไม่ควรมี AVP deficiencydยกเว้น postoperative อาจมีได้
  - Craniopharyngioma เกิดได้ตั้งแต่อายุน้อยdอาจมี AVP deficiency ร่วมด้วยได้

- **Sheehan syndrome** ประวัติตกเลือดหลังคลอด ไม่มีน้ำนมให้ลูกกิน หลังจากคลอดบุตรอาจจะไม่มีประจำเดือน

Physical Examination

- Vital signs: hypotension, postural hypotension, tachycardia
- Local tumor effect: VF defect (optic chiasm compression)
- Skin hyperpigmentation (primary adrenal insufficiency)
  - Location: palmar crease, knuckle, buccal mucosa, surgical scar
- Other signs (autoimmune)
  - Anemia (B12 deficiency), thyroid abnormalities, vitiligo, mucocutaneous candidiasis



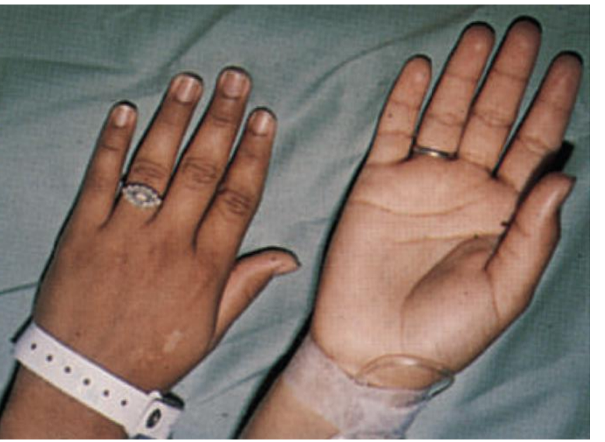
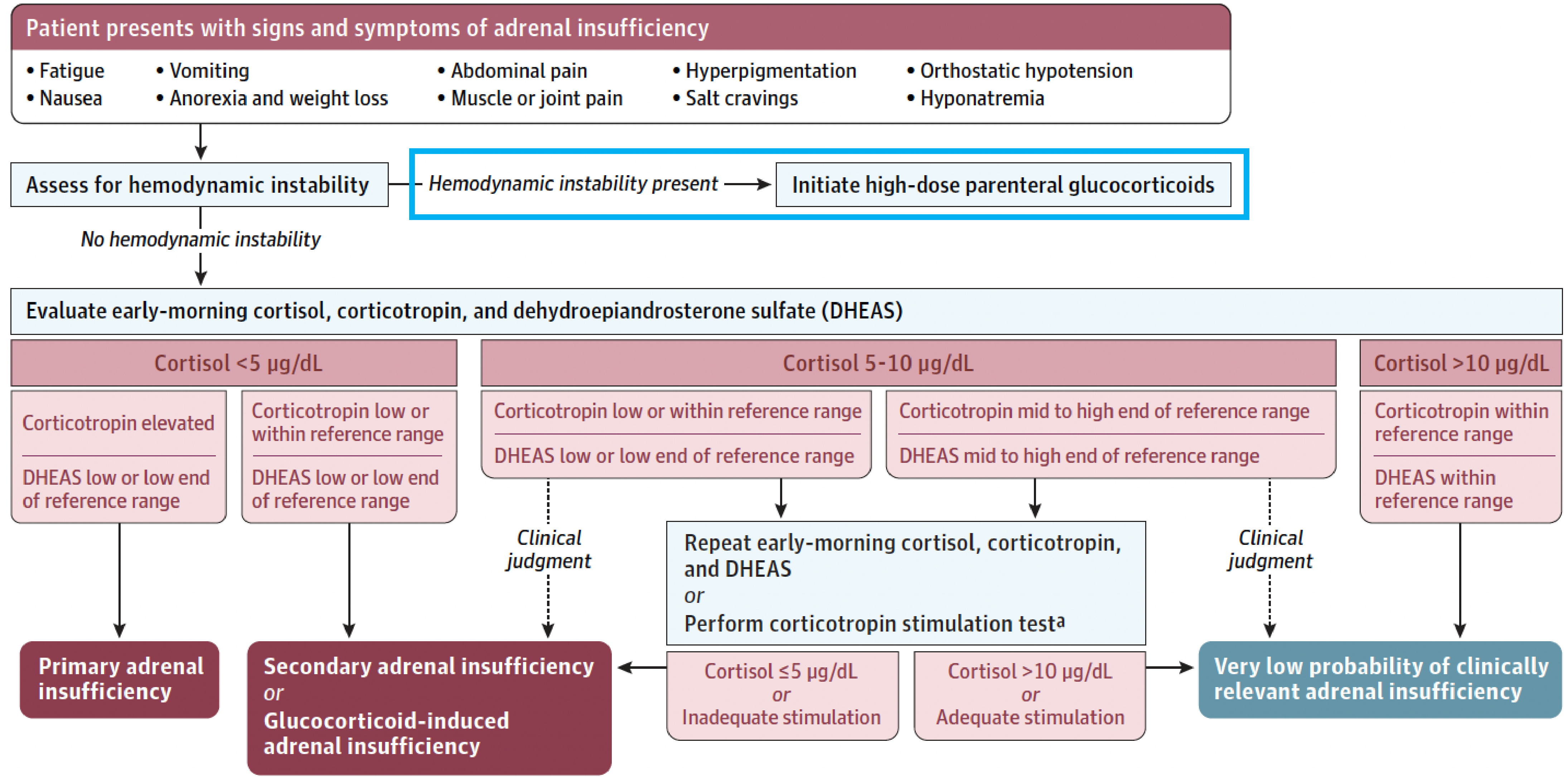


Image from Williams textbook of endocrinology 13th edition

Approach to Patients with Suspected Adrenal Insufficiency

- Signs & Symptoms
- Hemodynamic instability
  - Yes → Treatment first
  - No → Further test

Approach to Patients with Suspected Adrenal Insufficiency



Vaidya A, Findling J, Bancos I. JAMA 2025. PMID: 40522647.

Adrenal Crisis

- **Adrenal crisis = Medical emergency**
- Patients may manifest with signs and symptoms of circulatory failure
- The most severe manifestation of adrenal insufficiency
  - Could result from either primary or central adrenal insufficiency
- Mortality rate ~ 6%

Symptoms
- Anorexia, nausea, vomiting
- Severe fatigue
- Postural dizziness, syncope
- Confusion

Signs
- Hypotension
- Impaired consciousness
- Fever

Biochemical abnormalities
- Hyponatremia
- Hypoglycemia
- Eosinophilia

Rushworth RL et al. Adrenal Crisis. N Engl J Med 2019. PMID: 31461595.

Adrenal Crisis

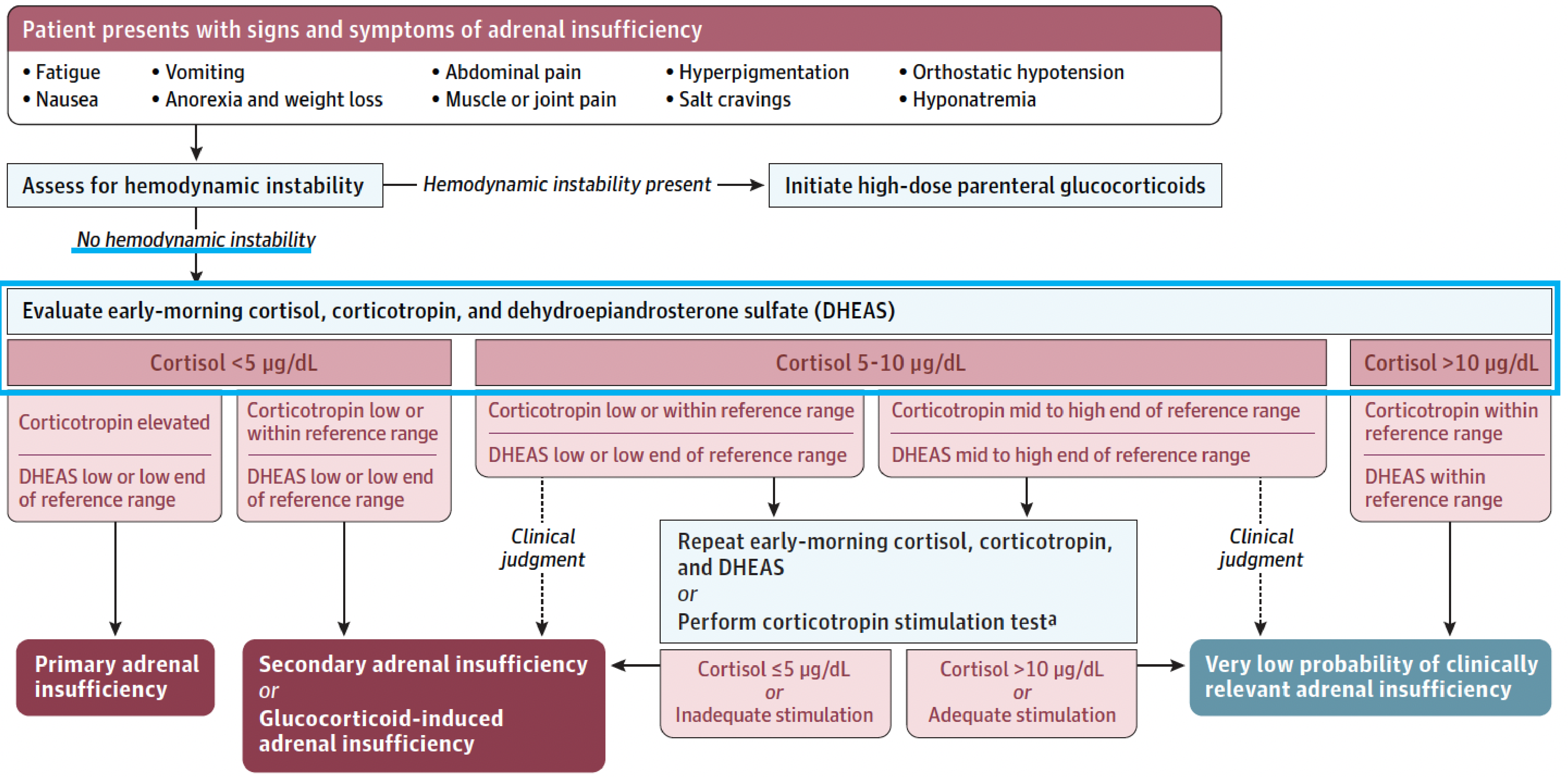
- If an adrenal crisis is suspected
  - **Draw blood for cortisol & ACTH**

**** Do not wait for cortisol results to start treatment****

- Prompt treatment with glucocorticoids is needed
  - **Hydrocortisone 100 mg IV (or IM) bolus, then 200 mg in 24 hrs**
    - Alternatives:
      - Dexamethasone 4 mg q 24 hrs
      - Prednisolone 25 mg then 25 mg x 2 doses (total 75 mg/24 hrs)
      - Methylprednisolone 40 mg q 24 hrs
  - Others: IV fluid, correct precipitating factors
- Symptoms will be markedly improved after 1-2 hours of parenteral glucocorticoid administration

Rushworth RL et al. Adrenal Crisis. N Engl J Med 2019. PMID: 31461595.

Approach to Patients with Suspected Adrenal Insufficiency



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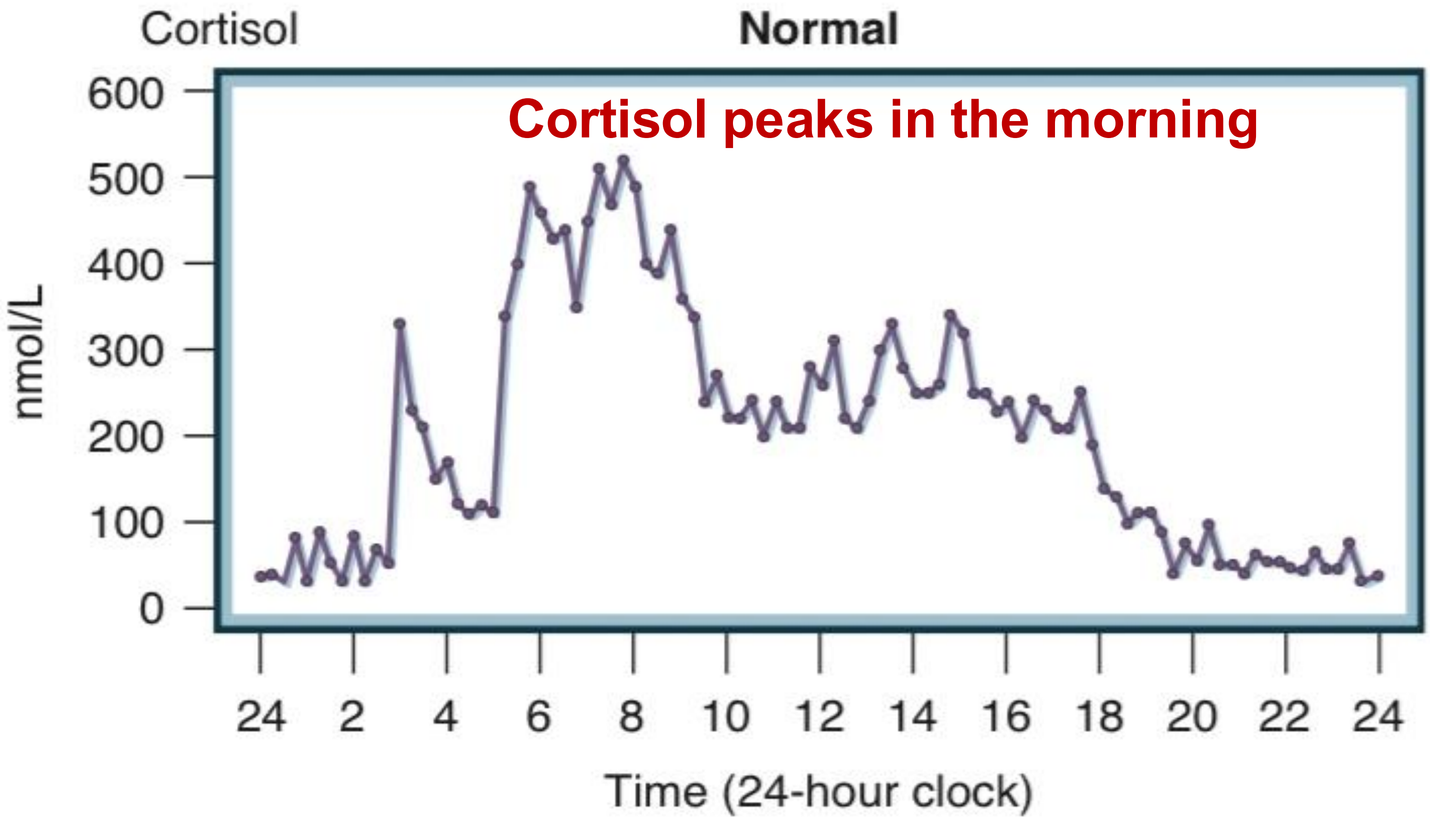
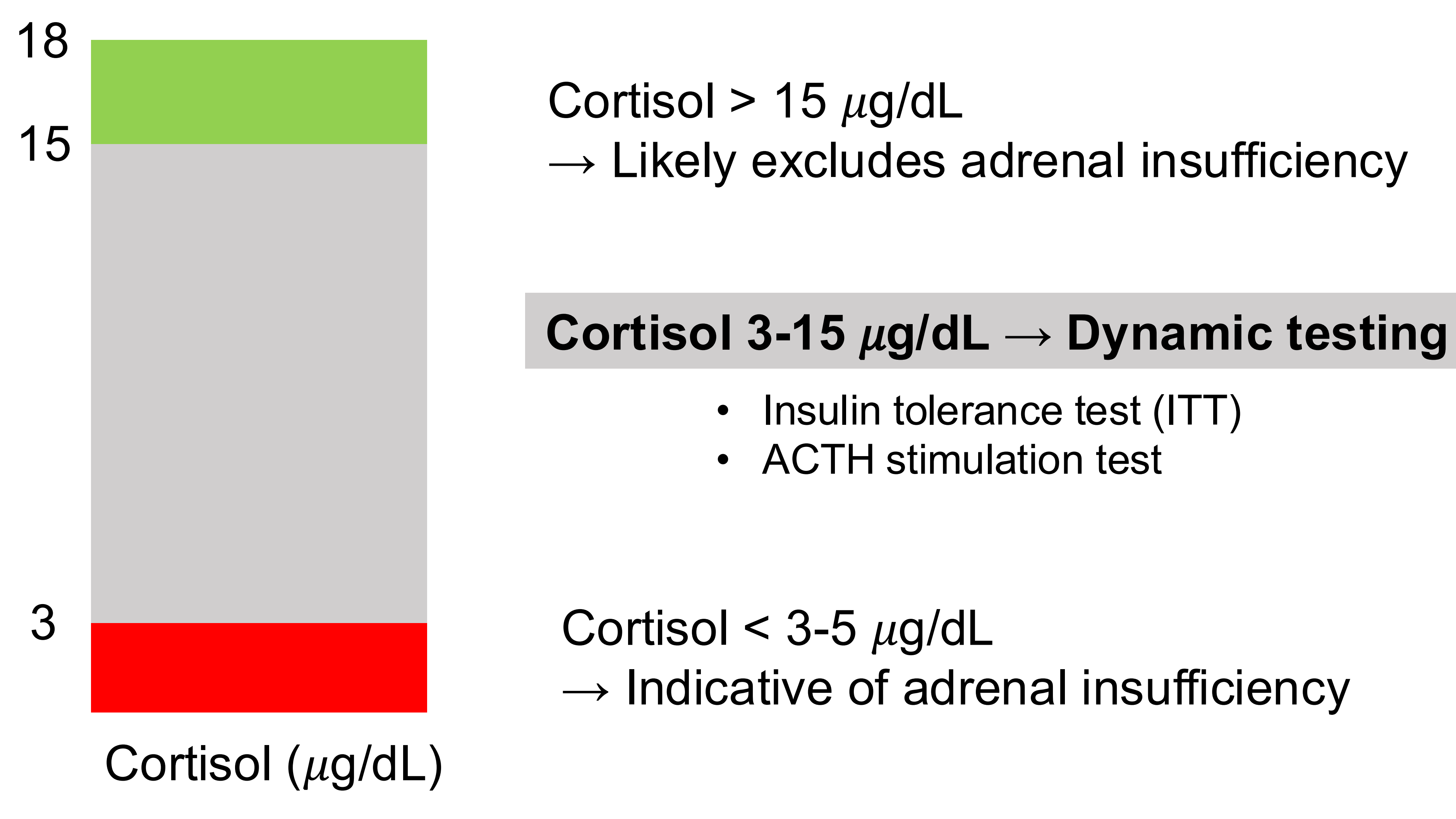
Diagnosis

- Initial test: Morning cortisol (7-9 am)



Williams textbook of endocrinology 14th edition

Morning cortisol



Bornstein SR et al. J Clin Endocrinol Metab 2016. PMID: 26760044.

Insulin Tolerance Test

- Administer insulin, 0.05-0.15 U/kg iv
- Sample blood at -30, 0, 30, 60 & 120 min for;
  - Cortisol, glucose
- Glucose < 40 mg/dL → peak cortisol > 18.1 -20 μg/dL

Fleseriu M et al. J Clin Endocrinol Metab 2016. PMID: 27736313.

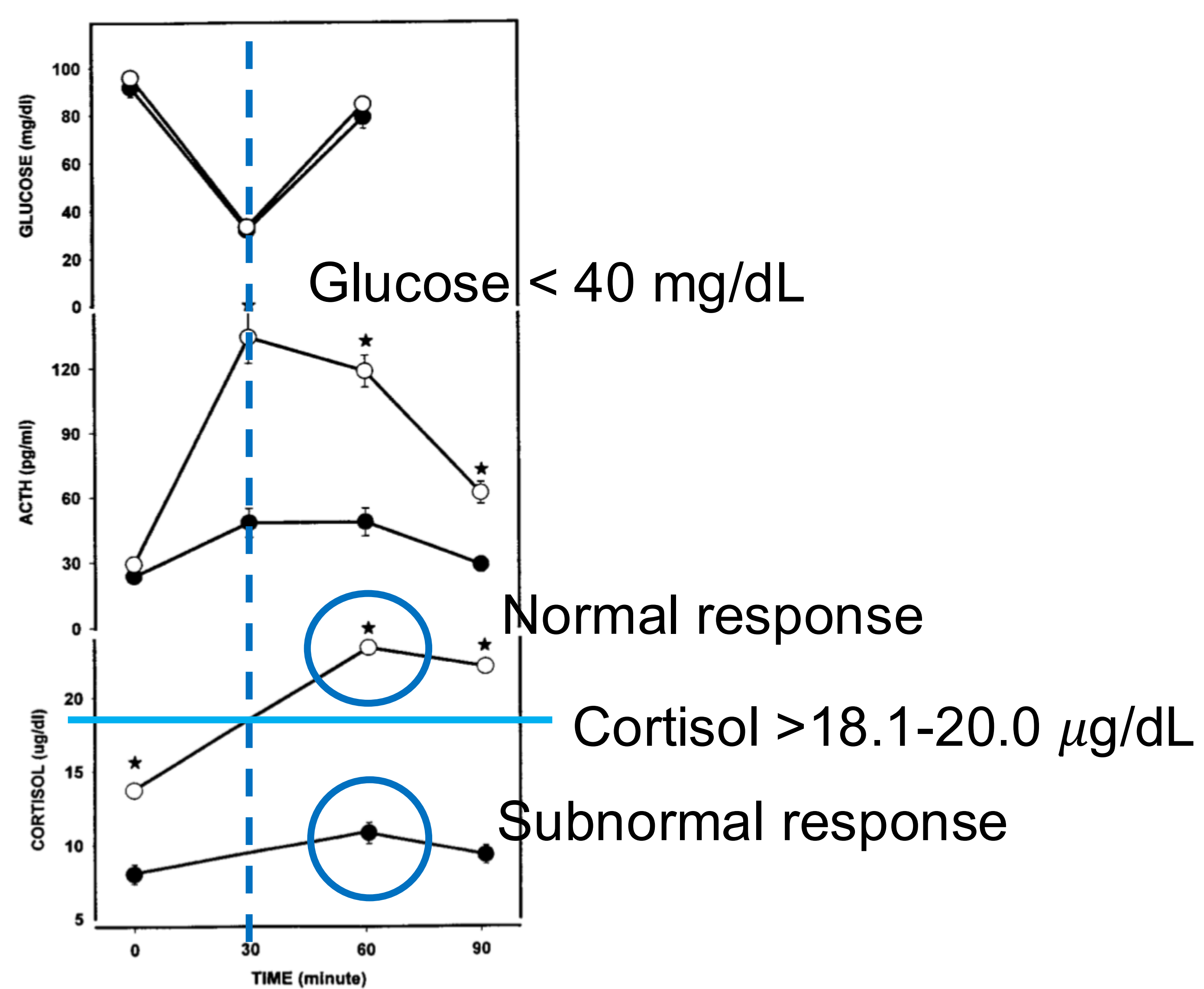
Insulin Tolerance Test

- Contraindication
  - Ischemic heart disease/arrhythmia
  - Epilepsy

- Not advisable in children and the elderly

Fleseriu M et al. J Clin Endocrinol Metab 2016. PMID: 27736313.

Insulin Tolerance Test



Erturk E, Jaffe CA, Barkan AL. J Clin Endocrinol Metab 1998. PMID: 9661607.

ACTH Stimulation Test

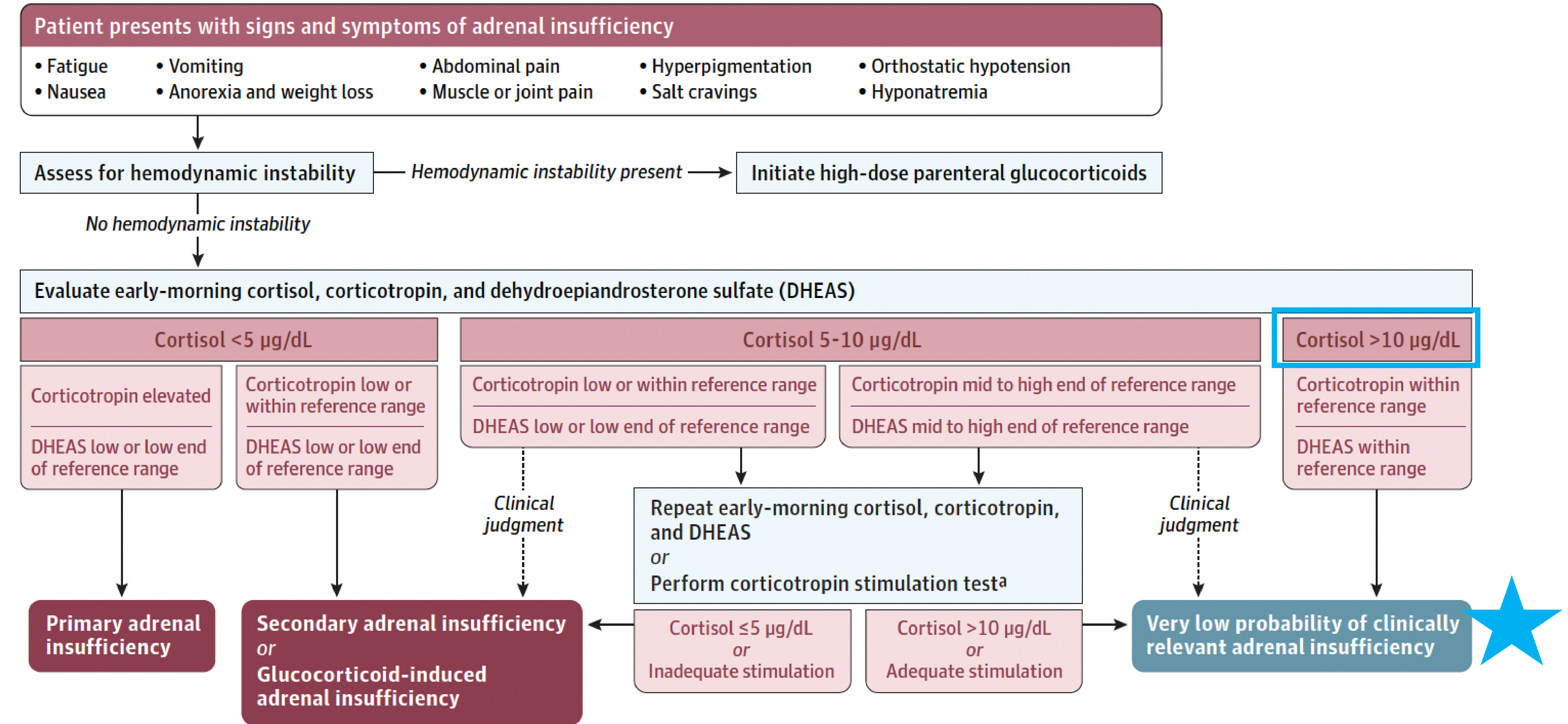
- Using synthetic ACTH-(1–24)
  - High dose or standard dose (250 mcg)
  - Low dose (1 mcg)
- Measure cortisol level at 30 or 60 min (or 20 & 40 min)
  - Peak cortisol < 18-20 mcg/dL → indicates adrenal insufficiency

Recent studies have shown that the cutoff for peak cortisol was lowered to 14-15 mcg/dL with newer cortisol assays.

Zha L et al. Endocr Pract 2022. PMID: 35487459.
Javorsky BR et al. J Endocr Soc 2021. PMID: 33768189.

Fleseriu M et al. J Clin Endocrinol Metab 2016. PMID: 27736313.

Approach to Patients with Suspected Adrenal Insufficiency



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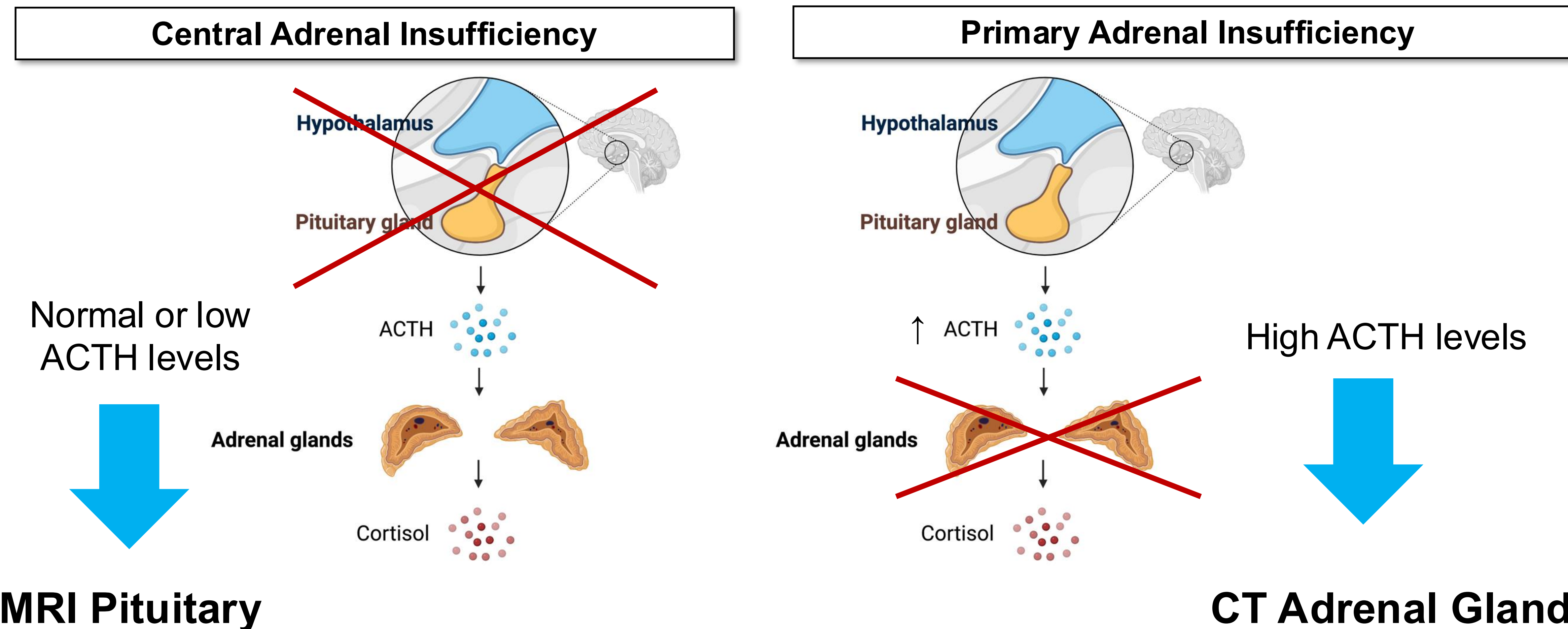
ACTH level



MRI Pituitary

CT Adrenal Glands

ACTH: Specimen Handling Technique

- Collected in pre-chilled EDTA tube
- Transported on ice to the lab
- ACTH is rapidly degraded → falsely low results
  - If not processing right away, it must be centrifuged immediately and kept at -20 °C

Jane Ellis M, Livesey JH, Evans MJ. Clin Biochem 2003. PMID: 12633759.

Adrenal Insufficiency: Hormonal Replacement

- Glucocorticoids:
  - หลักการ = ใกล้เคียง physiologic dose มากที่สุด (ถ้าขนาดมากไป → iatrogenic Cushing's syndrome แต่ถ้าน้อยไป → adrenal crisis)
    - Hydrocortisone 15-25 mg/day (2-3 ครั้ง/วัน) หรือ Prednisolone 5 mg/day (1-2 ครั้ง/วัน)
      - Dose ละเอียดๆ คือ 5-8 mg/m^2
    - หลีกเลี่ยง dexamethasone ในการ replacement เนื่องจากมี Cushingoid side effects เยอะ
  - Surgery/illness → ปรับเพิ่มขนาดตาม stress
  - กรณีที่ผู้ป่วยกินไม่ได้ → เปลี่ยน route เช่น SC, IM
  - Pregnancy → prefer hydrocortisone > prednisolone > dexamethasone (ผ่านรก)
- Central adrenal insufficiency
  - Other pituitary hormonal replacement, e.g., LT4 ในคนที่มี central hypothyroidism, etc.
- Primary adrenal insufficiency
  - Mineralocorticoids: fludrocortisone 50-100 mcg/day ในคนที่มี deficiency
  - Sex steroid: สามารถให้ DHEA ในผู้หญิง low libido, low energy level แม้จะได้การรักษาสองอย่างข้างต้นดีแล้ว

Adrenal Insufficiency: Monitoring & Education

- Monitor: BW, BP, postural hypotension, electrolyte, well-being
- Patient education: steroid emergency card, sick day management → prevent adrenal crisis
- Genetic counseling, if indicated

Steroid Management in Specific Situation

Condition	Suggested Action
Home management of illness + fever	Hydrocortisone dose x 2 if BT >38˚C Hydrocortisone dose x 3 if BT >39˚C
Unable to tolerate oral medication	Hydrocortisone 100 mg IM or SC
Minor-moderate surgical stress	Hydrocortisone 25-75 mg/24 h
Major surgery	- Hydrocortisone 100 mg iv then 200 mg iv drip in 24h or 50 mg q 6 h IV or IM - Rapid tapering and switch to oral regimen

Other procedures, e.g. dental procedure (extra morning dose 1 h before surgery, double the oral dose for 24 h then return to normal dose after sugery)

1. Bornstein SR et al. J Clin Endocrinol Metab 2016. PMID: 26760044;
2. Allolio B. Eur J Endocrinol 2015. PMID: 25288693; 3. UK Addison's disease self-help group; www.addisons.org.uk.

Patient education & Identification

- Sick day management
- Discussing signs & symptoms of adrenal insufficiency
- Situation which required dose adjustment
- Steroid emergency card

Bornstein SR et al. J Clin Endocrinol Metab 2016. PMID: 26760044

Further Reading

Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline

PMID: 26760044

Stefan R. Bornstein (chair), Bruno Allolio, Wiebke Arlt, Andreas Barthel, Andrew Don-Wauchope, Gary D. Hammer, Eystein S. Husebye, Deborah P. Merke, M. Hassan Murad, Constantine A. Stratakis, and David J. Torpy*

Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline

PMID: 27736313

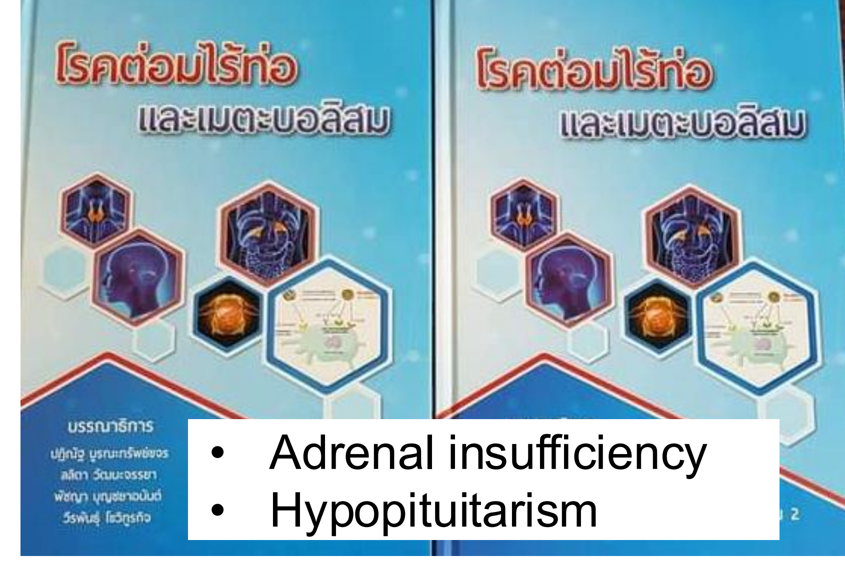
Maria Fleseriu (chair), Ibrahim A. Hashim, Niki Karavitaki, Shlomo Melmed, M. Hassan Murad, Roberto Salvatori, and Mary H. Samuels

European Journal of Endocrinology, 2024, **190**, G25–G51
https://doi.org/10.1093/ejendo/lvae029
Advance access publication 8 May 2024
Clinical Practice Guideline

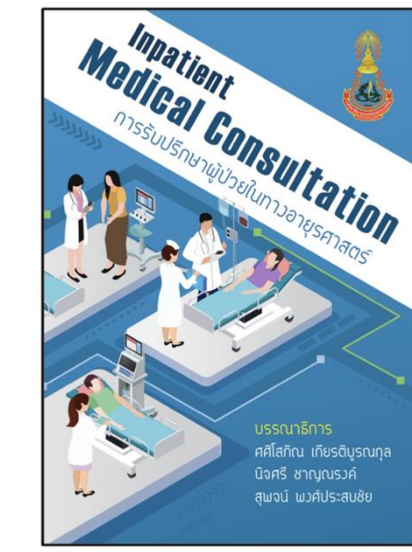
European Society of Endocrinology and Endocrine Society Joint Clinical Guideline: Diagnosis and therapy of glucocorticoid-induced adrenal insufficiency

PMID: 38724043

Felix Beuschlein,[1,2,3,*,†] Tobias Else,[4,†] Irina Bancos,[5,6] Stefanie Hahner,[7] Oksana Hamidi,[8] Leonie van Hulsteijn,[9,10] Eystein S. Husebye,[11,12] Niki Karavitaki,[13,14,15] Alessandro Prete,[13,14,16] Anand Vaidya,[17] Christine Yedinak,[18] and Olaf M. Dekkers[10,19,20]



- Adrenal insufficiency
- Hypopituitarism



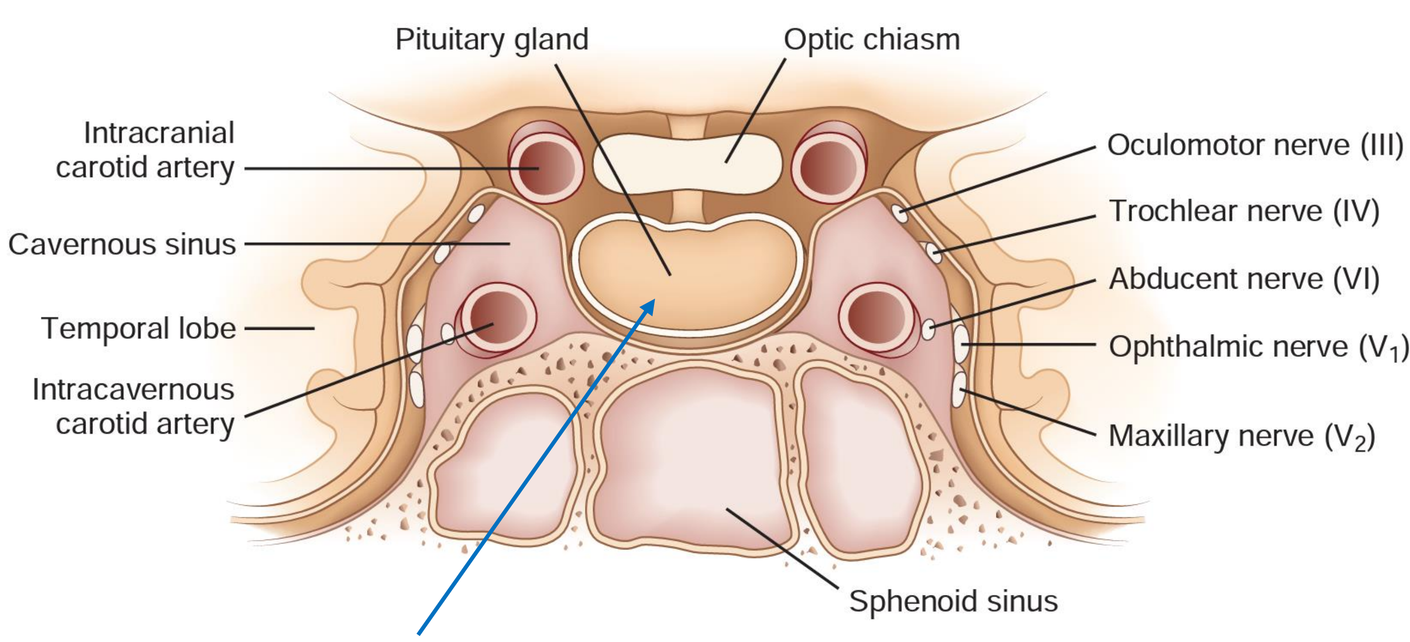
Hypopituitarism & Pituitary Tumors

Clinical Signs

- Local effect
- Pituitary hormones
  - Hypofunction
  - Hyperfunction

Clinical Signs: Local Effects

Coronal View



Sagittal View

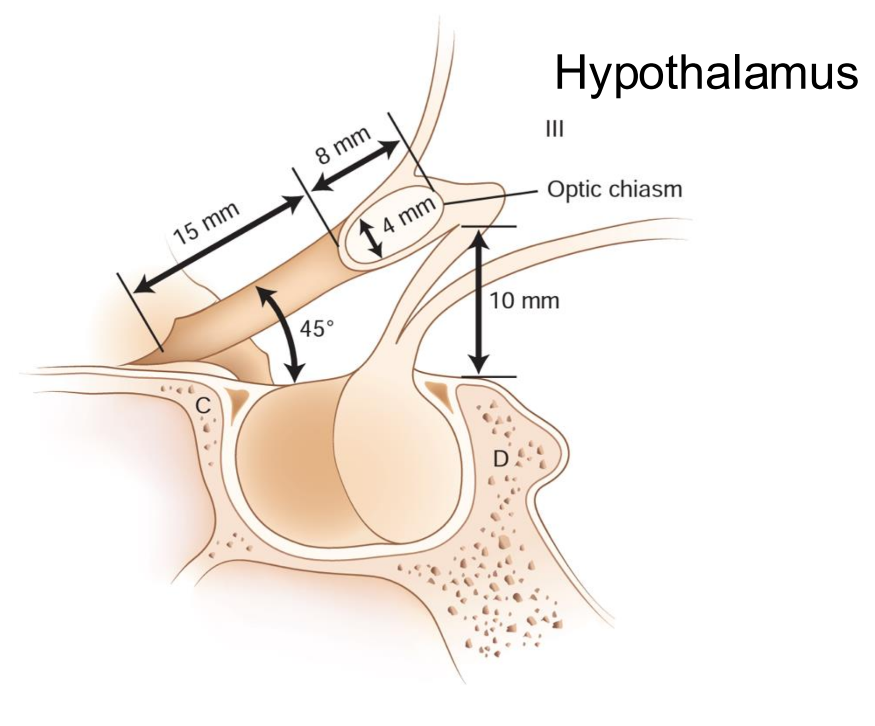
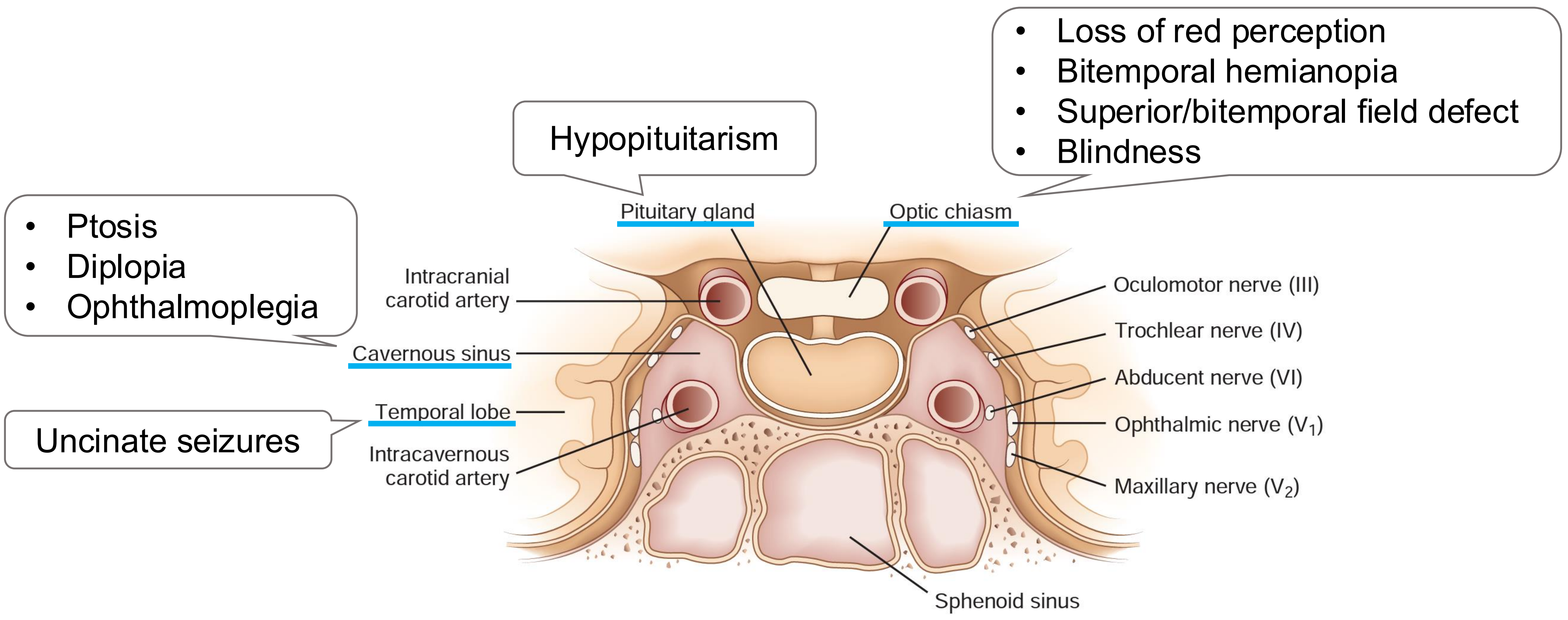


Image from Williams Textbook of Endocrinology 13th edition.

Clinical Signs: Local Effects

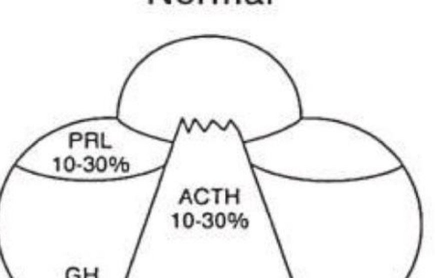


Central: Headache, hydrocephalus, laughing seizures
Hypothalamus: Temperature dysregulation, obesity, diabetes insipidus (AVP deficiency)
Frontal lobe: Personality disorder

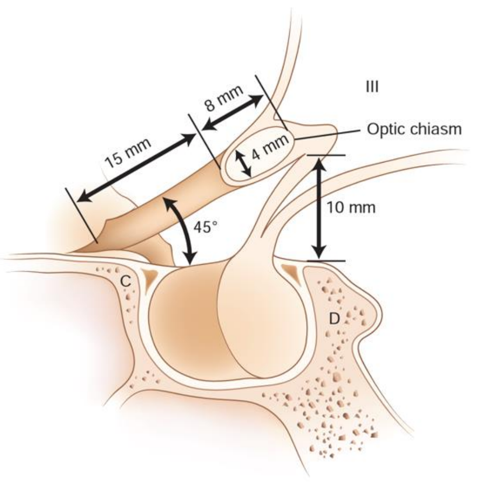
Image from Williams Textbook of Endocrinology 13th edition.

Hormonal Evaluation: Hypopituitarism

Anterior Pituitary



Posterior Pituitary



General

- Fatigue, weakness, decreased exercise capacity (TSH, ACTH, FSH/LH, GH)
- ↑ /↓ Weight (TSH, ACTH)

Gastrointestinal

- Anorexia, Nausea/vomiting (ACTH)
- Constipation (TSH)

Cardiovascular/metabolic

- ↓lean body mass, ↑fat mass (GH)
- Hypertension, bradycardia, impaired cardiac function (TSH)
- Dyslipidemia, Impaired glucose tolerance (TSH, GH)

Reproductive

- Oligo/amenorrhea (TSH, ACTH, FSH/LH)
- ED, low libido, vaginal dryness (FSH/LH)

Skin

- Loss of body hair (TSH, ACTH, FSH/LH)
- Dry skin (TSH, ACTH)

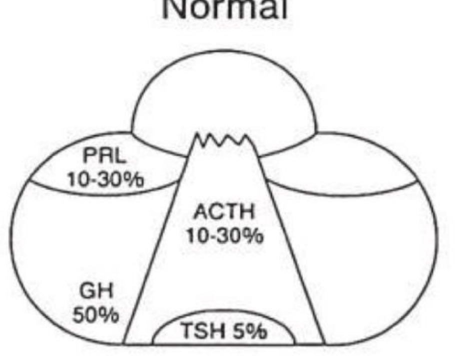
Vasopressin

- Polyuria
- Persistent thirst throughout day & night
- Desire for cold liquids

Fleseriu M et al. J Clin Endocrinol Metab 2016. PMID: 27736313.

Hormonal Evaluation: Hypopituitarism

Anterior Pituitary



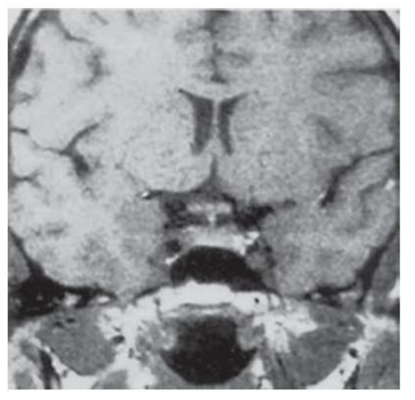
Disorder	Hormonal Measurement	Dynamic test
ACTH	8-9 AM cortisol	Insulin tolerance test ACTH stimulation test
TSH	FT4, TSH	Not recommended
GH	Single GH measurement = not recommended Except in patients with 3 other pituitary hormone deficiencies	Insulin tolerance test GHRH + Arginine test Glucagon stimulation test
FSH/LH	FSH, LH, PRL T in male, E2 in female	Not recommended

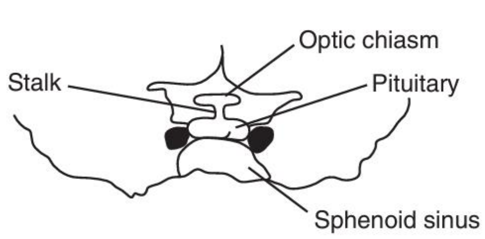
GHRH, growth hormone releasing hormone; T, testosterone; E2, estradiol

Fleseriu M et al. J Clin Endocrinol Metab 2016. PMID: 27736313.

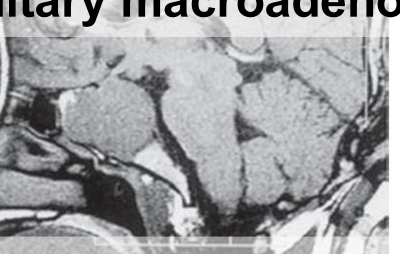
Pituitary Imaging: Look for Hypothalamic, Sellar/Parasellar Lesions!

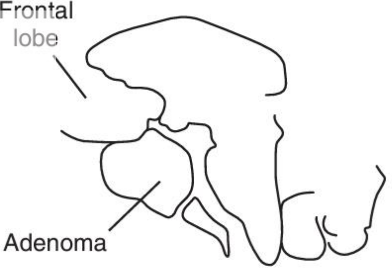
Normal MRI



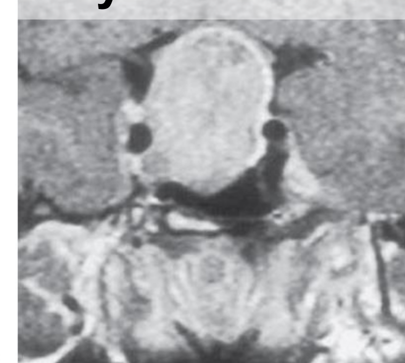


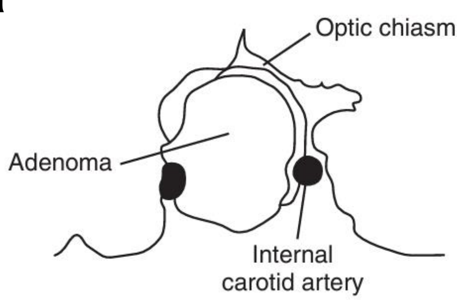
Pituitary macroadenoma

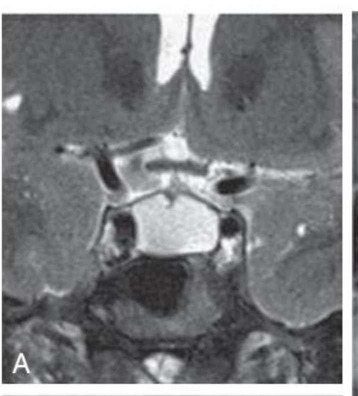


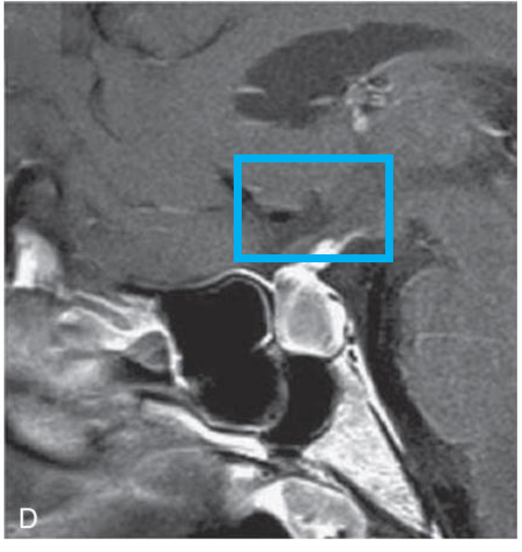


Pituitary macroadenoma









Infundibulohypophysitis

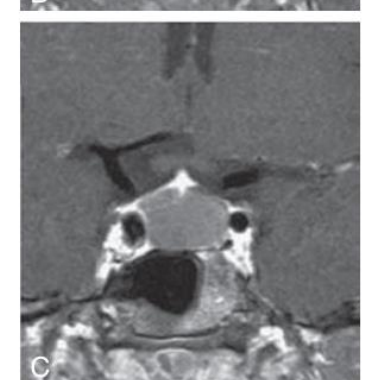
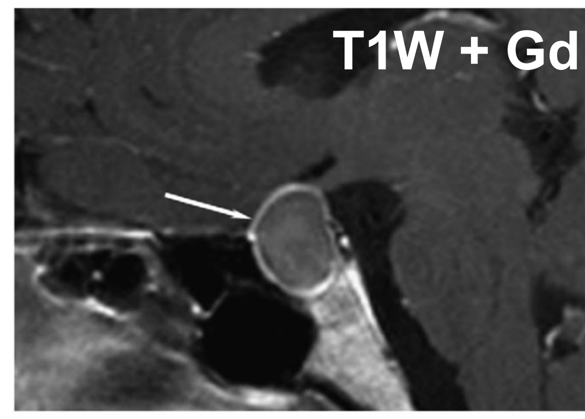


Image from Williams textbook of endocrinology 14th edition

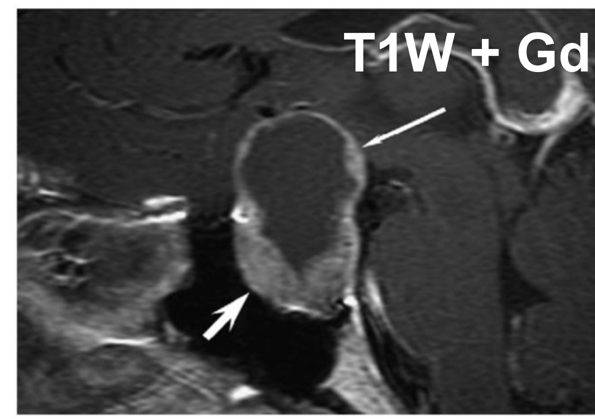
Pituitary Imaging

Rathke cleft cysts



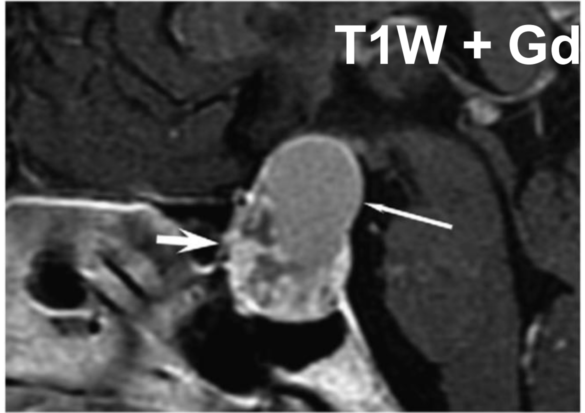
- An ovoid shape
- Small tumor volume
- Little or no cyst wall enhancement
- Rarely found calcifications

Pituitary adenomas with cystic degeneration



- A “snowman” shape
- Solid characteristics and homogeneous enhancement of the solid portion

Craniopharyngiomas



- Mixed solid and cystic characteristics
- Calcifications occurred in up to 80% (some types)
- Reticular enhancement of solid portions
- May have lobulated shape with third ventricle compression

Image from Choi SH et al. Clin Radiol 2007. PMID: 17398271.

A 66 YO female presented with sudden severe headache

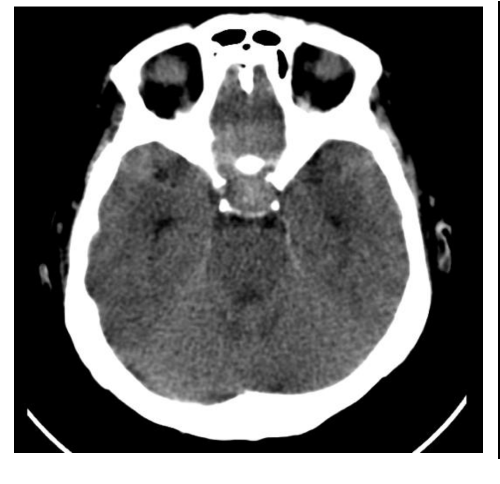
Physical examinations

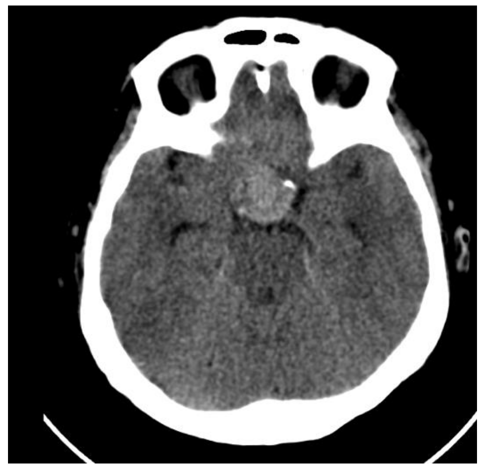
- BP 140/80 mmHg, PR 70 bpm
- E4M6V5
- Pupils 3 mm RTLBE (EOM/ptosis were not documented)

Laboratory investigations

- *Na 134 K 3.5 Cl 100 HCO_3 27*
- Hb 13.7 g/dl Hct 40 % WBC 5,800 (N 50% L 40%) Platelet 215,000
- PT 11.4 sec, INR 0.96, PTT 33.7 sec
- *FT4 0.28 ng/dl (0.54-1.24), TSH 1.74 uIU/ml (0.34-5.6)*
- 8 AM cortisol = 6 μg/dL

CT brain at 8 days after the onset of headache





T1W + Gd

T1W + G

🌟6. Pituitary

🔥HOT🔥สอนอ่าน MRI ep 1

https://www.facebook.com/CUEZendocrine/posts/614892555371391

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สอนอ่าน MRI ep2

https://www.facebook.com/CUEZendocrine/posts/618680144992632

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MRI pituitary quiz

https://www.facebook.com/CUEZendo.../posts/619952024865444:0

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pituitary apoplexy management

https://www.facebook.com/CUEZendocrine/posts/649527375241242

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Polyuria

- Definition
  - Urine volume >40-50 mL/kg/day **OR** >3 L/day

Polyuria ≠ Frequency

- Etiology
  - Water diuresis
    - AVP deficiency (known as "central DI")
    - AVP resistance (known as "nephrogenic DI")
    - Primary polydipsia
  - Solute diuresis
    - e.g., mannitol, hyperglycemia

Diagnosis

- History
  - Onset, age, desire for cold liquids
  - Associated symptoms → suggest etiology
- Physical examination
- Laboratory investigation
  - Electrolytes, serum/urine osmolarity
  - Additional test: water deprivation test
- Imaging
  - Posterior bright spot
  - Stalk/hypothalamic lesions

The Hypothalamic-Posterior Pituitary Axis

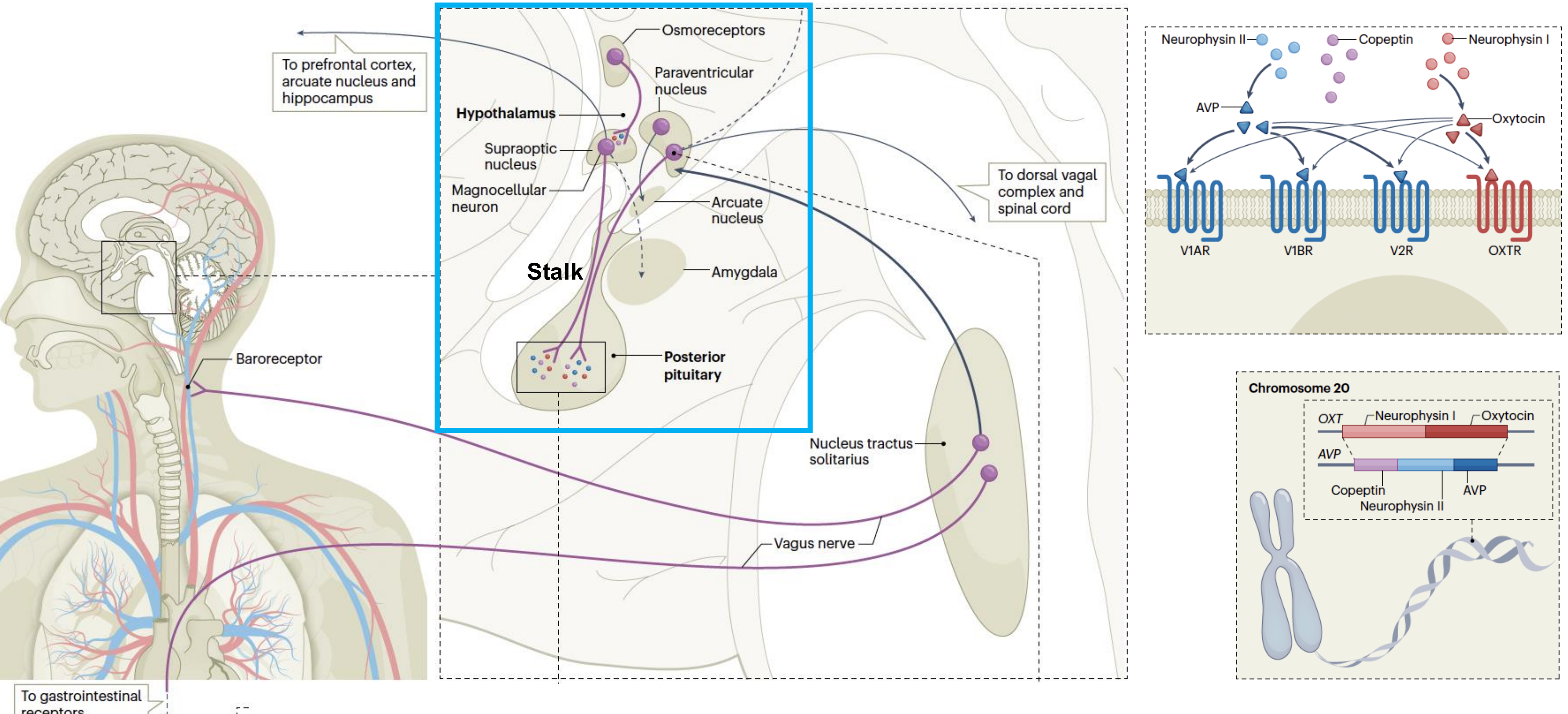
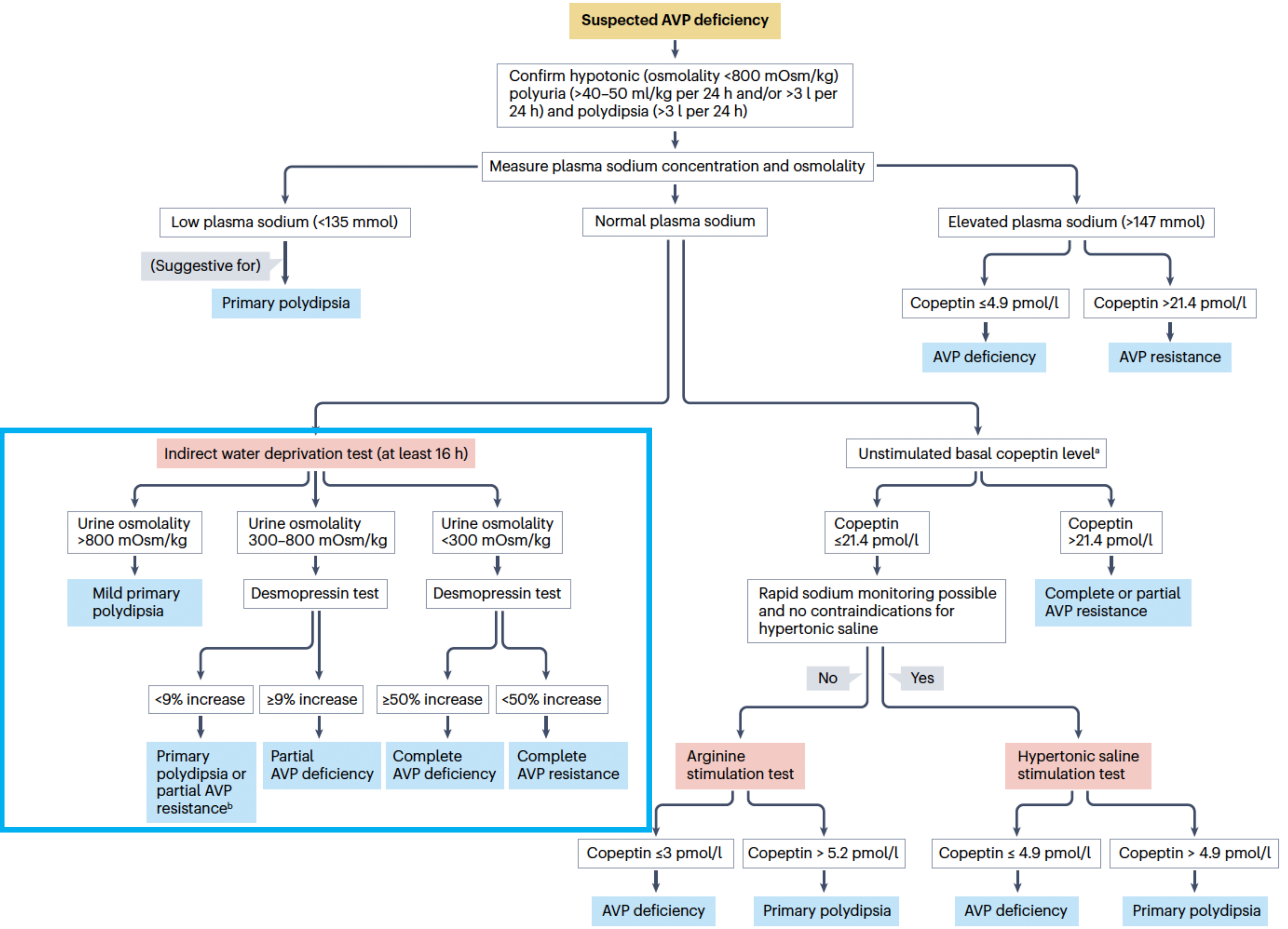


Image from Atila C, Refardt J, Christ-Crain M. Nat Rev Endocrinol 2024. PMID: 38693275.



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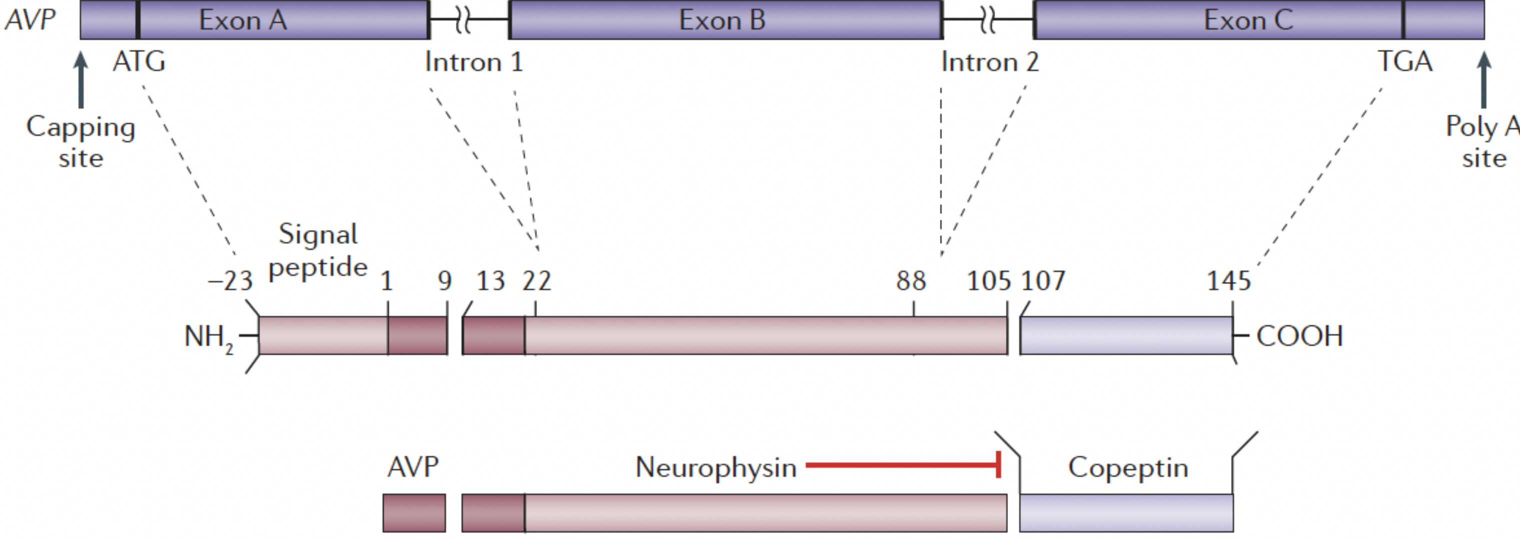


Image from PMID: 26794439

Water deprivation test

การเตรียมตัว

1. หลีกเลี่ยง alcohol อย่างน้อย 48 hrs, หลีกเลี่ยง nicotine และ caffeine อย่างน้อย 12 hrs ก่อนทำ test
2. ในกรณีที่ผู้ป่วยใช้ DDAVP อยู่แล้ว ให้หยุดยาก่อนมาทำ test อย่างน้อย 24 hrs
3. NPO โดยแพทย์กำหนดเวลา (พิจารณาตามปริมาณปัสสาวะ หากปริมาณปัสสาวะมาก ให้ NPO 6.00 น.)
4. ให้ผู้ป่วยชั่งน้ำหนักก่อนเริ่มทำ test

ขั้นตอนการทำ

1. ชั่งน้ำหนักตอนเริ่มอาการตรวจ (0 min)
2. เจาะ serum osmolarity และ ส่ง urine osmolarity ตอนเริ่มการตรวจ
3. เจาะ serum osmolarity (optional), ส่ง urine osmolarity และ ชั่งน้ำหนักตัวทุกชั่วโมง จนกระทั่ง (ข้อใดข้อหนึ่ง) ** ไม่ต้องครบทุกข้อ**
    a. น้ำหนักตัวลดลงจากเริ่มต้น 3-5%
    b. Urine osmolarity เปลี่ยนแปลงน้อยกว่า 10% *หรือ* 30 mOsm/kg ติดต่อกัน 2 ครั้ง (3 samples, ส่วนต่าง 2 ครั้ง)
    c. Serum osmolarity > 288 mOsm/kg
    d. Serum Na > 145 mmol/L
4. ฉีด DDAVP 1 mcg (0.25 mL) IV หรือ พ่น nasal solution 10 mcg (0.1 mL)
5. เจาะ serum osmolarity และ ส่ง urine osmolarity ต่อไปอีก 1-2 hrs หลังให้ DDAVP
   (optional)

Indirect Criteria of Miller-Moses Test

		Urine Osmolarity	
		Before DDAVP	**After DDAVP**
AVP deficiency	Complete	< 300	> 50%
	Partial	300-800	9-50%
AVP resistance	Complete	< 300	< 9%
	Partial	< 300-500	9-50%
Polydipsia		> 500	< 9%

Interpretation of Water Deprivation

Time (hour)	Urine Osm.	Serum Osm.	BW (kg)
0	135	300	61.4
1	141		61.2
2	146	305	60.6
3	270		60.6

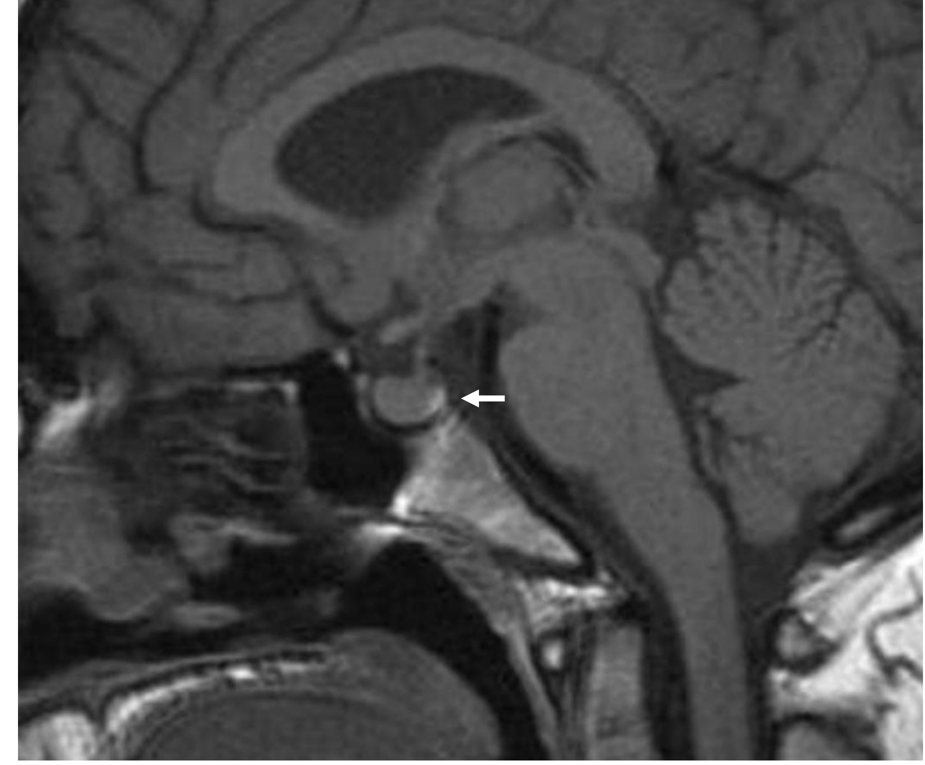
$(270-146)/146 \times 100 = 85\%$

Etiology of AVP Deficiency and AVP Resistance

	AVP Deficiency	AVP Resistance
Congenital	• AVP gene mutations (AD or AR) • Wolfram syndrome (AR) **DIDMOAD = DI, DM, optic atrophy, deafness**	• AVPR2 gene mutations (X-linked recessive) • AQP2 gene mutations (AR>AD)
Acquired	• Trauma • Tumors • Ischemic encephalopathy • Infiltrative • Autoimmune • Infectious diseases • Idiopathic	• Drug-induced • Hypercalcemia • Renal diseases • Infiltrating lesions of the kidney • Sickle cell disease or trait

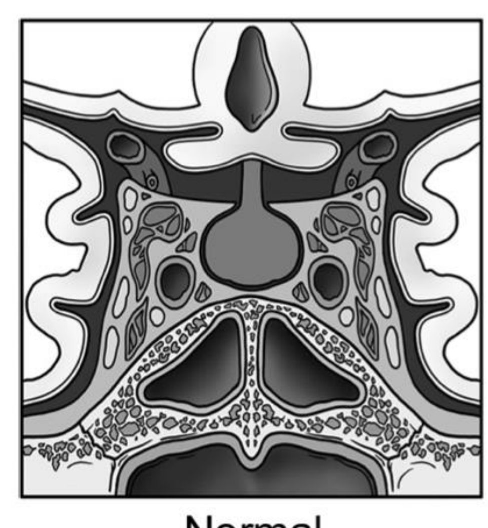
Imaging

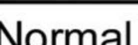
- Posterior bright spot
  - Appear bright in T1W
  - Present in ~80% of normal subjects.
  - Patients with AVP deficiency may have a persistent bright spot
- Stalk lesions
- Hypothalamic lesions



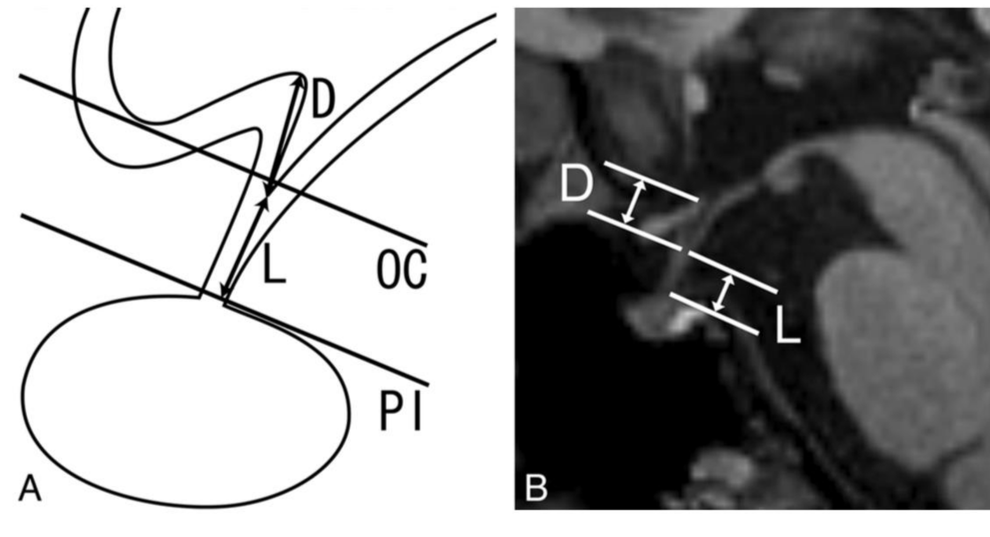
Williams textbook of endocrinology 14th edition

Stalk Measurement





AP



Lateral View

Consider stalk thickening

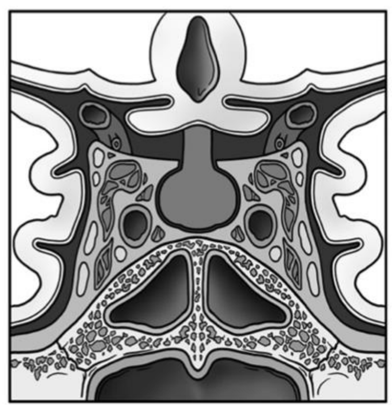
> 4 mm at optic chiasm

> 3 mm at pituitary insertion

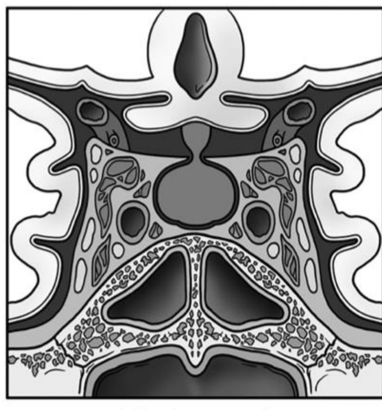
Image from Williams textbook of endocrinology 14th edition
Turcu AF et al. J Clin Endocrinol Metab 2013. PMID: 23533231.

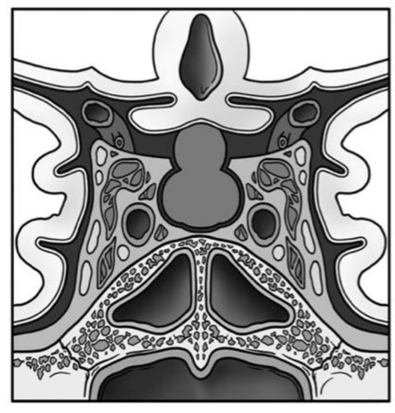
Diseases Associated with Enlarged Stalk

- Germ cell tumor
- Craniopharyngioma
- Metastatic cancer
- Hypophysitis
  - Lymphocytic infundibulohypophysitis
  - Langerhans & non-Langerhans cell histiocytosis
  - IgG4-related
  - Immune-checkpoint inhibitors-related
  - Infection



Uniform thickening


V-shaped


Round/Diamond

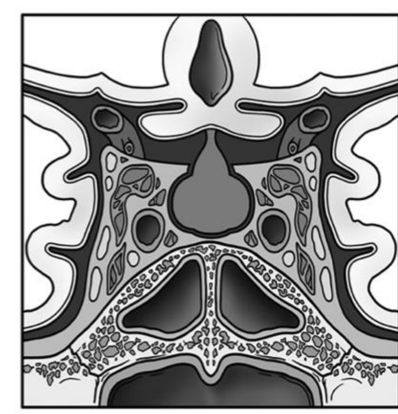
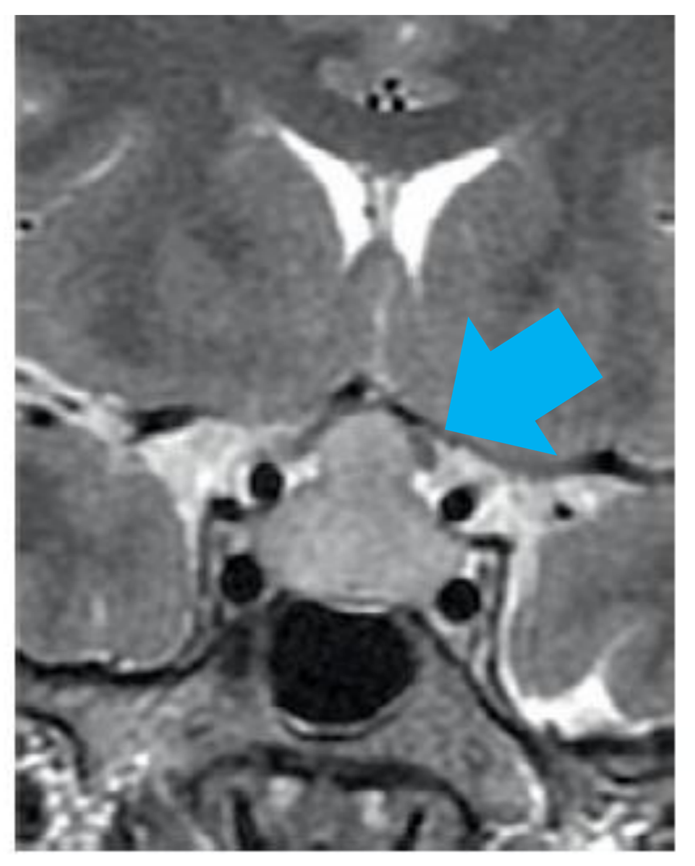
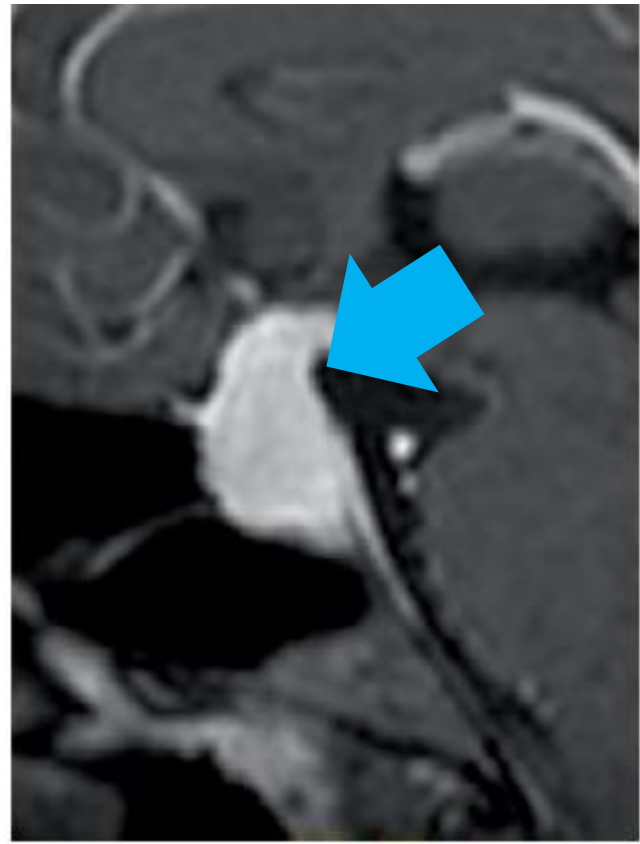

Pyramid

Image from Williams textbook of endocrinology 14th edition

Hypophysitis





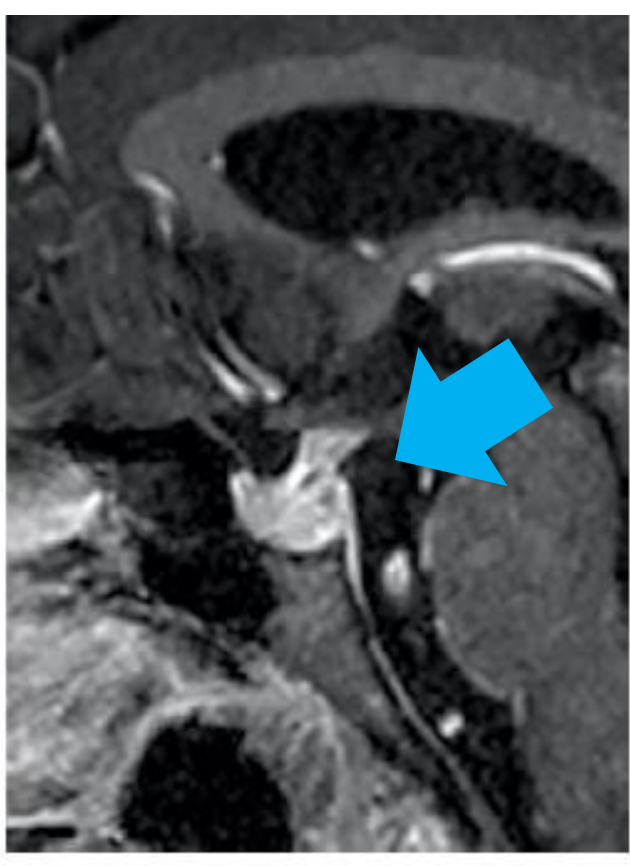


Image from Miquel L et al. Nat Rev Endocrinol 2025. PMID: 41310157.

Hypopituitarism: Treatment

- Specific: Depending on the etiology
- Supportive
  - Hormonal replacement, if indicated
    - Central adrenal insufficiency
      - Glucocorticoid replacement (NO need for mineralocorticoid replacement)
      - Monitor clinical symptoms
    - Central hypothyroidism
      - LT4 and monitor FT4 (keep upper half of the reference range)
    - AVP deficiency
      - Desmopressin
      - Monitor clinical symptoms and Na

nature reviews endocrinology https://doi.org/10.1038/s41574-025-01200-1

Review article

An update on hypophysitis

Lea Miquel[1,2], Benoit Testud[2,3], Frederique Albarel[2,4], Romain Appay[2,5], Thomas Graillon[2,6], Thomas Cuny[2,4], Henry Dufour[2,6], Mikael Ebbo[2,7], Thierry Brue[2,4], Pierre-André Jarrot[1,2], Nicolas Schleinitz[2,7] & Frederic Castinetti[2,4]

Functioning Pituitary Tumors

- ACTH-secreting pituitary adenoma (AKA Cushing’s disease)
- Acromegaly
- TSHoma
- Prolactinoma

Hypertension

Screening Features Suggesting Secondary Hypertension

Does the patient have any of the following conditions associated with secondary HTN?

- Drug-resistant/induced HTN
- Abrupt onset of HTN
- Onset of HTN at <30 y
- Exacerbation of previously controlled HTN
- Disproportionate TOD for degree of HTN
- Accelerated/malignant HTN
- Onset of diastolic HTN in older adults (age ≥65 y)
- Unprovoked or excessive hypokalemia
- Insomnia or daytime sleepiness
- Concomitant adrenal nodule
- History of early-onset stroke
- Family history of primary aldosteronism

YES

Screen for primary aldosteronism and other secondary forms of HTN — 1

Image from Jones DW et al. AHA ACC Guideline. Hypertension 2025. PMID: 40811516.

ESC 2024: Recommended Screening Tests

Primary Aldosteronism

- Aldosterone, renin, ARR

Pheochromocytoma/Paraganglioma

- Metanephrines
  - Plasma or 24-h urine

Cushing's Syndrome

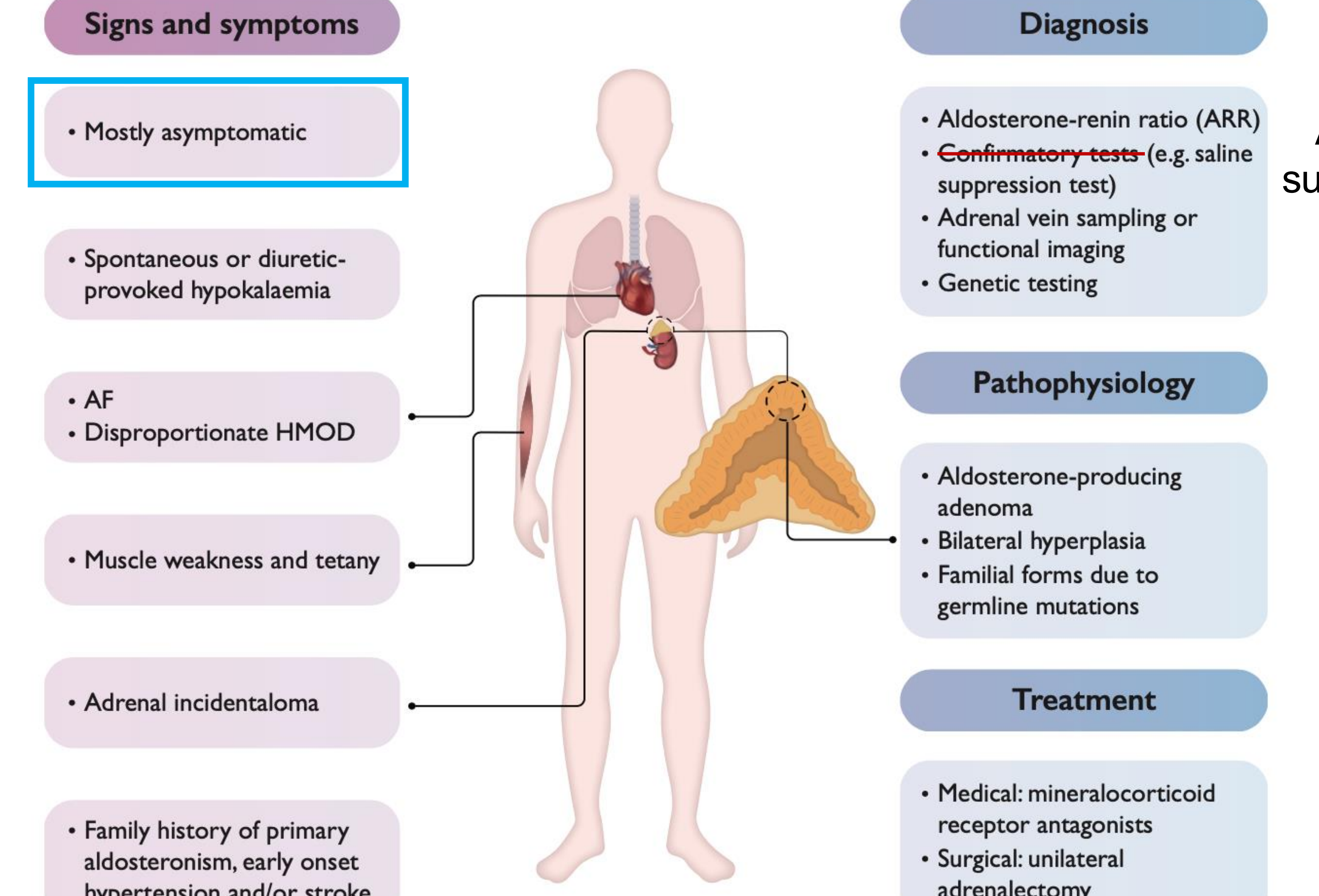
- 24-h urinary free cortisol
- Low-dose dexamethasone suppression test
- Late night salivary cortisol

Other causes of secondary hypertension include thyroid disorders (hyper- or hypothyroidism), hyperparathyroidism, renovascular hypertension, renal parenchymal disease, and coarctation of the aorta.

ARR, aldosterone-to-renin ratio

Adapted from McEvoy JW et al. Eur Heart J 2024. PMID: 39210715.

Primary Aldosteronism

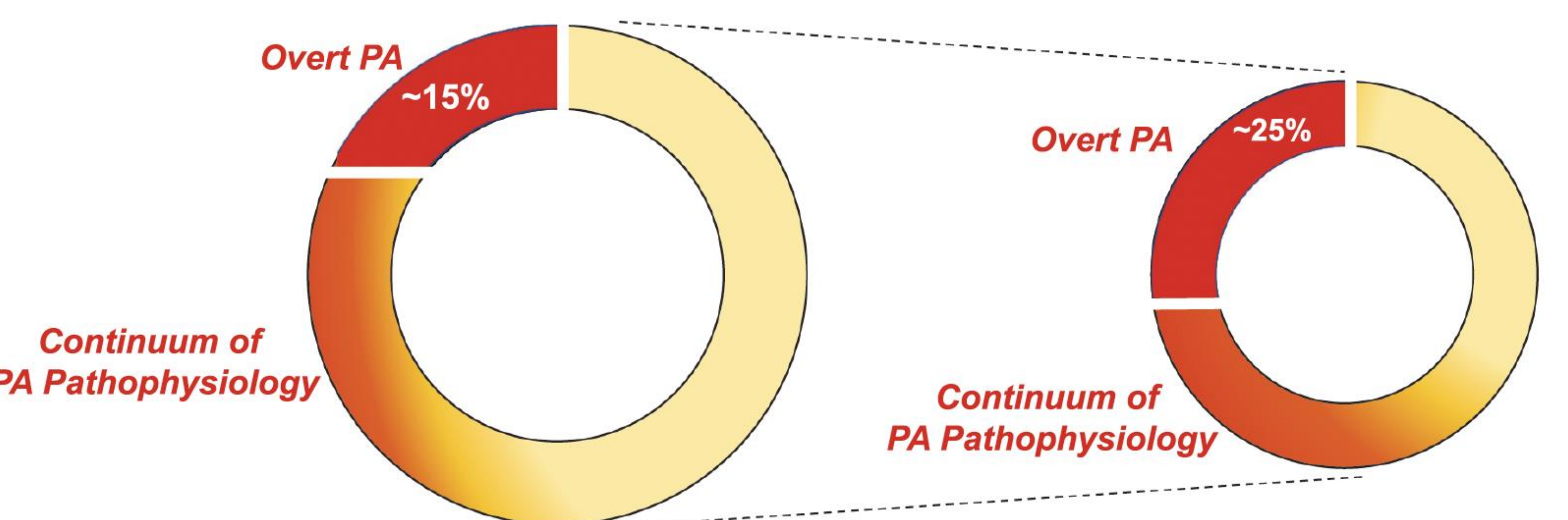


Aldosterone suppression test

Image adapted from McEvoy JW et al. Eur Heart J 2024. PMID: 39210715.

Primary Aldosteronism: Common Causes of Secondary Hypertension

Resistant Hypertension

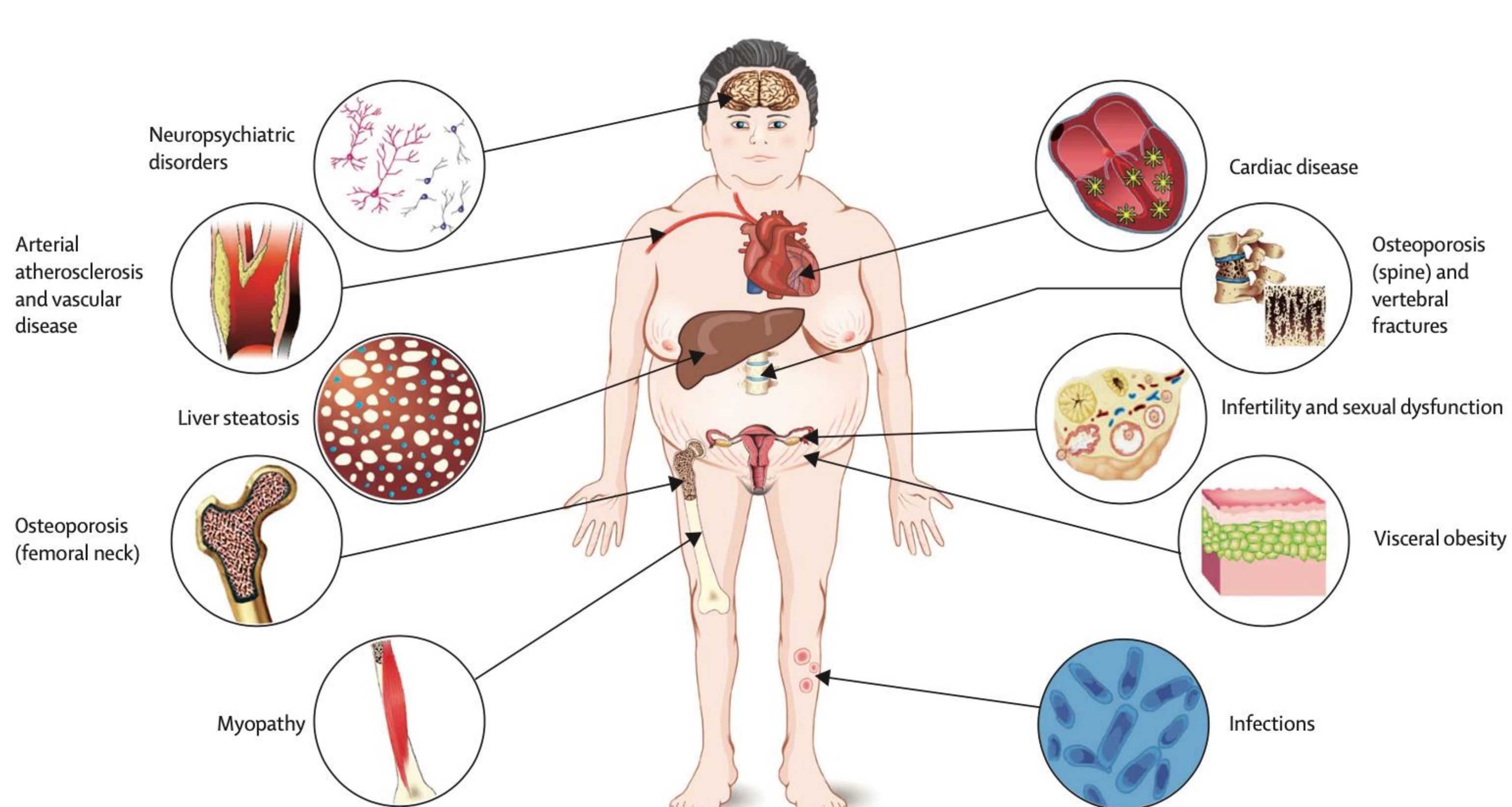


Other groups with high prevalence, e.g.,

- Hypertension with hypoK
- Hypertension with AF
- Young adults (<40 YO)
- BP ≥160/100 mmHg (≥ Grade 2 hypertension)

Image from Vaidya A et al. Am J Hypertens 2022. 1. Brown JM. Ann Intern Med 2020; 2. Sinclair AM et al. Arch Intern Med 1987; 3. Vasan RS et al. N Engl J Med 2004; 4. Markou A et al. J Clin Endocrinol Metab 2013; 4. Baudrand R et al. Hypertension 2017; 5. Inoue K et al. Hypertension 2020; 6. Monticone S et al. J Am Coll Cardiol 2017; 7. Baudrand R et al. J Clin Endocrinol Metab 2016.

Cushing's Syndrome



Appearance: Cushing's
Biochemical profile: Central
Adrenal insufficiency

Etiology

- Exogenous Cushing's
- Endogenous Cushing's
  - ACTH-dependent
    - ACTH-secreting pituitary adenoma
    - Ectopic ACTH
  - ACTH-independent

History taking - Onset, hypertension (or worsening hypertension), hyperglycemia/DM, weight gain, secondary amenorrhea, infection, fracture, thromboembolism, muscle weakness, psychiatric disorders

Image from Pivonello R et al. Lancet Diabetes Endocrinol 2016. PMID: 27177728.

Pheochromocytoma: Signs and Symptoms of Catecholamine Excess

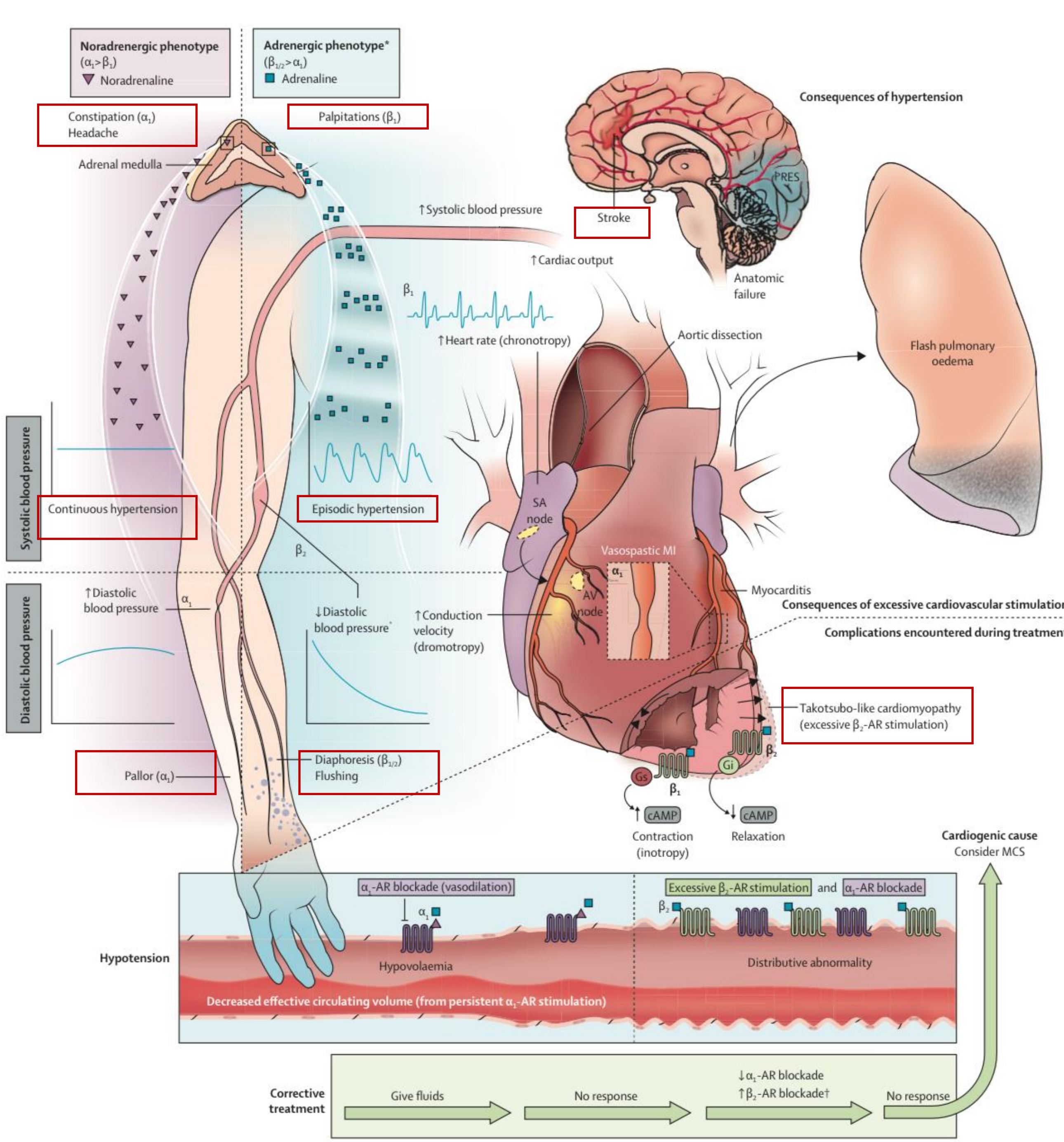
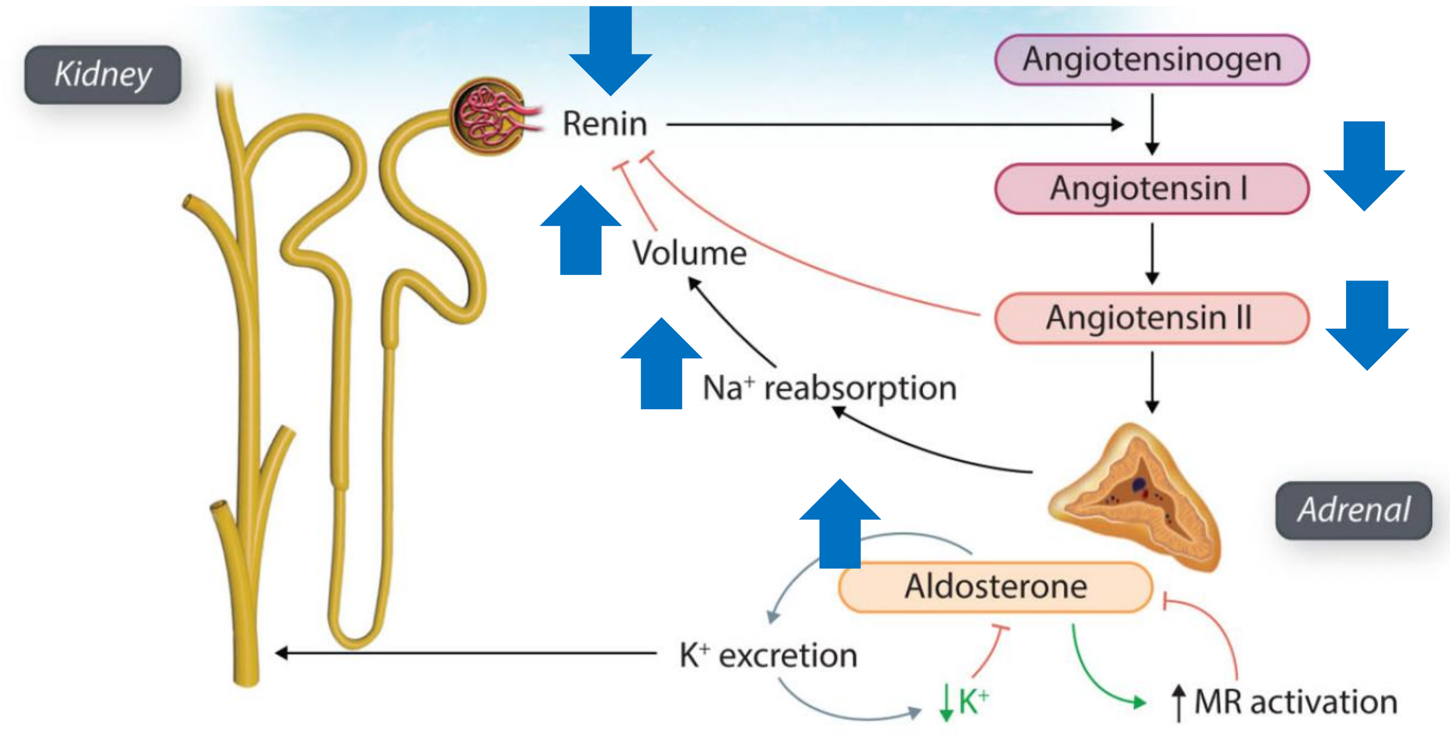


Image from Eisenhofer G et al. Endocr Rev 2023. PMID: 36996131.

The Renin-angiotensin-aldosterone System



Assessing Aldosterone/Renin In Hypertension

- **↑ Aldosterone, ↓Renin**
  - **Primary Aldosteronism**
    - Aldosterone-producing lesion in one or both adrenal glands
- **↑ Aldosterone, ↑Renin**
  - Secondary Aldosteronism
    - Pheochromocytoma, renal artery stenosis, reninoma (renin-producing tumor)
- **↓ Aldosterone, ↓Renin**
  - Something else is causing MR activation
    - e.g., Cushing's syndrome, CAH

MR, mineralocorticoid receptor; CAH, congenital adrenal hyperplasia

Image from Parksook WW, Williams GH. Cardiovasc Res 2023. PMID: 35388416.

Primary Aldosteronism

- Hallmark biochemical diagnosis of primary aldosteronism
  - Renin suppression

Plasma renin activity (PRA) ≤1 ng/mL/h OR
Direct renin concentration (DRC) ≤8.2 mU/L

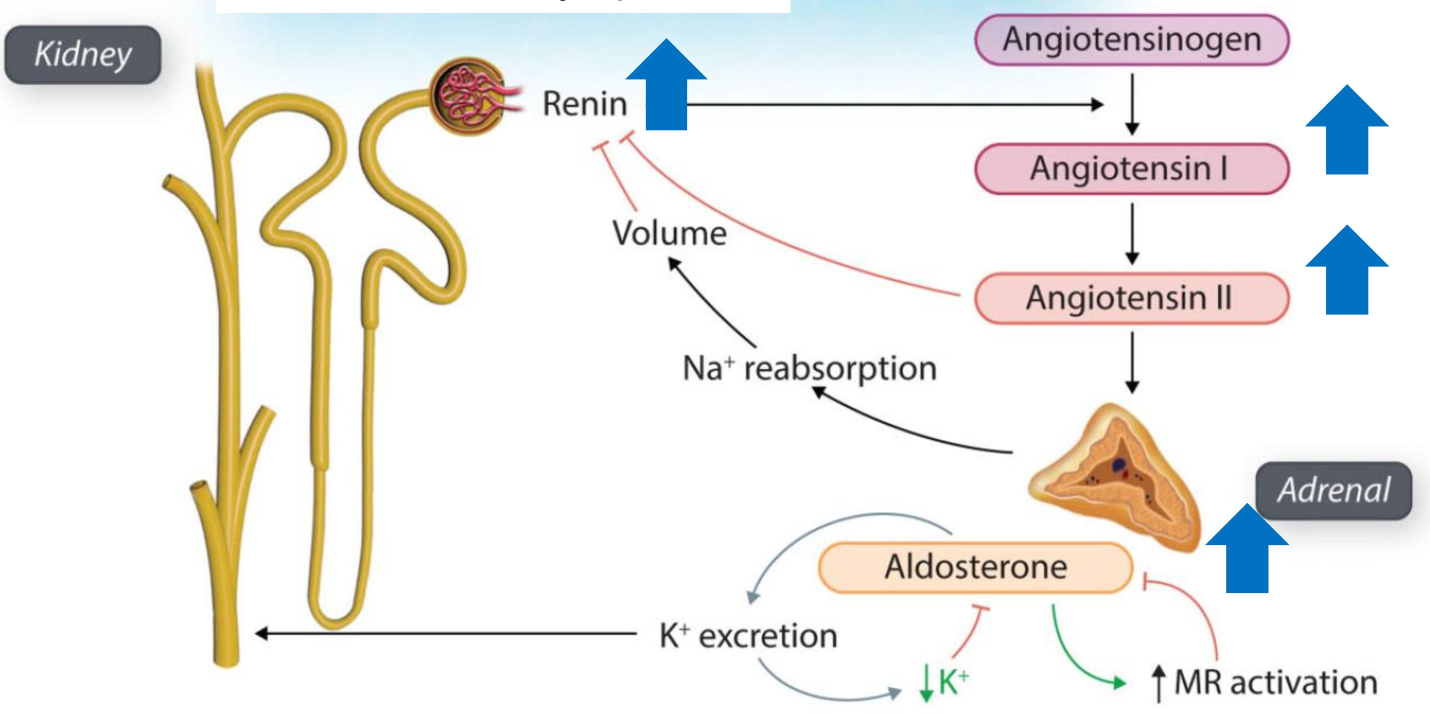
AND

- Inappropriate/dysregulated/non-suppressible aldosterone production

Plasma aldosterone concentration (PAC) ≥10 ng/dL

The Renin-angiotensin-aldosterone System

Volume depletion, ↓ renal blood flow, and sympathetic



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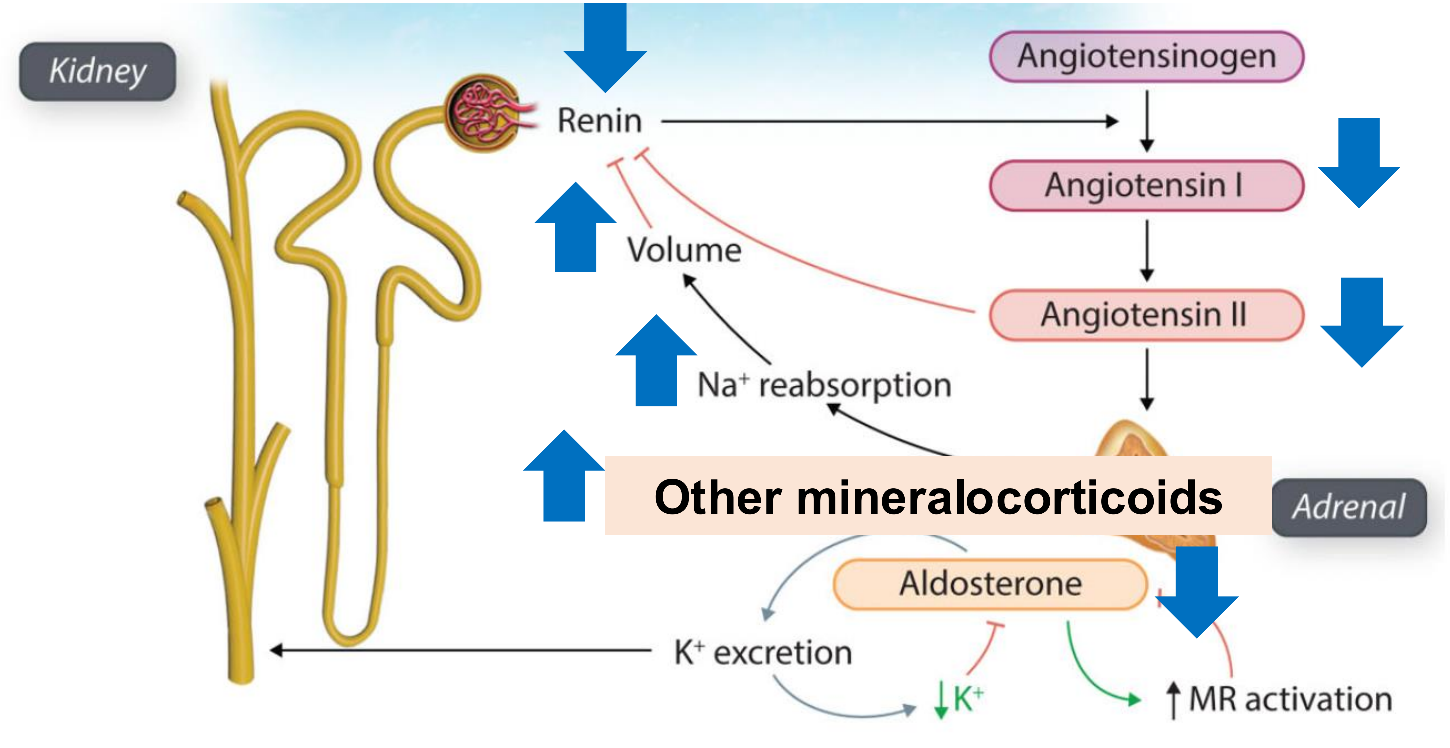
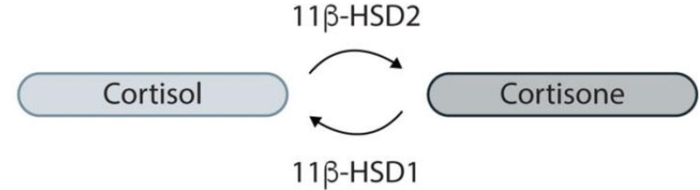
The Renin-angiotensin-aldosterone System





Cortisol can bind with MR in the presence of excess cortisol

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Image from Parksook WW, Williams GH. Cardiovasc Res 2023. PMID: 35388416.

Wrap up

- Characteristics of individuals indicated to screen for secondary hypertension
- Adrenal causes needed to be screened
- Biochemical hallmarks in primary aldosteronism
- Interpreting aldosterone, renin in evaluating hypertension

A 50 YO Thai male with hypertension and hypokalemia

- Hypertension onset: 47 YO
- Lowest K = 2.7 mmol/L
- Cr = 1.0 mg/dL, eGFR = 81 mL/min/1.73 m^2, UACR = 16 mg/g Cr
- EKG: Sinus rhythm, no LVH
- Medications: Amlodipine 10 mg/day

- PAC (IA) = 24 ng/dL, PRA = 0.19 ng/mL/h, K = 3 mmol/L

PAC, plasma aldosterone concentration; PRA, plasma renin activity; IA, immunoassay; UACR, urine albumin-creatinine ratio

Primary Aldosteronism: Screening

SUPPRESSED Renin		HIGH Aldosterone		INCREASED Aldosterone-to-Renin Ratio
• PRA ≤1 ng/mL/h **OR** • DRC ≤8.2 mU/L	+	• Aldosterone (IA) ≥10 ng/dL **OR** • Aldosterone (LC-MS/MS) ≥7.5 ng/dL	+	• Aldosterone (IA)/PRA >20 ng/dL per ng/mL/h **OR** • Aldosterone (IA)/DRC >70 pmol/L per mU/mL

PRA, plasma renin activity; DRC, direct renin concentration;
IA, immunoassay; LC-MS/MS, liquid chromatography mass spectrometry

Adler GK et al. J Clin Endocrinol Metab 2025. PMID: 40658480.

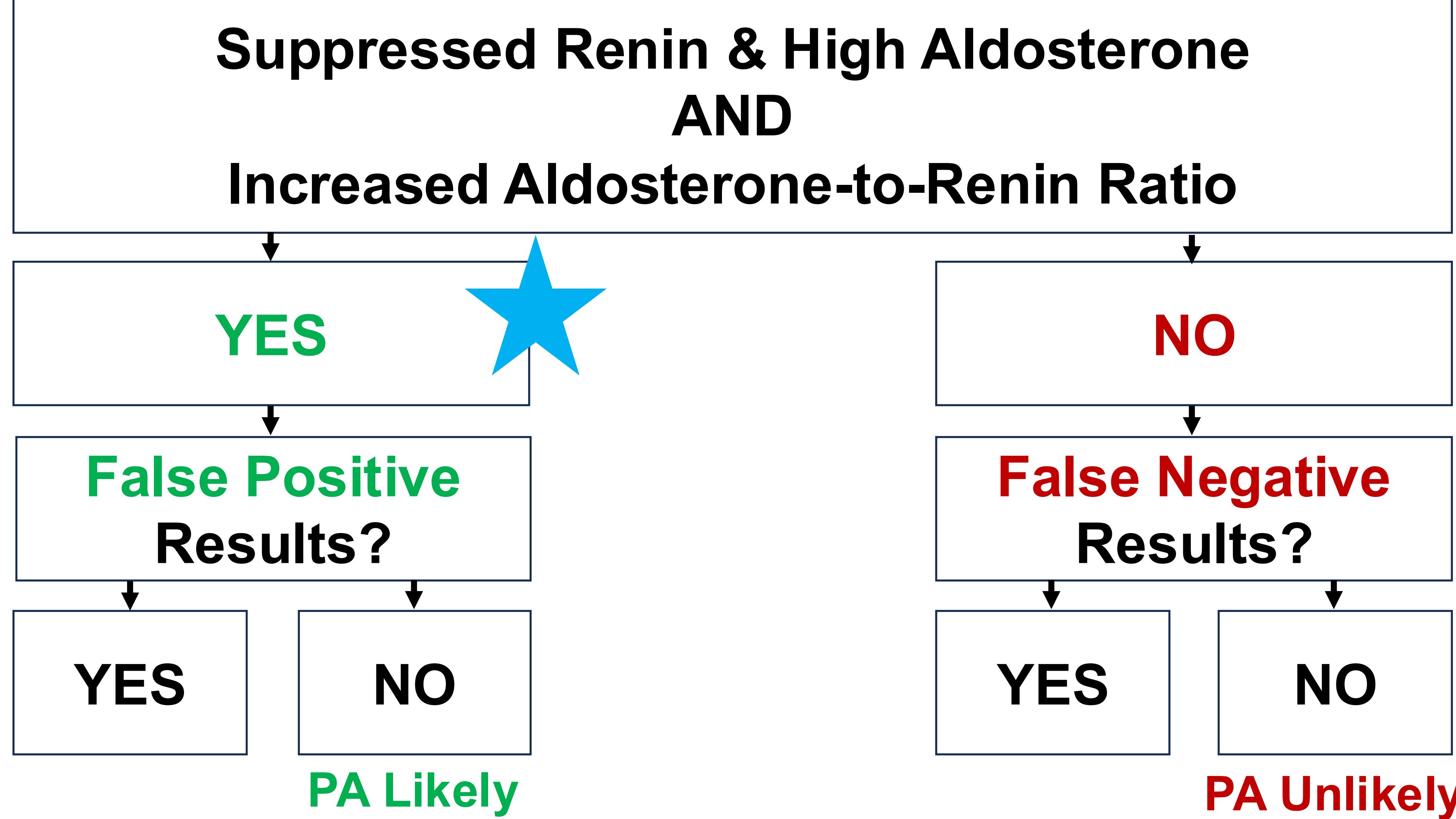
A 50 YO Thai male with hypertension and hypokalemia

- Medications: Amlodipine 10 mg/day

- **PAC (IA) = 24 ng/dL, PRA = 0.19 ng/mL/h, K = 3 mmol/L**
- **ARR = 126 ng/dL per ng/mL/h**

PAC, plasma aldosterone concentration; PRA, plasma renin activity; IA, immunoassay; UACR, urine albumin-creatinine ratio

Interpreting Screening Results



Adapted from Adler GK et al. J Clin Endocrinol Metab 2025. PMID: 40658480.

Interpreting Screening Results

- **False-Positives?**
  - Conditions that decreased renin, e.g., beta-blockers or NSAIDs
    - **YES** → Consider withdrawing medication & retest
    - **NO** → **PA Likely**
- **False-Negatives?**
  - Hypokalemia while testing
  - Drugs that decrease aldosterone or increase renin
  - Intraindividual variability of aldosterone
    - High pretest probability of PA & low renin with aldosterone 5-10 ng/dL

Adapted from Adler GK et al. J Clin Endocrinol Metab 2025. PMID: 40658480.

Factors Affecting the Interpretation of the Screening Test

Factors	Ideal condition
Medication	Withdraw antihypertensive medications that affect ARR
Potassium levels	Normokalemia
Posture	Upright
Sodium intake	Liberalized sodium diet
Timing	Mid morning, up for at least 2 hours, seated for 5-15 minutes

Funder JW et al. J Clin Endocrinol Metab 2016. PMID: 26934393

Management of Interfering Antihypertensive Medication During Primary Aldosteronism Screening

	Management strategy	Medication to withdraw	Timeline of withdrawal	Replacement antihypertensive agents
1	No medication withdrawal	None	–	–
2	Minimal medication withdrawal	Stop MRAs and ENaC inhibitors (amiloride, triamterene)	4 weeks before testing	Hydralazine[a] α_1-adrenergic blockers Non-dihydropyridine CCBs Moxonidine
		Stop β-adrenergic blockers and centrally acting α_2-agonists (clonidine, α-methyldopa)	2 weeks before testing	
3	Ideal full medication withdrawal	Stop MRAs, ENaC inhibitors (amiloride, triamterene), and other diuretics	4 weeks before testing	Hydralazine[a] α_1-adrenergic blockers Non-dihydropyridine CCBs Moxonidine
		β-adrenergic blockers ACE inhibitors ARBs Dihydropyridine CCBs Centrally acting α_2-agonists (clonidine, α-methyldopa) SGLT2 inhibitors	2 weeks before testing	

If results are in doubt
→ either repeat screening with **2** OR **3**

If results are in doubt
→ Repeat screening with **3**

Image from Adler GK et al. J Clin Endocrinol Metab 2025. PMID: 40658480.

Drugs and Conditions and their effects on aldosterone, renin, ARR.

Factor	Effect on plasma aldosterone levels	Effect on renin levels	Effect on ARR
Serum potassium status			
Hypokalaemia	↓	→↑	↓ **(FN)**
Potassium loading	↑	→↓	↑
Sodium restriction	↑	↑↑	↓ **(FN)**
Sodium loading	↓	↓↓	↑ **(FP)**
Drugs			
Beta-adrenergic blockers	↓	↓↓	↑ **(FP)**
Calcium channel blockers (DHPs)	→↓	→↑	→↓ (**FN** with short-acting DHPs)
ACE inhibitors	↓	↑↑	↓ **(FN)**
ARBs	↓	↑↑	↓ **(FN)**
Potassium-sparing diuretics	↑	↑↑	↓ **(FN)**
Potassium-wasting diuretics	→↑	↑↑	↓ **(FN)**
Alpha-2 agonists (clonidine, methyldopa)	↓	↓↓	↑ **(FP)**
NSAIDs	↓	↓↓	↑ **(FP)**
Steroids	↓	→↓	↑ **(FP)**
Contraceptive agents (drospirenone)	↑	↑	↑ **(FP)**

↑, raised; ↓, lowered; →, no effect; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARR, aldosterone-to-renin ratio; DHPs, dihydropyridines; FN, false negative; FP, false positive; NSAID, non-steroidal anti-inflammatory drug.

FN: Hypokalaemia; Sodium restriction

FP: Beta-adrenergic blockers

FN: ACE inhibitors; ARBs; Potassium-sparing diuretics; Potassium-wasting diuretics

FP: NSAIDs

ARR, aldosterone-to-renin ratio

Image from McEvoy JW et al. Eur Heart J 2024. PMID: 39210715.

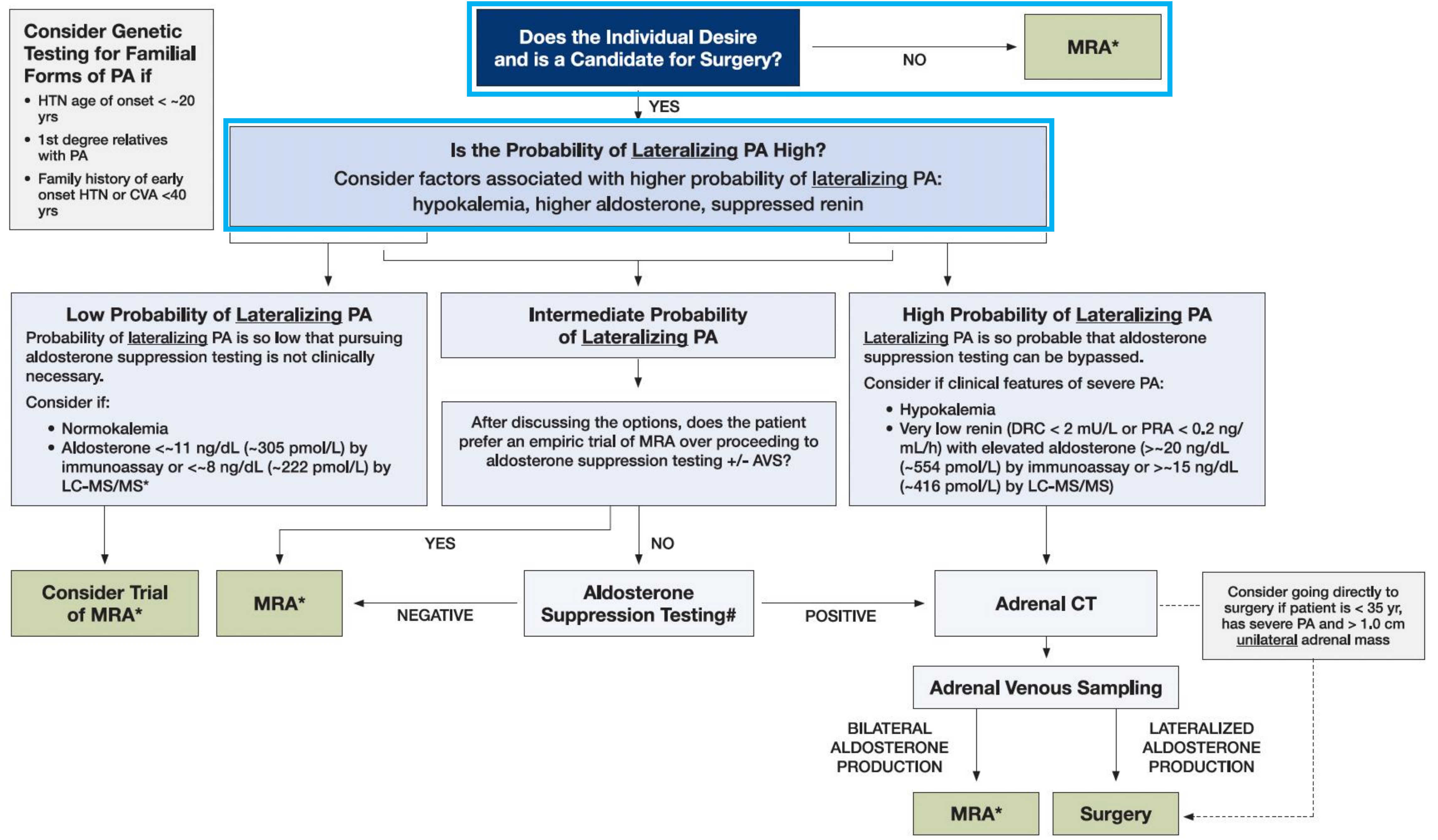
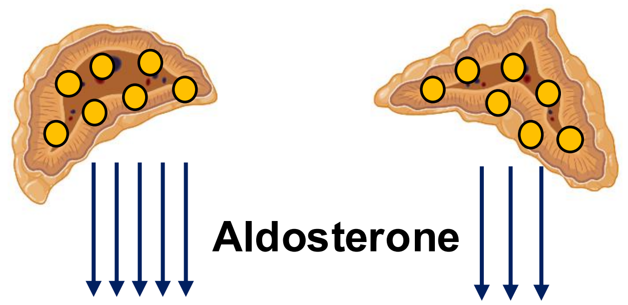


Figure from Adler GK et al. J Clin Endocrinol Metab 2025. PMID: 40658480.

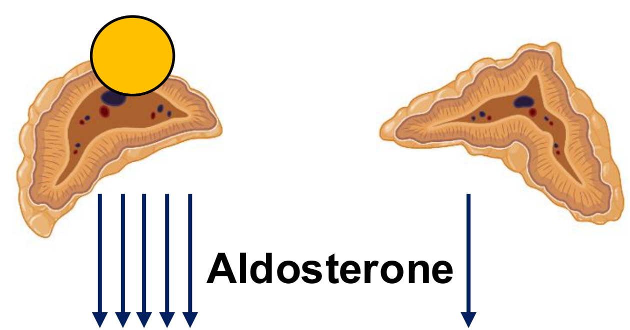
PA: Subtyping

- **Gold standard: Adrenal venous sampling (AVS)**
- To classify between
  - **Lateralizing (known as unilateral)**
  - **Non-lateralizing or Bilateral PA**

Non-Lateralizing Disease



Lateralizing Disease



Prevalence

Severity

↑ BP, aldosterone, ARR
↓ Serum K levels, renin

APA, aldosterone producing adenoma; APMs, aldosterone-producing micronodules

Image created with Biorender

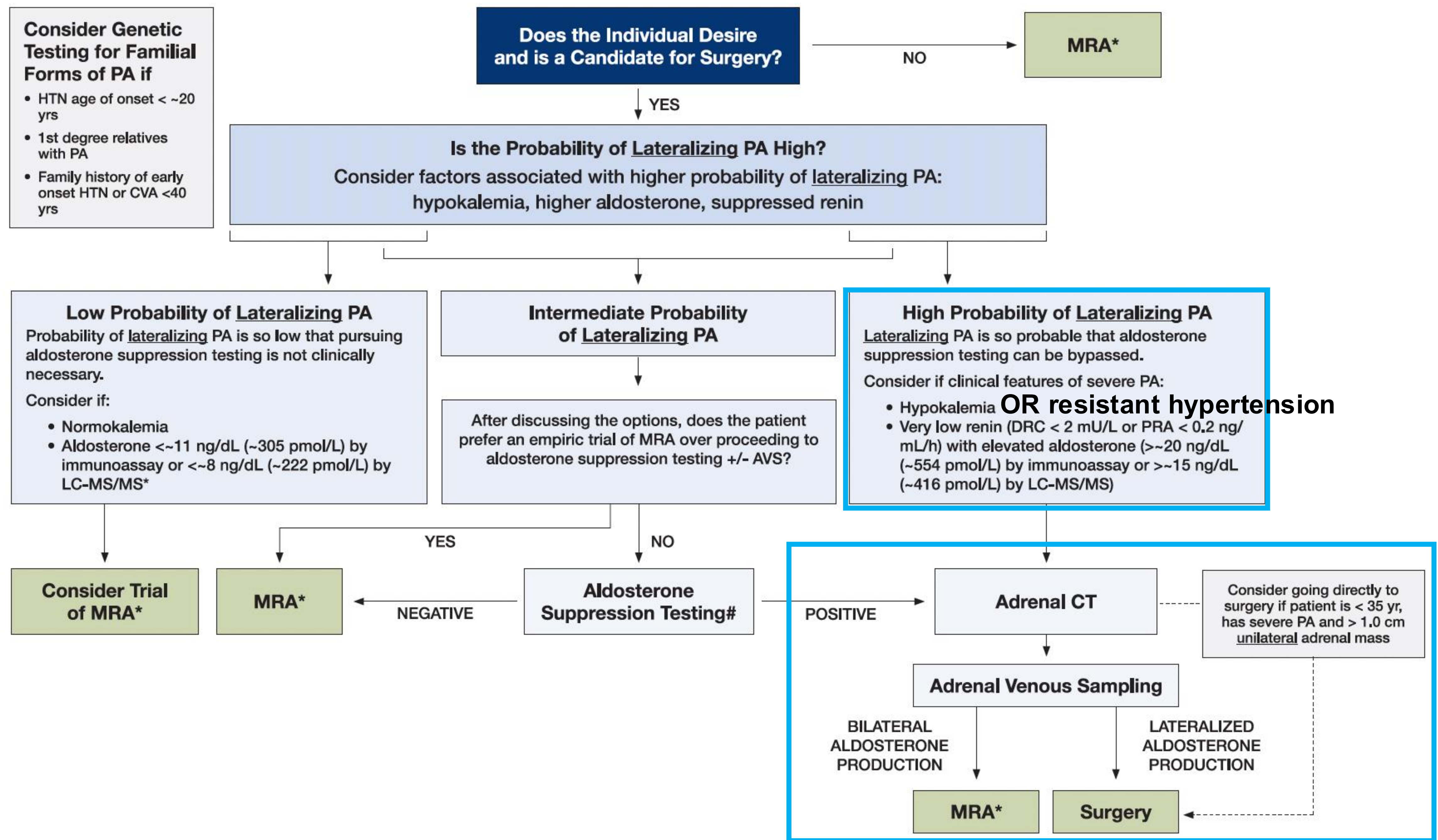


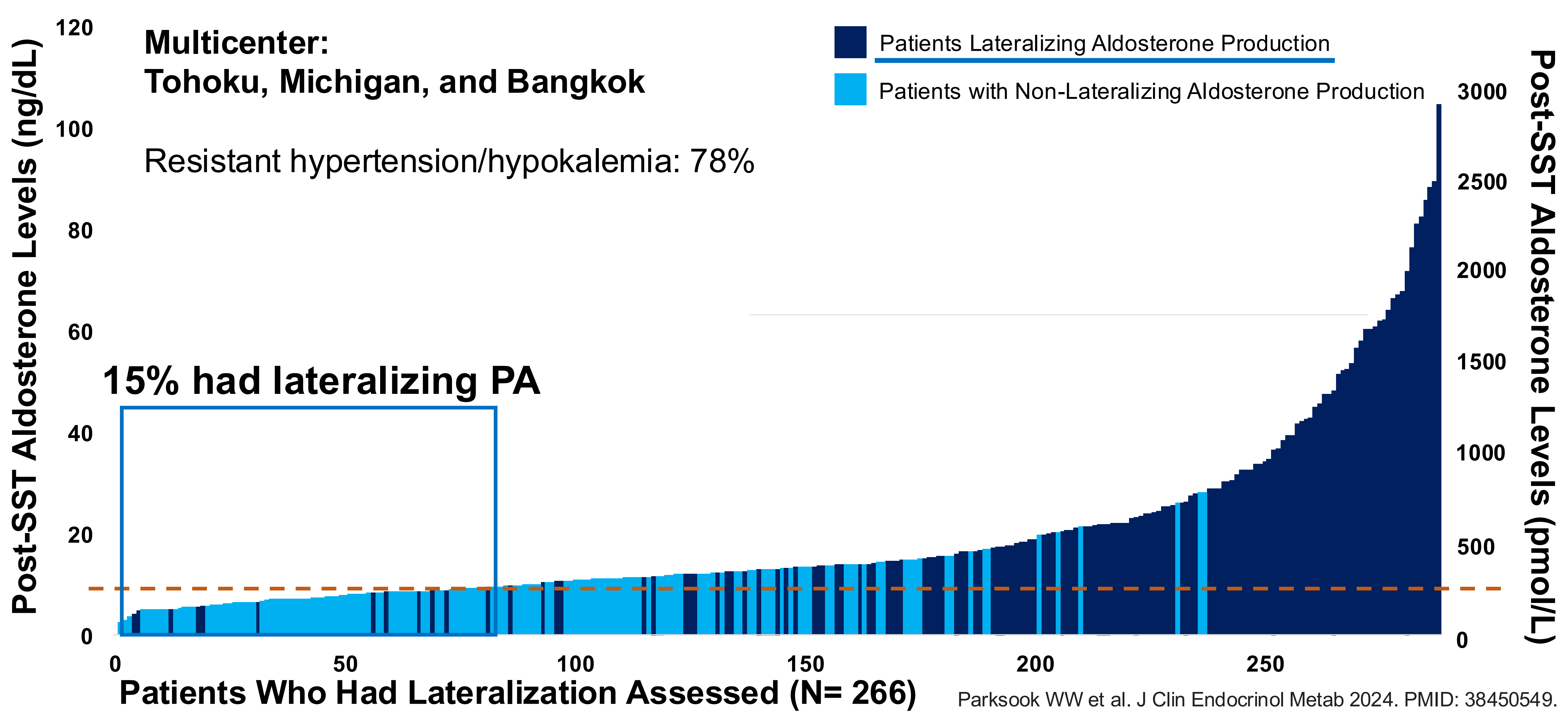
Figure from Adler GK et al. J Clin Endocrinol Metab 2025. PMID: 40658480.

Aldosterone Suppression Testing

- e.g., saline suppression test, captopril challenge test, etc.
- The Endocrine Society Guideline 2016 recommended performing these tests in patients with positive ARR to **CONFIRM** or **EXCLUDE** the diagnosis.
  - **EXCEPT** in the settings of spontaneous hypokalemia, renin below detection levels, and aldosterone levels >20 ng/dL

Funder JW et al. J Clin Endocrinol Metab 2016. PMID: 26934393

Aldosterone suppression testing could falsely exclude patients with lateralizing PA.



Parksook WW et al. J Clin Endocrinol Metab 2024. PMID: 38450549.

❌ **Aldosterone suppression test** is **NOT recommended** due to the risk of **FN** → miss opportunity for curative treatment

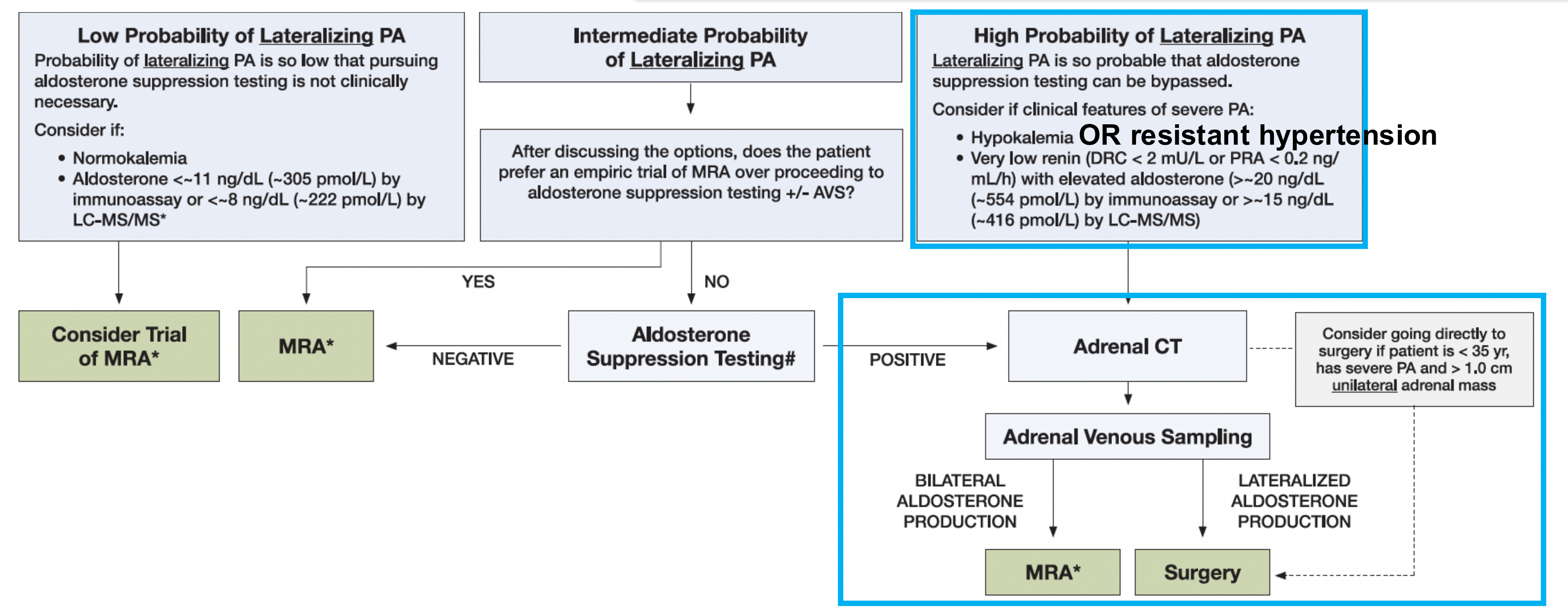
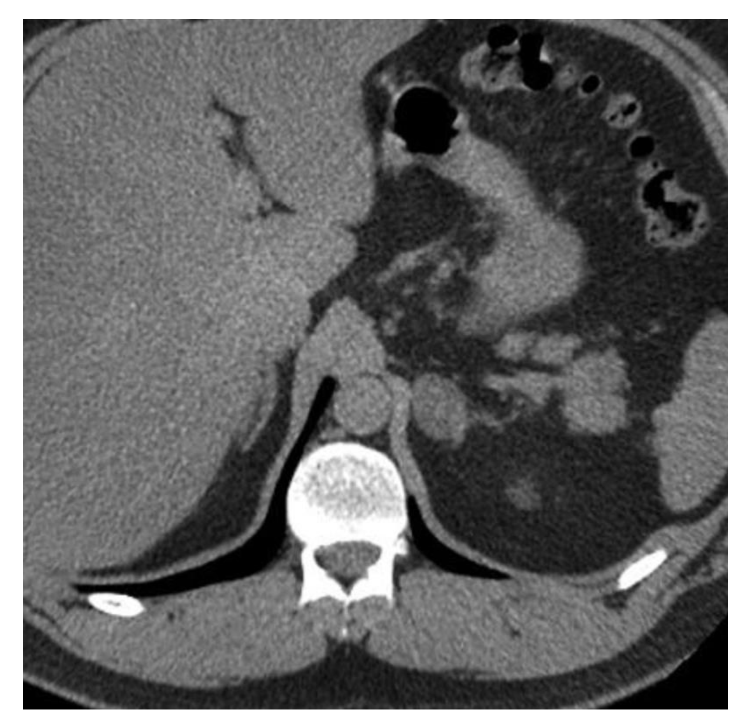


Figure from Adler GK et al. J Clin Endocrinol Metab 2025. PMID: 40658480.

30 YO patient, hypertension & hypoK
PAC = 50 ng/dL, PRA 0.2 ng/mL/h



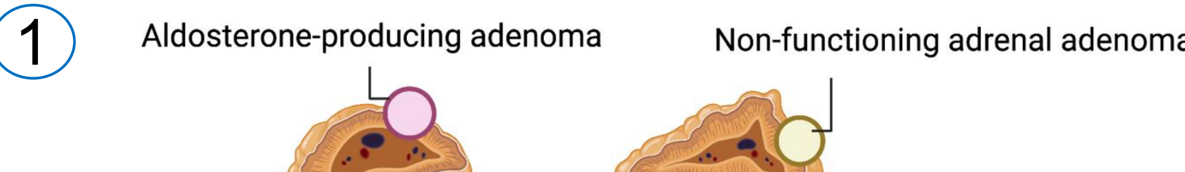
Unilateral left adrenal adenoma

May skip AVS and proceed to left unilateral adrenalectomy

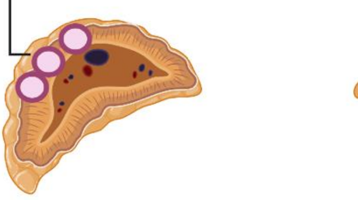
- In other settings, AVS is necessary or suggested if surgery is desired, e.g.,
  - A 0.6 cm adrenal nodule
  - Bilateral adrenal lesions
  - No visible adrenal abnormalities
  - Age >35 YO

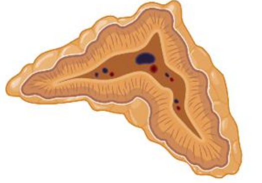
Cross-sectional Imaging (CT/MRI)

- Pros: convenient, more accessible than other tools in subtyping
- Limitations: the cross-sectional imaging **CANNOT**
    1. Differentiate aldosterone-producing foci from non-functioning adrenal masses OR
    2. Detect aldosterone-producing micronodules within the morphologically normal adrenal gland



Bilateral adrenal abnormalities on imaging





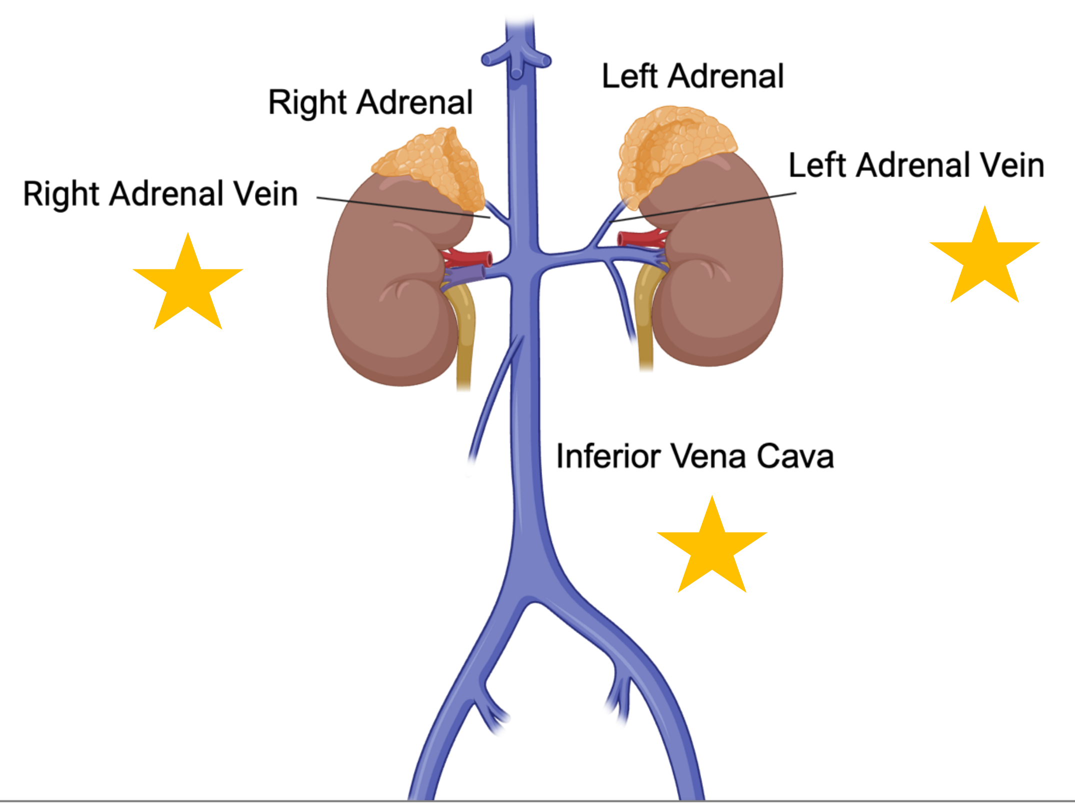
Morphologically normal adrenal gland on imaging

Created with Biorender

Adrenal Venous Sampling

Examples of widely used cutoffs to determine lateralizing PA

- Non-cosyntropin-stimulated: LI ≥2
- Cosyntropin-stimulated: LI ≥4



$$\text{Lateralization index} = \frac{\text{Aldosterone/Cortisol in the dominant adrenal vein}}{\text{Aldosterone/Cortisol in the non-dominant adrenal vein}}$$

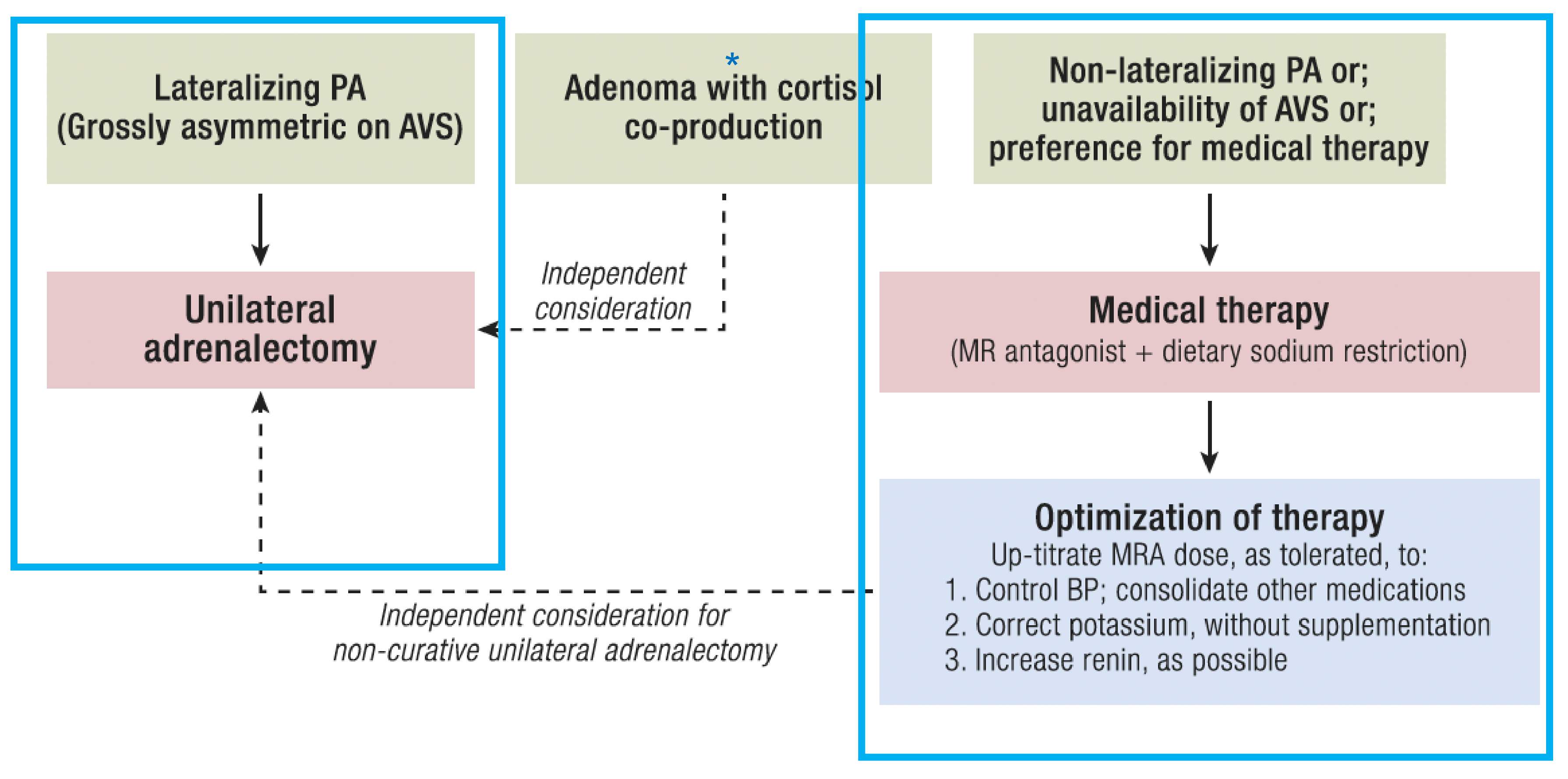
Image created with Biorender

A 50 YO Thai male with hypertension and hypokalemia

- CT: Unilateral left adrenal adenoma 0.6 cm
- 1 mg DST <1.0 mcg/dL

DST, dexamethasone suppression test; LI, lateralization index; AVS, adrenal venous sampling

Treatment in Primary Aldosteronism



Spironolactone

- Starting dose: 12.5-25 mg/day
  - 50 mg/day in severe PA
- Doses up to 200-300 mg/day

Salt intake <5 g/day

*Assess cortisol co-production in patients with adenoma: 1 mg DST

Endocrine Society 2025

Image from Hundemer GL et al. Endocr Rev 2023. PMID: 37439256.

Summary: Primary Aldosteronism

Who to Screen:

All hypertensives have an indication to screen

High-risk groups, e.g.,

- Hypertension with hypoK
- Hypertension with AF
- Young adults (<40 YO)
- Resistant hypertension
- BP ≥160/100 mmHg (≥ Grade 2 hypertension)

How to Screen:

Plasma aldosterone, Renin, K

Subtyping:

AVS (gold standard), CT

- AVS is unnecessary if undesired or unfit for surgery
- May skip AVS in young patients (<35 YO) with severe PA and have a unilateral adrenal mass (> 1 cm)

Treatment:

Adrenalectomy or MRA

Abbreviation: AVS, adrenal venous sampling; MRA, mineralocorticoid receptor antagonist

A 34 YO Thai female presented with hypertension 3 years PTA

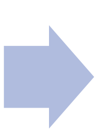
3 Years PTA

Diagnosed with hypertension

BP 160/100 mmHg

2 Years PTA

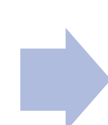
Diagnosed with diabetes mellitus



2 Months PTA

BP 200/105 mmHg

(no target organ damage)



Refer to KCMH

Current medications

- Amlodipine 10 mg/day
- Losartan 100 mg/day
- HCTZ 25 mg/day
- Metformin 1000 mg/day

A 34 YO Thai female presented with hypertension 3 years PTA

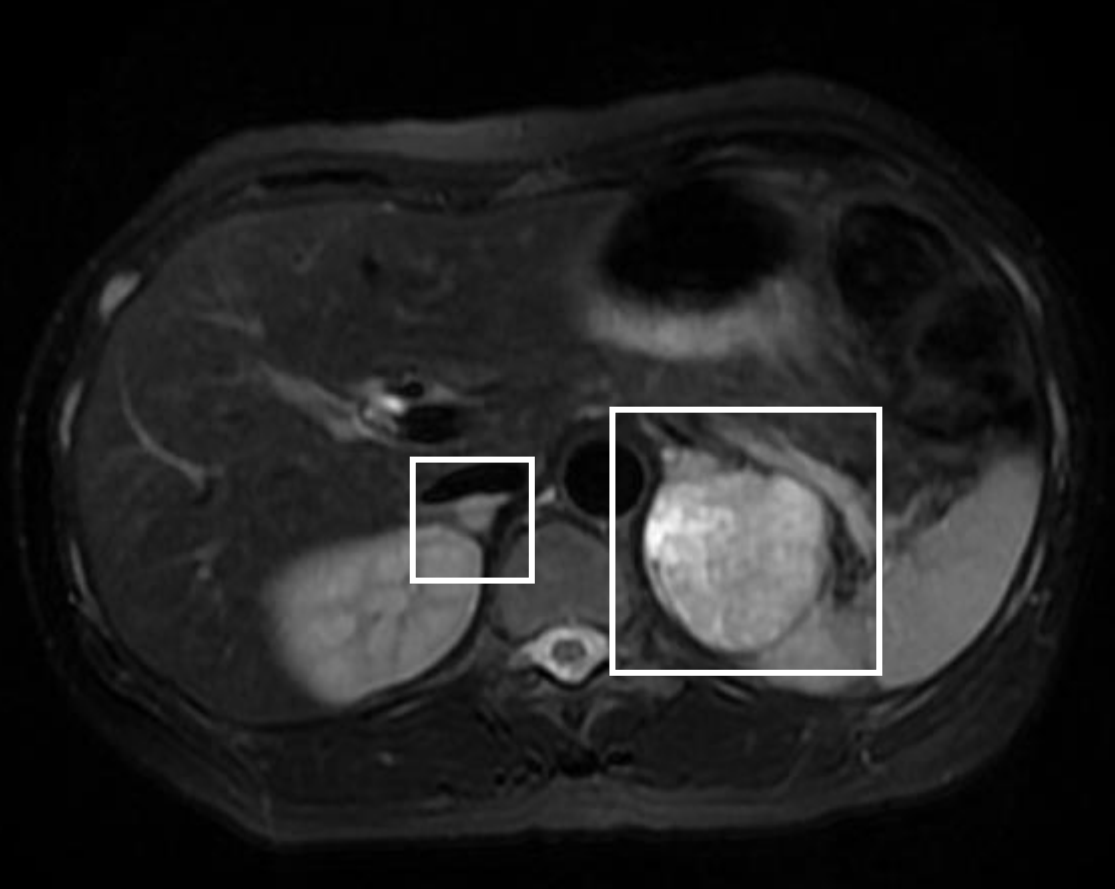
- One episode of hypokalemia (K = 3.4 mmol/L), weight gain 10 kg/3 years
- BP 170/100 mmHg, no orthostatic hypotension
- No cushingoid appearance
- Renal bruit +ve

Investigations: **Secondary aldosteronism**

- PAC 27.7 ng/dL, PRA 9.6 ng/mL/h, K = 3.8 mmol/L
- Cortisol after 1 mg DST = 1.1 mcg/dL **<1.8 mcg/dL**
- MRA renal arteries

DST, dexamethasone suppression testing; PAC, plasma aldosterone concentration; PRA, plasma renin activity

MRA Renal Arteries

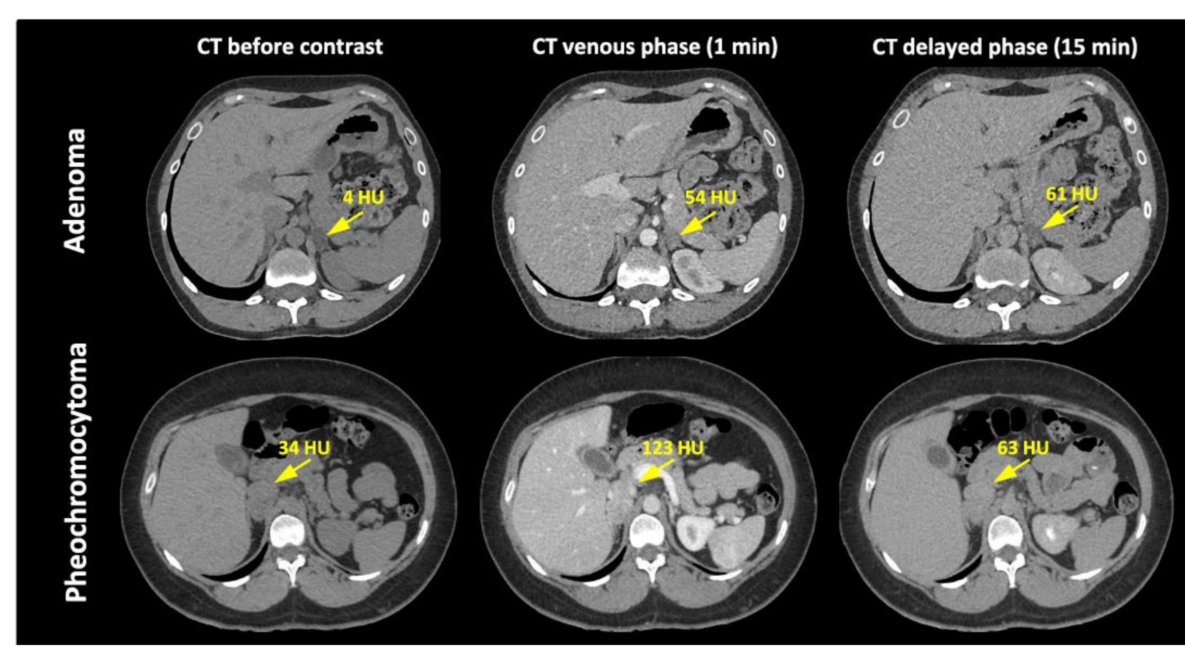


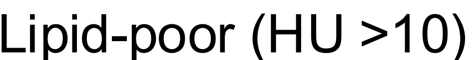
- A 5.9x4.7 cm well-defined left suprarenal mass with multiple small cysts and internal calcification or hemorrhage
- A 0.9x0.8 cm mild high signal intensity nodule on T1WI and hypersignal intensity on T2WI at right adrenal gland genu

What’s the next step in management?

Pheochromocytoma: Imaging

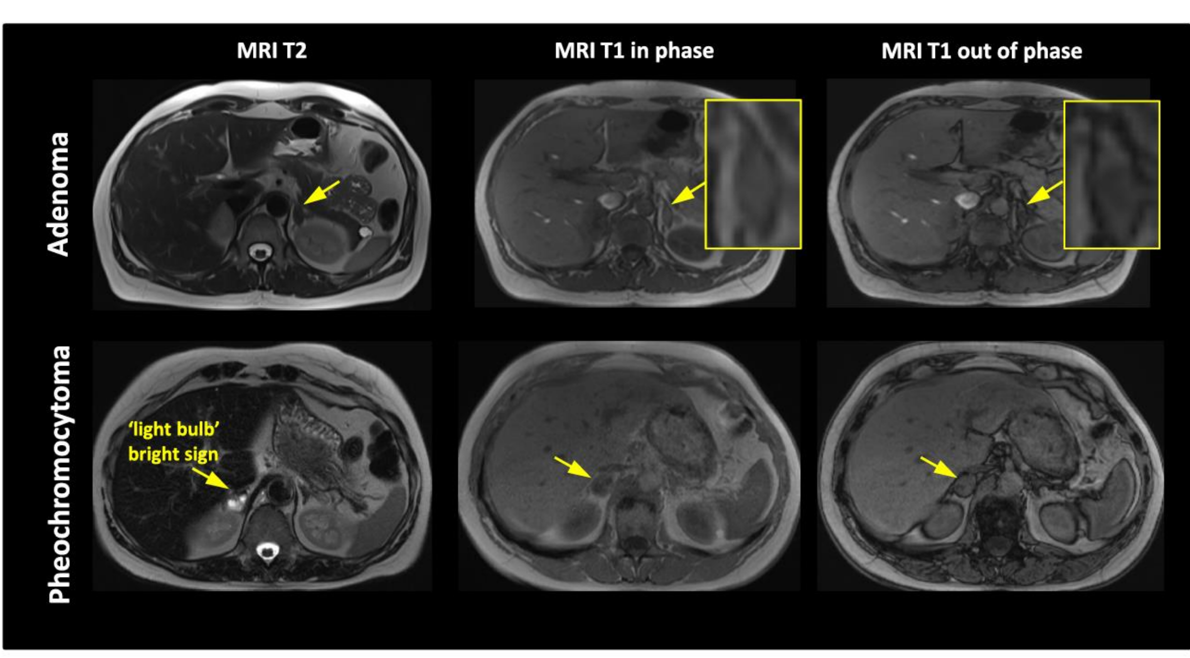
CT





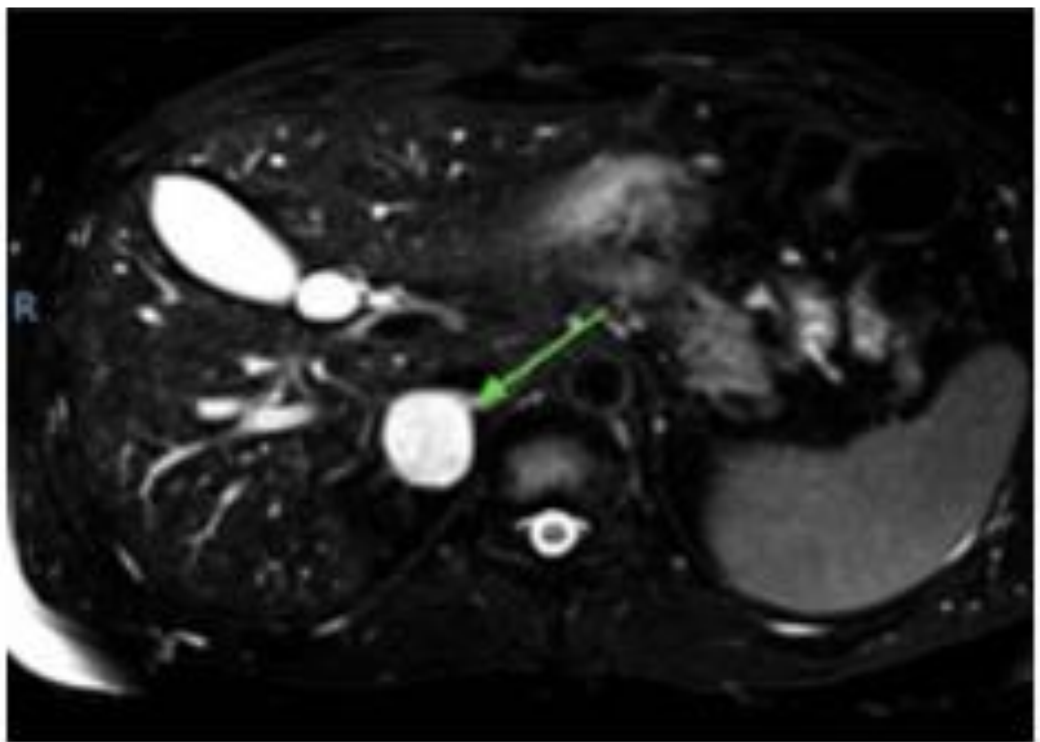
Lipid-poor (HU >10)

MRI



Hypersignal intensity on T2W

Image from Timmers HJLM, et al. Endocr Rev 2024. PMID: 38206185



T2 weighted MR with fat suppression showing a hypersignal intensity lesion at right suprarenal area (arrow)

“Light bulb sign”💡

- Found in 11-65% of patients with PHEO
- No biopsy!!! If biopsy ⟶ PHEO crisis!!

Image from Fonseca EKUN et al. Abdom Radiol (NY) 2017. PMID: 28580539.

3 key criteria to be fulfilled prior to adrenal biopsy

- ❌ The lesion is **HORMONALLY INACTIVE** (pheochromocytoma has been excluded)
- ❑ The lesion has **NOT** been conclusively characterized as **BENIGN** by imaging
- ❑ Clinical management would be **ALTERED** by knowledge of the histology.

Fassnacht M et al. Eur J Endocrinol 2023. PMID: 37318239.

A 34 YO Thai female presented with hypertension 3 years PTA

- Plasma metanephrine: 1425 pg/mL (0-93)
- Plasma normetanephrine: 821 pg/mL (0-163)

DIAGNOSIS:

- Bilateral pheochromocytoma

Pheochromocytoma

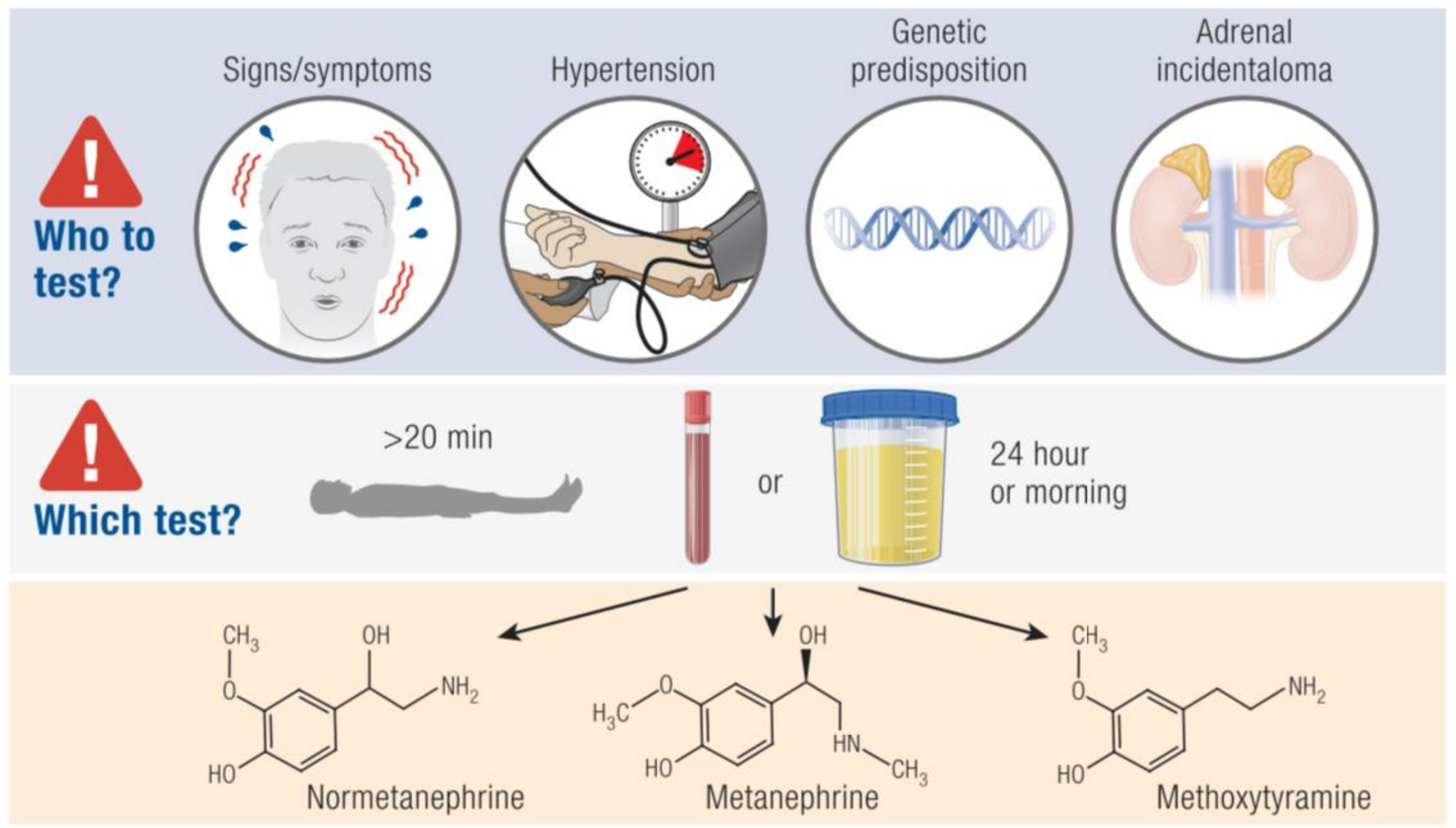


Image from Eisenhofer G et al. Endocr Rev 2023. PMID: 36996131.

Biochemical Testing

HPLC
Radioenzymatic assays
LC-MS/MS
Colorimetric assays
Immunoassays
1960 1970 1980 1990 2000 2010 20
Shift from catecholamines to metanephrines
VMA
Urine total metanephrines
Urine & plasma catecholamines
Urine fractionated metanephrines
Plasma free metanephrines
Urine free metanephrines

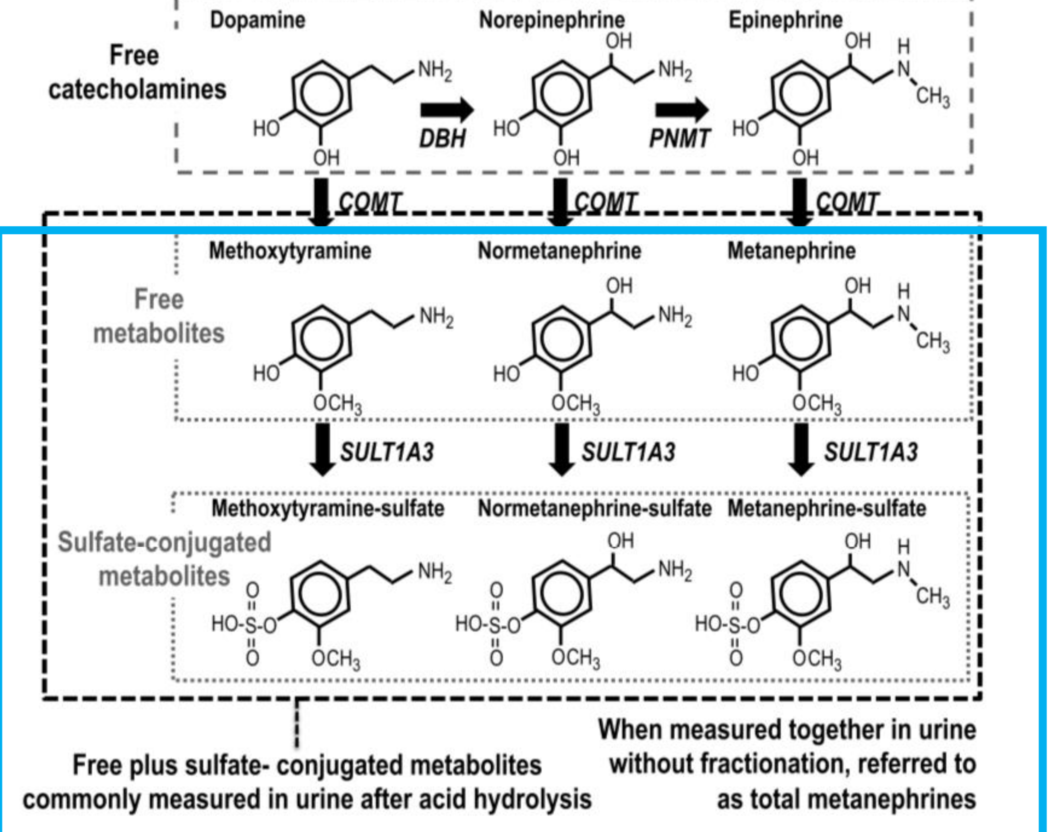
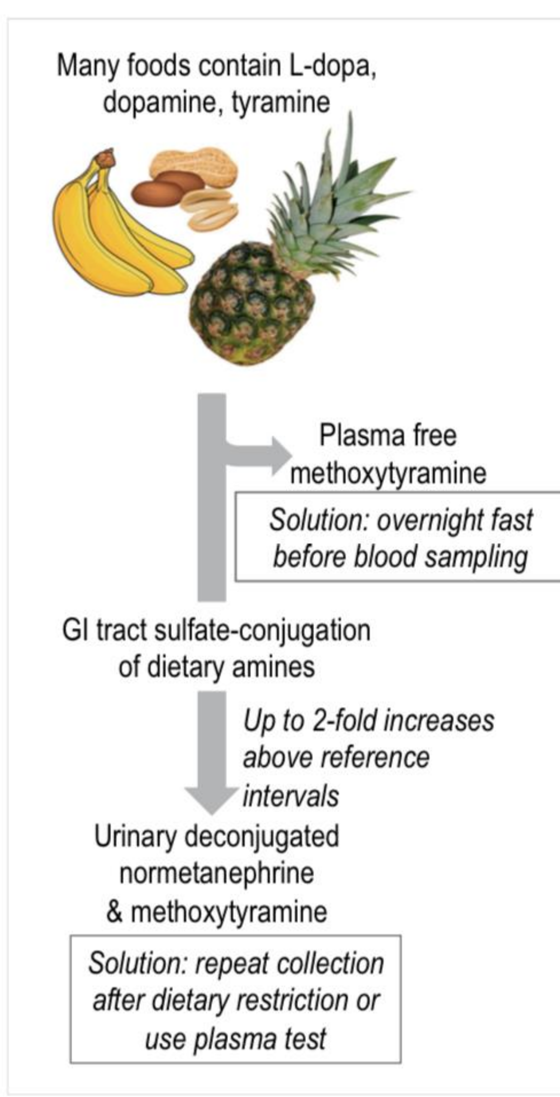


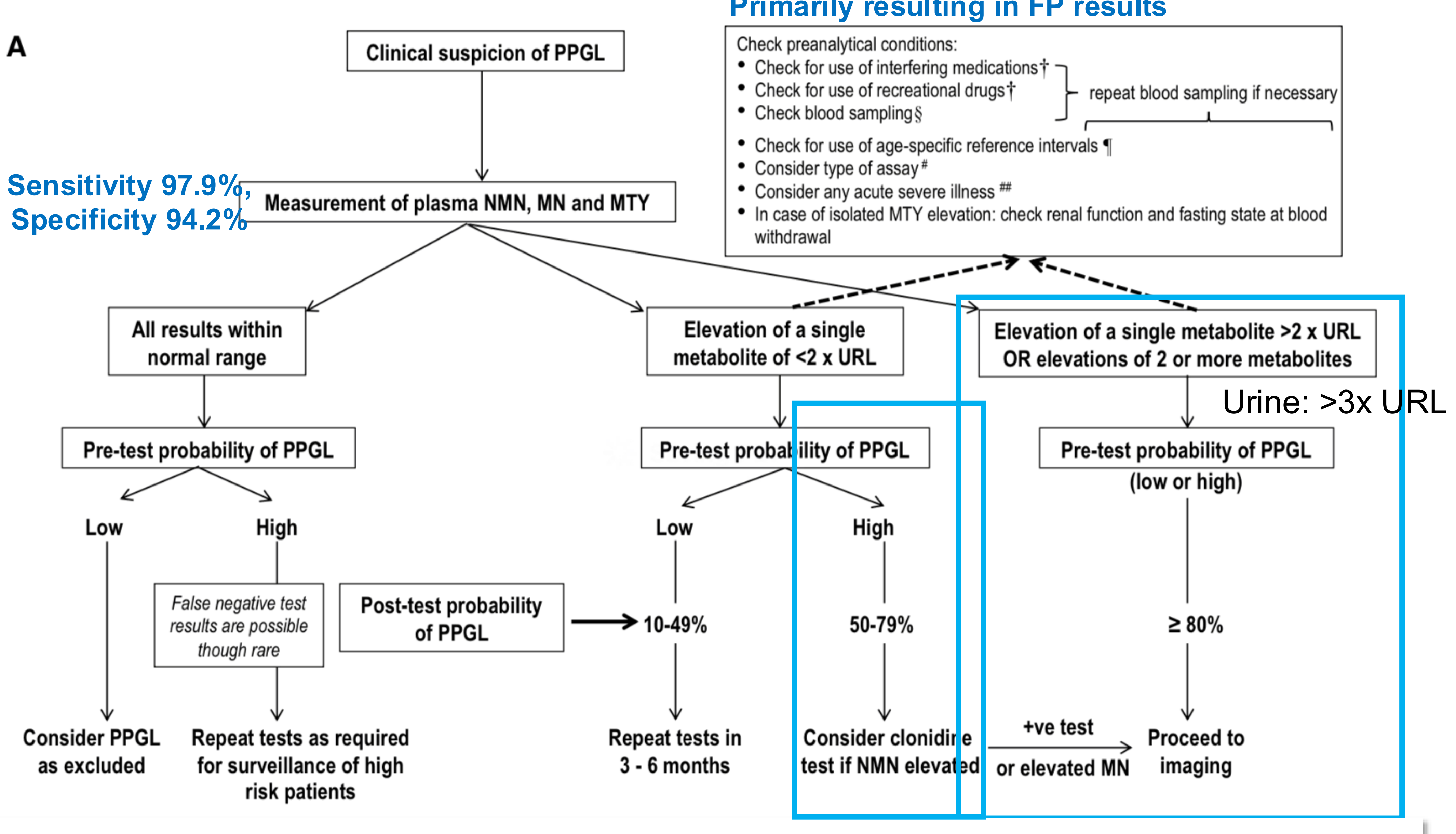
Image from Eisenhofer G et al. Endocr Rev 2023. PMID: 36996131.

Foods and certain drugs can interfere with biochemical testing.



Drug category	Pharmacodynamic actions	Main impact
Stimulants		
Nicotine	• Activation of nicotinic cholinergic receptors	Increased adrenal epinephrine secretion
Caffeine	• Mobilization of intracellular calcium stores	Increased adrenal epinephrine secretion
Sympathomimetics		
Amphetamine Methamphetamine	• Increased release of monoamines from vesicular stores of sympathetic nerves • Inhibition of monoamine oxidase • Blockade of neuronal cell membrane norepinephrine (NE) transporters (NET)	Increased NE concentrations in the neuronal cytoplasm Reversed transport of NE by NET from cytoplasm to extracellular space Increased NE escape from reuptake
Ephedrine Pseudoephedrine	• Activation of alpha and beta-adrenergic receptors • Inhibits function of vesicular monoamine transporters • Inhibits NE reuptake (indirectly)	Increased NE release Increased NE release from secretory vesicles
Norepinephrine reuptake blockers		
Tricyclic antidepressants Venlafaxine/Duloxetine Cocaine	• Blockade of neuronal cell membrane NE transporters • Centrally mediated sympathoinhibition	Decreased sympathetic nerve firing and secretion of NE from sympathetic nerves, but opposing increased escape of NE from reuptake after neuronal secretion
Alpha$_2$ adrenoreceptor antagonists		
Phenoxybenzamine Mirtazapine Yohimbine	• Antagonism of alpha2-adrenoreceptors at central sympathoinhibitory sites and on sympathetic neurons	Increased sympathetic nerves firing secretion of NE from sympathetic nerves
Monoamine oxidase (MAO) inhibitors	• Blockade of the deamination of the O-methylated catecholamine metabolites	Increased plasma and urinary metanephrines with normal catecholamines
Atypical antipsychotics		
Quetiapine, Clozapine, Risperidone	• Inhibition of dopaminergic, adrenergic, and serotoninergic receptors • Antagonism to α_2-adrenoreceptors	Increased secretion of NE from sympathetic nerves

Image and Table from Eisenhofer G et al. Endocr Rev 2023. PMID: 36996131.



High probability of PPGL: previous PPGL, hereditary predisposition, adrenal incidentaloma
Low probability of PPGL: signs and symptoms of catecholamine excess

PPGL, pheochromocytomas/paraganglioma

Image from Eisenhofer G et al. Endocr Rev 2023. PMID: 36996131.

Pheochromocytoma: Management

- **Preoperative: Adequate alpha-blockers** & high sodium intake
- **Perioperative medical management**
  - Admit 7-14 days prior to surgery
  - High sodium intake (with cautions/careful monitoring in patients with cardiac compromise)
  - Monitor BP and PR
- **Surgery** ★
  - Laparoscopic adrenalectomy
  - Consider open adrenalectomy for large (> 6cm) or invasive disease
- **Lifelong follow-up**
  - Clinical + biochemical evaluation
- **Always look for syndromic PPGL**
  - Genetic counseling

PPGL, pheochromocytomas/paraganglioma

Syndromic PPGLs that internists need to know!

Syndrome	Pattern of Inheritance	Clinical findings
MEN 2A	AD	MTC, primary hyperparathyroidism, and cutaneous lichen amyloidosis
MEN 2B	AD	MTC, mucocutaneous neuromas, skeletal deformities, joint laxity, myelinated corneal nerves, and intestinal ganglioneuromas
VHL	AD	Hemangioblastoma, retinal angioma, clear cell RCC, pancreatic NET, and serous cystadenomas, endolymphatic sac tumors of the middle ear, papillary cystadenomas of the epididymis and broad ligament
NF1	AD	Neurofibromas, multiple café-au-lait spots, axillary and inguinal freckling, iris hamartomas (Lisch nodules), bony abnormalities, CNS gliomas, macrocephaly, cognitive deficits

MEN; multiple neuroendocrine neoplasia; VHL, Von Hippel-Lindau; NF, neurofibromatosis; MTC, medullary thyroid carcinoma;
RCC, renal cell carcinoma; NET, neuroendocrine tumor; CNS, central nervous system; AD, autosomal dominant

Lenders JW et al. J Clin Endocrinol Metab 2014. PMID: 24893135.

Von Hippel-Lindau Syndrome (VHL)

	Mean (range) age of onset (years)	Frequency in patients (%)
CNS		
Retinal haemangioblastomas	25 (1–67)	25–60%
Endolymphatic sac tumours	22 (12–50)	10%
Craniospinal haemangioblastomas		
Cerebellum	33 (9–78)	44–72%
Brainstem	32 (12–46)	10–25%
Spinal cord	33 (12–66)	13–50%
Lumbosacral nerve roots	Unknown (..)	<1%
Supratentorial	Unknown (..)	<1%
Visceral		
Renal cell carcinoma or cysts	39 (16–67)	25–60%
Phaeochromocytomas	30 (5–58)	10–20%
Pancreatic tumour or cyst	36 (5–70)	35–70%
Epididymal cystadenoma	Unknown (..)	25–60%
Broad ligament cystadenoma	Unknown (16–46)	Unknown

See references 5,7–17.

Table 1: **Frequency of lesions and age at onset of von Hippel-Lindau disease lesions**

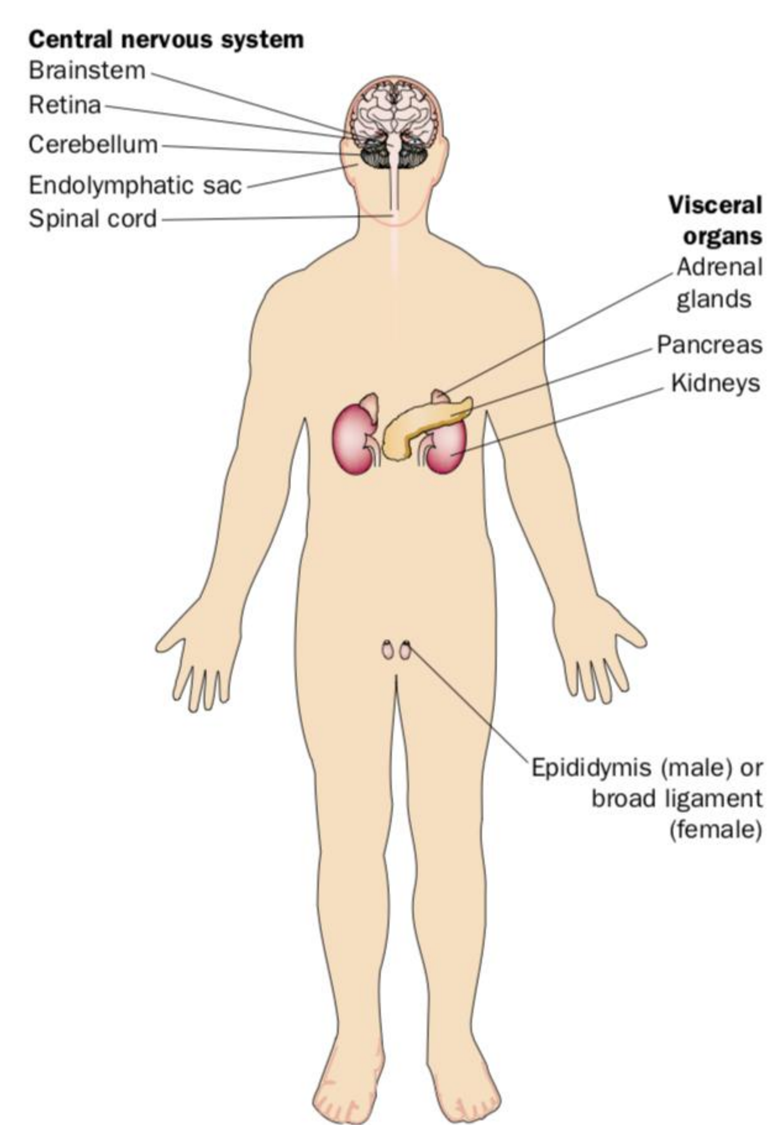


Image from Lonser RR et al. Lancet 2003. PMID: 12814730.

Summary: Pheochromocytoma

Who to test

How to Screen:
Metanephrines (plasma or 24-h urine)

Imaging:
CT/MRI, nuclear imaging

Treatment:
Alpha-blockers and high-sodium diet
Surgery

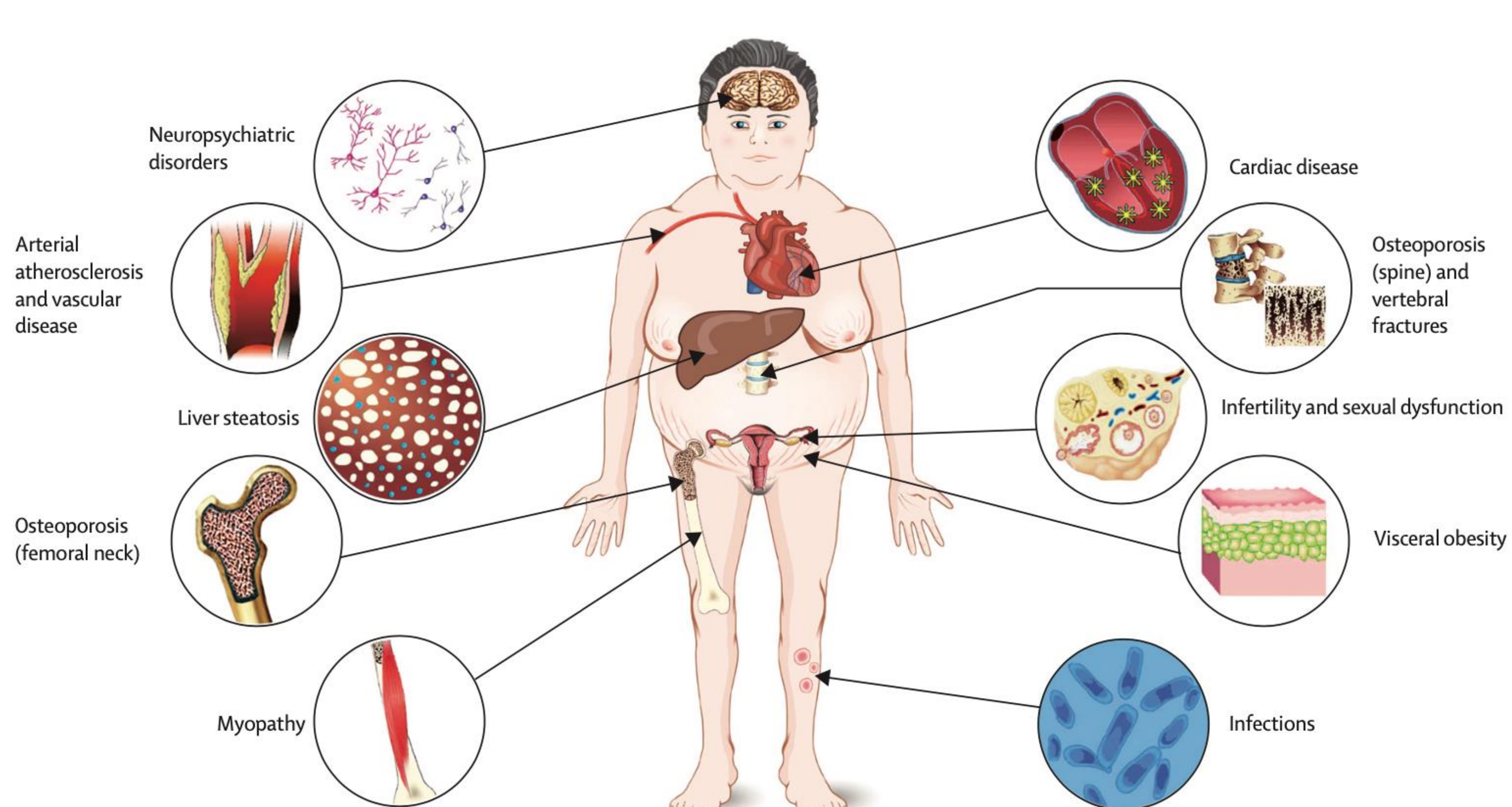
Germline Testing, Genetic Counseling, and Lifelong Follow-Up

High pretest probability

- Previous PPGL
- Hereditary predisposition
- Adrenal incidentaloma

PPGL, pheochromocytoma and paraganglioma

Cushing's Syndrome



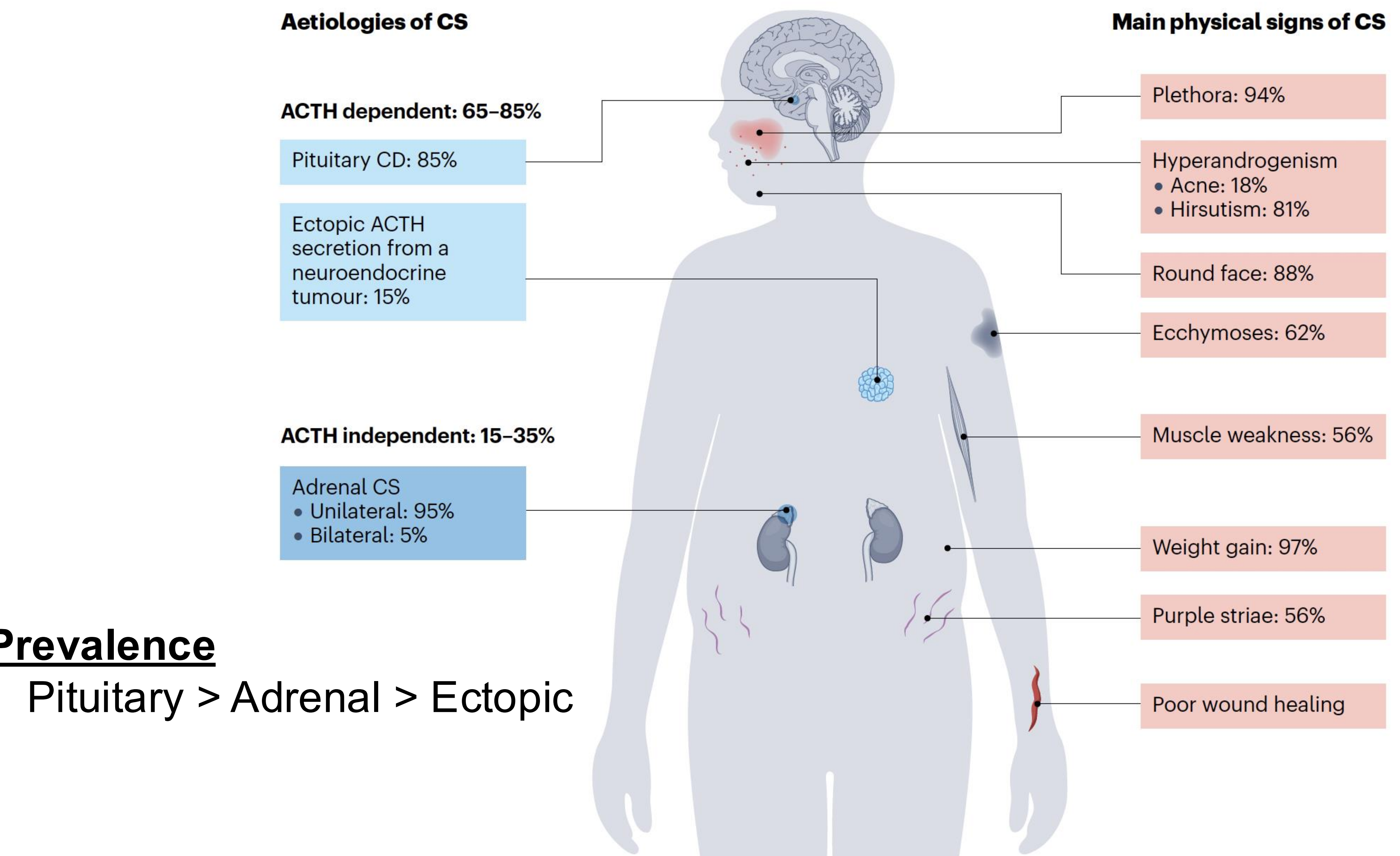
Appearance: Cushing's
Biochemical profile: Central
Adrenal insufficiency

Etiology

- Exogenous Cushing's
- Endogenous Cushing's
  - ACTH-dependent
    - ACTH-secreting pituitary adenoma
    - Ectopic ACTH
  - ACTH-independent

History taking - Onset, hypertension (or worsening hypertension), hyperglycemia/DM, weight gain, secondary amenorrhea, infection, fracture, thromboembolism, muscle weakness, psychiatric disorders

Image from Pivonello R et al. Lancet Diabetes Endocrinol 2016. PMID: 27177728.



Prevalence

- Pituitary > Adrenal > Ectopic

Image from Nieman LK et al. Nat Rev Dis Primers 2025. PMID: 39848955.

Symptoms	Signs	Overlapping conditions
Features that best discriminate Cushing's syndrome; most do not have a high sensitivity		
	Easy bruising	
	Facial plethora	
	Proximal myopathy (or proximal muscle weakness)	
	Striae (especially if reddish purple and > 1 cm wide)	
	In children, weight gain with decreasing growth velocity	
Cushing's syndrome features in the general population that are common and/or less discriminatory		
Depression	Dorsocervical fat pad ("buffalo hump")	Hypertension[b]
Fatigue	Facial fullness	Incidental adrenal mass
Weight gain	Obesity	Vertebral osteoporosis[b]
Back pain	Supraclavicular fullness	Polycystic ovary syndrome
Changes in appetite	Thin skin[b]	Type 2 diabetes[b]
Decreased concentration	Peripheral edema	Hypokalemia
Decreased libido	Acne	Kidney stones
Impaired memory (especially short term)	Hirsutism or female balding	Unusual infections
Insomnia	Poor skin healing	
Irritability		

Purplish striae

Cushing's syndrome is more likely if these conditions develop at a young age

Nieman LK et al. J Clin Endocrinol Metab 2008. PMID: 18334580.
Image from https://doi.org/10.1016/j.clindermatol.2006.04.012

History Taking & Physical Examination

History

- ☐ Changes in appetite
- ☐ Weight gain
- ☐ Back pain
- ☐ Menstrual abnormalities
- ☐ Decreased libido
- ☐ Back pain
- ☐ Depression
- ☐ Fatique
- ☐ Impaired memory
- ☐ Insomnia
- ☐ Irritability

Concomitant medication

- ☐ OCPs
- ☐ exogenous steroid

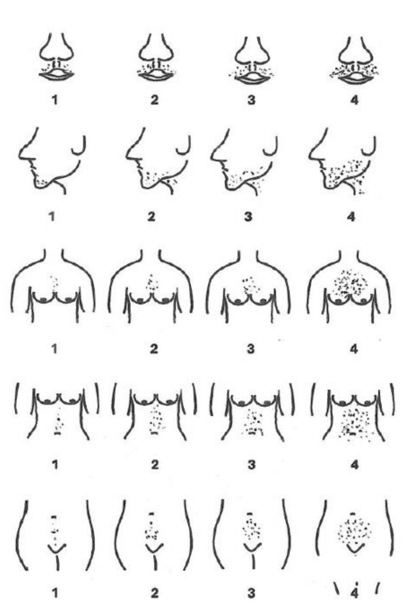
Physical examination:

- SBP……………mmHg
- DBP……………mmHg
- Height……….cm
- Weight……….kg
- BMI………..kg/m^2
- Waist-to-hip ratio………………

- ☐ Easy bruising
- ☐ Facial plethora
- ☐ Striae
- ☐ Proximal myopathy
- ☐ Acne
- ☐ Hirsutism
- ☐ Thin skin
- ☐ Dorsocervical fat pad
- ☐ Facial fullness
- ☐ Poor skin healing
- ☐ Supraclavicular fullness
- ☐ Hyperpigmentation
- ☐ Peripheral edema
- ☐ Central obesity

CO-MORBIDITIES

- ☐ Diabetes mellitus/onset(months)….
- ☐ Hypokalemia
- ☐ Incidental adrenal mass
- ☐ Infection
- ☐ Hypertension/onset…
- ☐ Vertebral osteoporosis/onset…
- ☐ Kidney stones/onset…
- ☐ Dyslipidemia/onset…
- ☐ Obesity
- ☐ PCOS



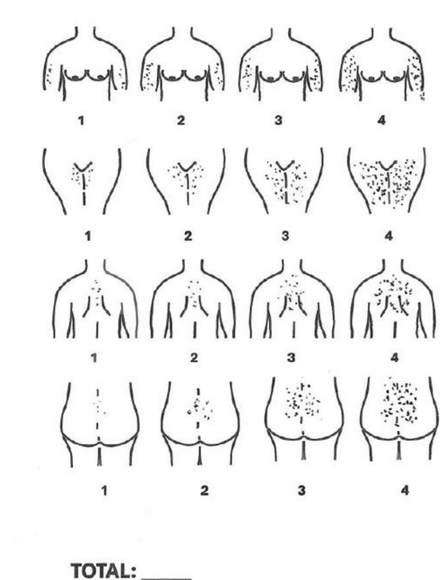


Image from PMID: 40200552.

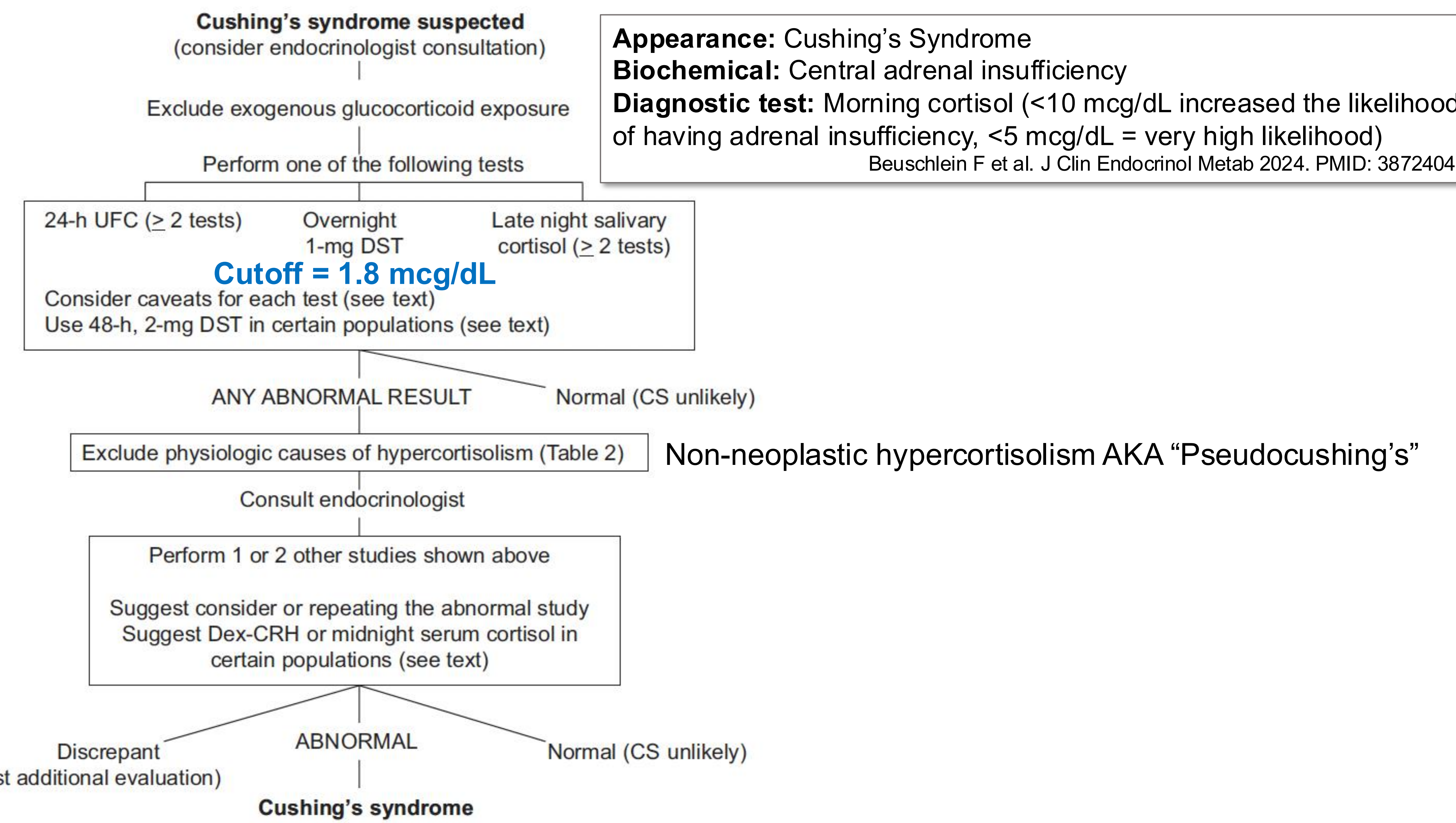


Image from Nieman LK et al. J Clin Endocrinol Metab 2008. PMID: 18334580

✍🏻Cushing's syndrome เป็นกลุ่มอาการที่เกิดจาก glucocorticoid เกินในร่างกายเป็นเวลานาน
โดย glucocorticoid จะส่งผลต่อทุกระบบในร่างกายตั้งแต่หัวจรดเท้า ดังอาการทั้งหมดที่แสดงในรูปที่ 1 ครับ
เมื่อดูรูปที่ 1 กรอบล่างๆจะเห็นว่ามีอาการและอาการแสดงบางอย่างพบได้ในคนทั่วไป โรคอ้วน หรือ คนไข้โรคอื่นๆได้ เช่น อ่อนเพลีย น้ำหนักขึ้น ความจำไม่ค่อยดี ซึมเศร้า ฯลฯ
แต่อาการในกรอบแดงคือสิ่งที่ต้องจำให้ได้ เพราะเป็นอาการที่พบในโรคอื่นๆได้น้อย เรียกว่า "best discriminate Cushing's syndrome" ได้แก่ จ้ำเลือดง่าย หน้าแดง 👹 กล้ามเนื้อส่วนต้นอ่อนแรง รอยแตกม่วง (มากกว่า 1 cm.) เคสที่เอามาสอบ Cushing's syndrome ระดับ resident น่าจะต้องมี signs พวกนี้ครับ

.

✍🏻ขั้นตอนการ work up เมื่อสงสัย Cushing's syndrome ค่อยไปทีละขั้นนะคับ ไม่ข้ามขั้น

1️⃣ ขั้นตอน 1 ถามประวัติยา เพื่อแยก exogenous Cushing's syndrome ออกไปก่อน ไม่ได้ถามแค่ยากิน💊นะครับ 💉ยาฉีดเข้าข้อ ฉีดเข้ากล้าม ยาทา ยาพ่น สวนก้น ฯลฯ ต้องถามให้หมด
ถามว่าใช้ยานั้นรักษาโรคอะไร ลักษณะยาเป็นยังไง (ยาเม็ด ผง ใบสมุนไพร ลูกกลอน ฯลฯ) ช่วงที่ได้ยาอาการเป็นไง ไม่ได้ยาแล้วเป็นไง หยุดยาไปแล้วนานเท่าไหร่ ฯลฯ
ถ้ามียาสงสัย ให้หยุดยา 7 วัน เจาะ 8am cortisol ถ้าค่า < 3 ug/dl วินิจฉัยเลยว่ามีภาวะ adrenal insufficiency จาก exogenous steroid (secondary adrenal insufficiency)

2️⃣ ขั้นตอน2 ตรวจเพื่อยืนยันภาวะ glucocorticoid excess ดูรูปที่ 2 ประกอบกัน สิ่งสำคัญในขั้นตอนนี้ คือ การเลือกtest ให้เหมาะสมกับคนไข้ อ่านดีดีนะครับ

.

*** ต้องระวังภาวะ pseudo Cushing ดูในรูป 3 ครับ ท่องง่ายๆ "อ้วน เศร้า เหล้า ท้อง poor controlled DM" ต้องเลือก test ที่จำเพาะกับภาวะนั้นๆครับ ***

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👉🏻UFC (ตรวจอย่างน้อย 2 ครั้ง)

✔️ใช้ใน คนที่มีการกวน CBG เพราะวัด free cortisol จาก urine
Pregnancy, คนที่ทำงานเป็นกะ

❌ไม่ใช้ใน
GFR< 60
กินน้ำมากกว่า 5 ลิตรต่อวัน
คนที่ใช้ยาที่กวนการตรวจ เช่น carbamazepine, fenofibrate (วิธี HPLC), ยาที่ยับยั้ง enzyme 11- beta HSD2 เช่น licorice, carbenoxolone

.

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👉🏻1 mg overnight DST, 2 day low dose DST
ทำง่ายแต่ข้อจำกัดเยอะ

✔️ใช้ใน เฉพาะ 2 day low dose DST ใช้ใน pseudoCushing พวก psychiatric conditions, morbid obesity, DM, alcoholism

❌ไม่ใช้ใน
คนที่มี CBG เปลี่ยนแปลง เช่น กิน estrogen (ต้องหยุด 6 สัปดาห์) nephrotic syndrome (CBG ต่ำ)
คนที่ใช้ยาที่กวน dexamethasone metabolism ดังรูป 2 นะครับ เช่น ใช้ยาที่เร่ง dexamethasone metabolism ทำให้ค่า cortisol สูงกว่าความเป็นจริง (falsely high) คือกลุ่ม ยากันชัก, rifampicin เป็นต้น

.

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👉🏻Late night salivary cortisol (ตรวจอย่างน้อย 2 ครั้ง)
ในประเทศไทยยังไม่แพร่หลาย

✔️ใช้ใน คนที่มีการกวน CBG เพราะวัด free form

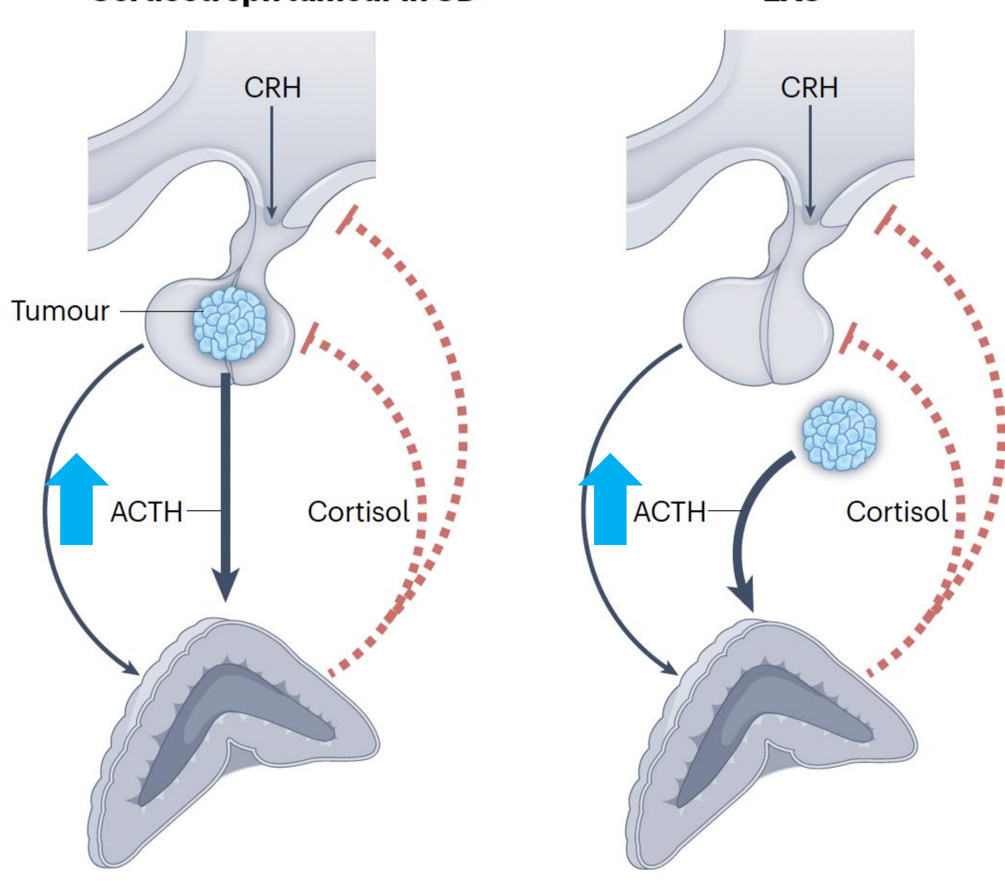
❌ ไม่ใช้ใน กิน licorice (ต้องไปอ่านเรื่องชะเอมในวงราวน์นะครับ) chewing tobacco ใช้ steroid ป้ายปาก
ระวังเก็บเลือดปนน้ำลาย

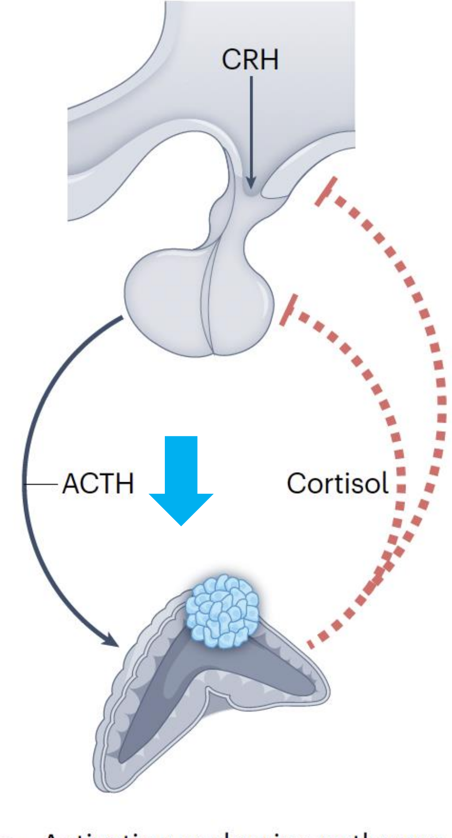
CUEZ endocrine
39K likes • 42K followers

ACTH Levels

ACTH-dependent

ACTH-independent





ACTH-secreting tumor

Image from Nieman LK et al. Nat Rev Dis Primers 2025. PMID: 39848955.

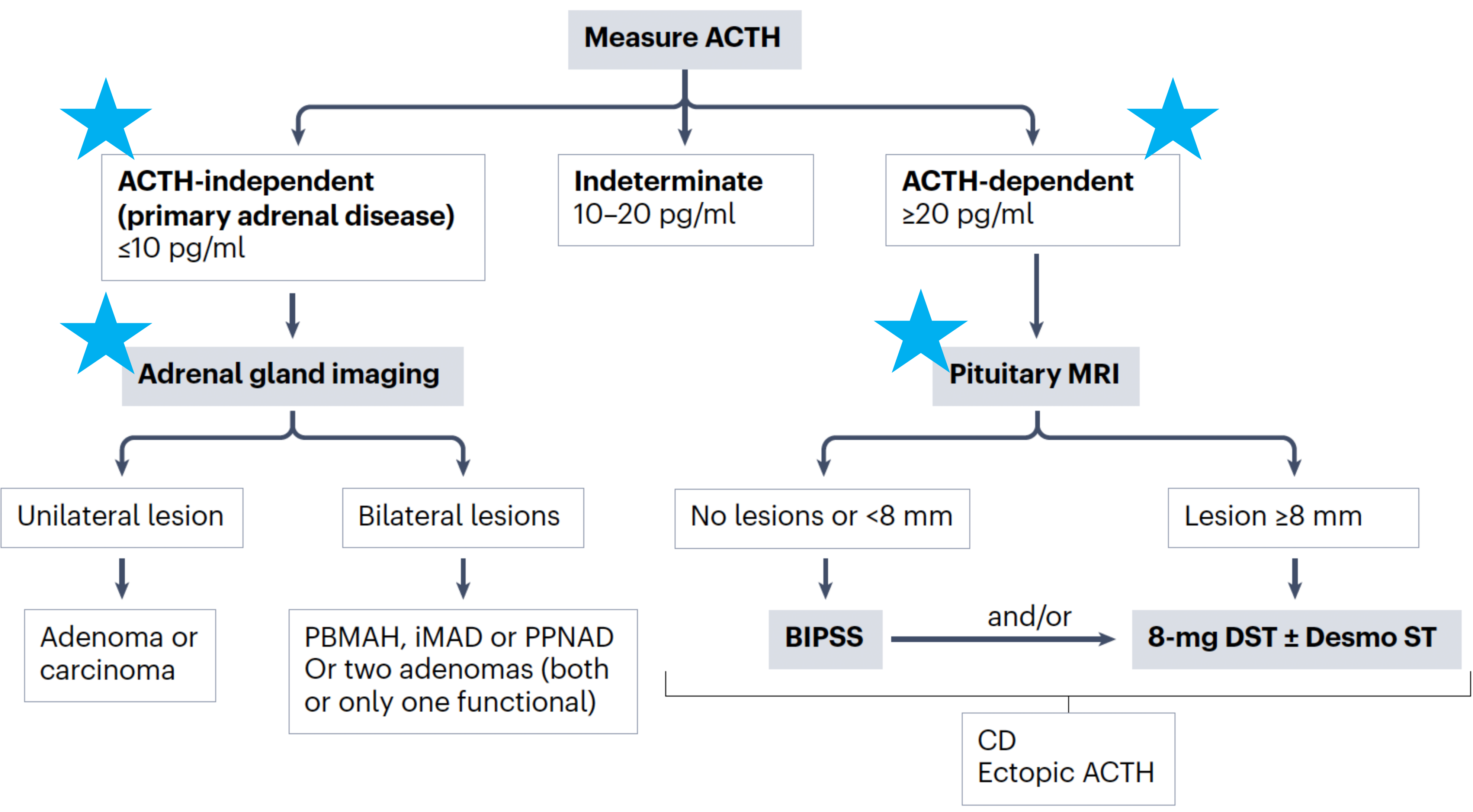


Image from Nieman LK et al. Nat Rev Dis Primers 2025. PMID: 39848955.

Treatment

- Supportive
  - Metabolic complications: DM, hypertension, dyslipidemia
  - Infection, thromboembolism, and osteoporosis if present

- Specific treatment
  - Unilateral cortisol-producing adrenal adenoma
    - Laparoscopic adrenalectomy → postoperative adrenal insufficiency
      → Glucocorticoid replacement (until HPA axis recovery) & advise sick day management

  - Adrenocortical carcinoma
    - Adrenalectomy ± adjuvant treatment if indicated
  - Cushing's disease (Pituitary Cushing's)
    - Transsphenoidal surgery with tumor removal
    - Remission – postoperative cortisol = 2 mcg/dL

Fleseriu M et al. Lancet Diabetes Endocrinol 2021. PMID: 34687601.

Summary: Cushing's Syndrome

Suspect Cushing's Syndrome

Exclude exogenous Cushing's syndrome

How to Screen:
1 mg DST, LNSC, 24-h UFC

Rule out non-neoplastic hypercortisolism

Diagnose Cushing's Syndrome

Measure ACTH

Imaging:
ACTH ≤10 pg/mL → Adrenal imaging
ACTH ≥20 pg/mL → Pituitary MRI

Additional testing may be necessary

Treatment: Surgery
& Control other comorbidities

DST, dexamethasone suppression test; LNSC, late-night salivary cortisol; UFC, urinary free cortisol

Wrap Up: History & Physical Examination

- **Primary Aldosteronism**
  - Only being hypertensive is enough to think of primary aldosteronism
  - Think more, if hypokalemia, resistant hypertension, young-onset, AF
- **Cushing's syndrome**
  - Weight gain (no need to be obese, particularly in Thai people), amenorrhea, fracture, infection, hypertension (or worsening hypertension), DM
- **Pheochromocytoma**
  - Hypertension, constipation, HF, weight changes, DM, family history
  - Paroxysm, postural hypotension

Other examinations: BP 4 extremities, eye ground (hypertensive retinopathy, retinal hemangioblastoma in VHL), renal bruits, no aggressive abdominal palpation if suspected PHEO, thyroid examinations (hyper/hypothyroid/thyroid nodule [MTC]), short stature (Turner), Acromegalic features

MEN1 and Common Tumors

Prolactinoma

Acromegaly

Multiple Neuroendocrine Neoplasm Type 1

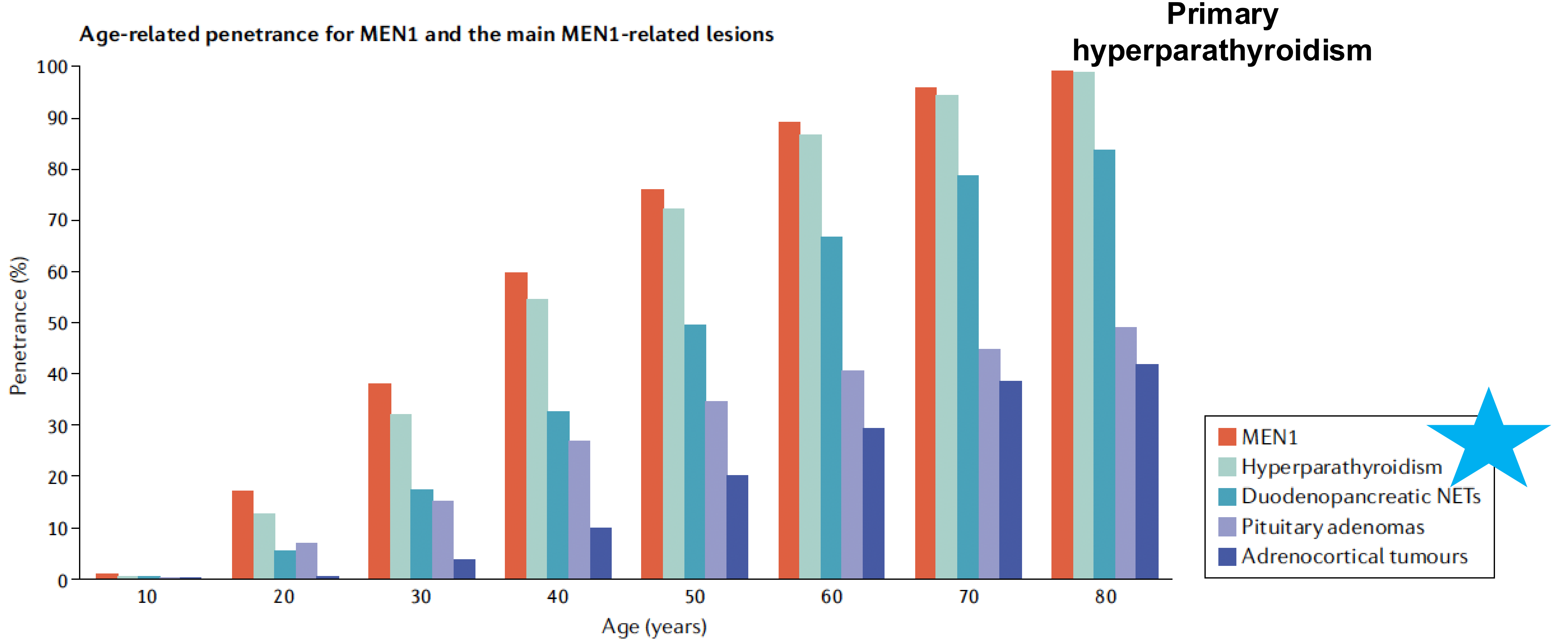


Image from Al-Salameh A et al. Nat Rev Endocrinol 2021. PMID: 33564173.

Multiple Neuroendocrine Neoplasm Type 1

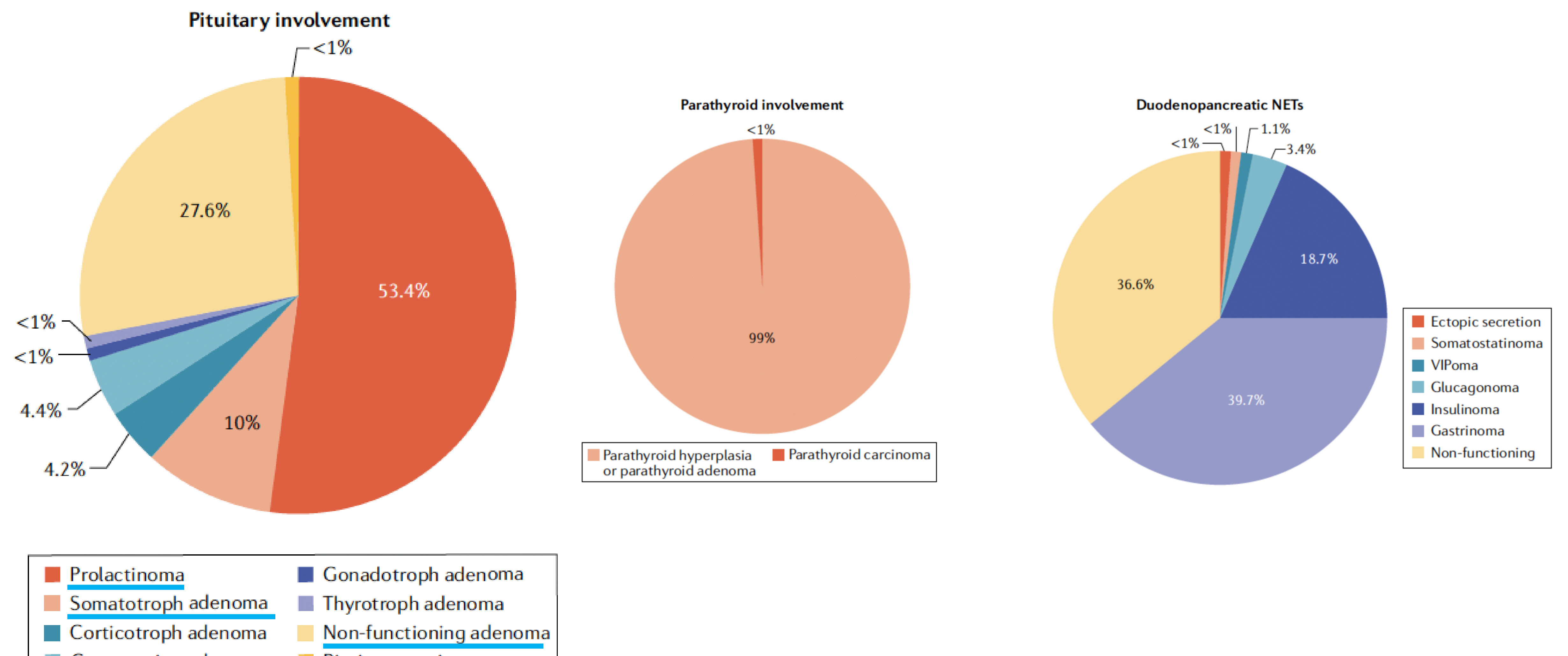


Image from Al-Salameh A et al. Nat Rev Endocrinol 2021. PMID: 33564173.

Multiple endocrine neoplasia type 1 (MEN1): recommendations and guidelines for best practice

Maria Luisa Brandi, Carolina R C Pieterman*, Katherine A English*, Kate E Lines*, Omair A Shariq*, Francesca Marini, Thomas Cuny, Mark A Lewis, Constantine A Stratakis, Nancy D Perrier, Steven G Waguespack, Frederic Castinetti, Gerlof D Valk†, Rajesh V Thakker†, on behalf of the Delphi Expert Panel‡*

Genetic testing in apparently sporadic *MEN1*-related tumours		
#49	Offer genetic testing including *MEN1*, to patients with apparently sporadic primary hyperparathyroidism aged <30 years and/or patients with multi-gland disease. (Unchanged)	Suggestion
#50	In patients aged <40 years diagnosed with an apparently sporadic solitary pancreatic neuroendocrine tumour, genetic testing for *MEN1* can be considered. (New)	Consideration
#51	*MEN1* genetic testing can be considered in adults aged <30 years with an apparently sporadic, functioning pituitary adenoma (with the exception of a microprolactinoma in women) or a non-functioning pituitary adenoma >1 cm. (New)	Consideration
#52	Genetic testing, including *MEN1*, should be considered in children and adolescents with an apparently sporadic pituitary adenoma. (New)	Consideration

Image from Brandi ML et al. Lancet Diabetes Endocrinol 2025. PMID: 40523372.

Prolactinoma: Signs & Symptoms

Associated with hyperprolactinemia

- Galactorrhea
- Amenorrhea, oligomenorrhea
- Infertility
- Decreased libido, impotence, premature ejaculation, and oligospermia
- Osteoporosis

Resulting from hypogonadism

Associated with tumor mass

- Visual field abnormalities
- Blurred vision or decreased visual acuity
- Hypopituitarism
- Headaches
- Cranial nerve palsies
- Pituitary apoplexy

PRL, prolactin; FSH, follicle stimulating hormone; LH, luteinizing hormone

Image from Williams textbook of Endocrinology 14th edition

Hyperprolactinemia results in hypogonadotrophic hypogonadism

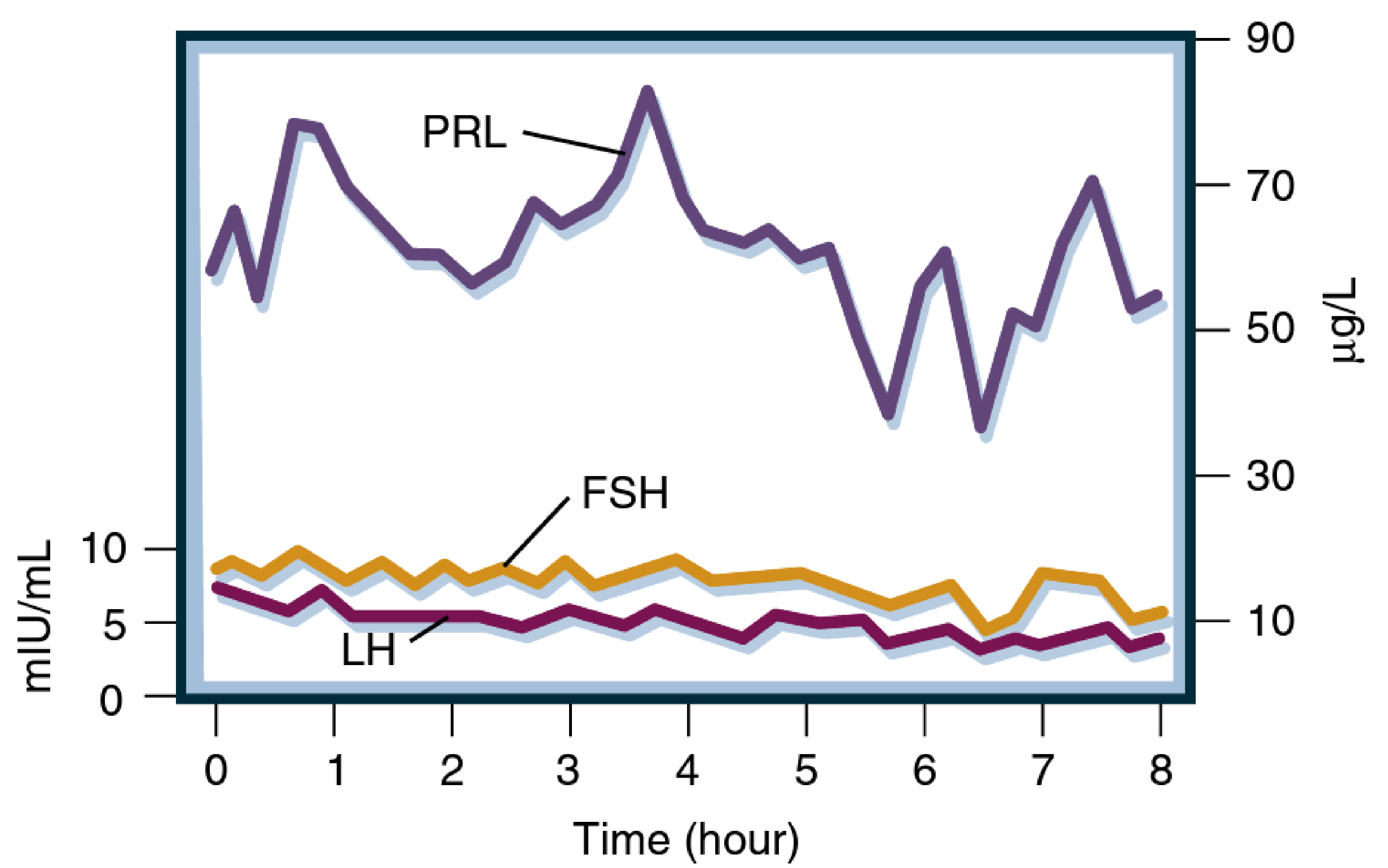


Image from Williams textbook of endocrinology 14th edition

Approach to Patients with Hyperprolactinemia

Hyperprolactinemia

Amenorrhea, oligoamenorrhea
Galactorrhea
Infertility
Decreased libido, impotence, oligospermia

If asymptomatic, consider macroprolactinemia

No recommended dynamic testing

Rule out secondary causes

Pregnancy
Lactation
Drugs
Primary hypothyroidism
Liver cirrhosis
Renal failure

Pituitary MRI

Prolactinoma

- Prolactinomas are classified by their size
  - Size <1 cm: microprolactinoma
  - Size ≥1 cm: macroprolactinoma
    - Size ≥4 cm: Giant prolactinoma

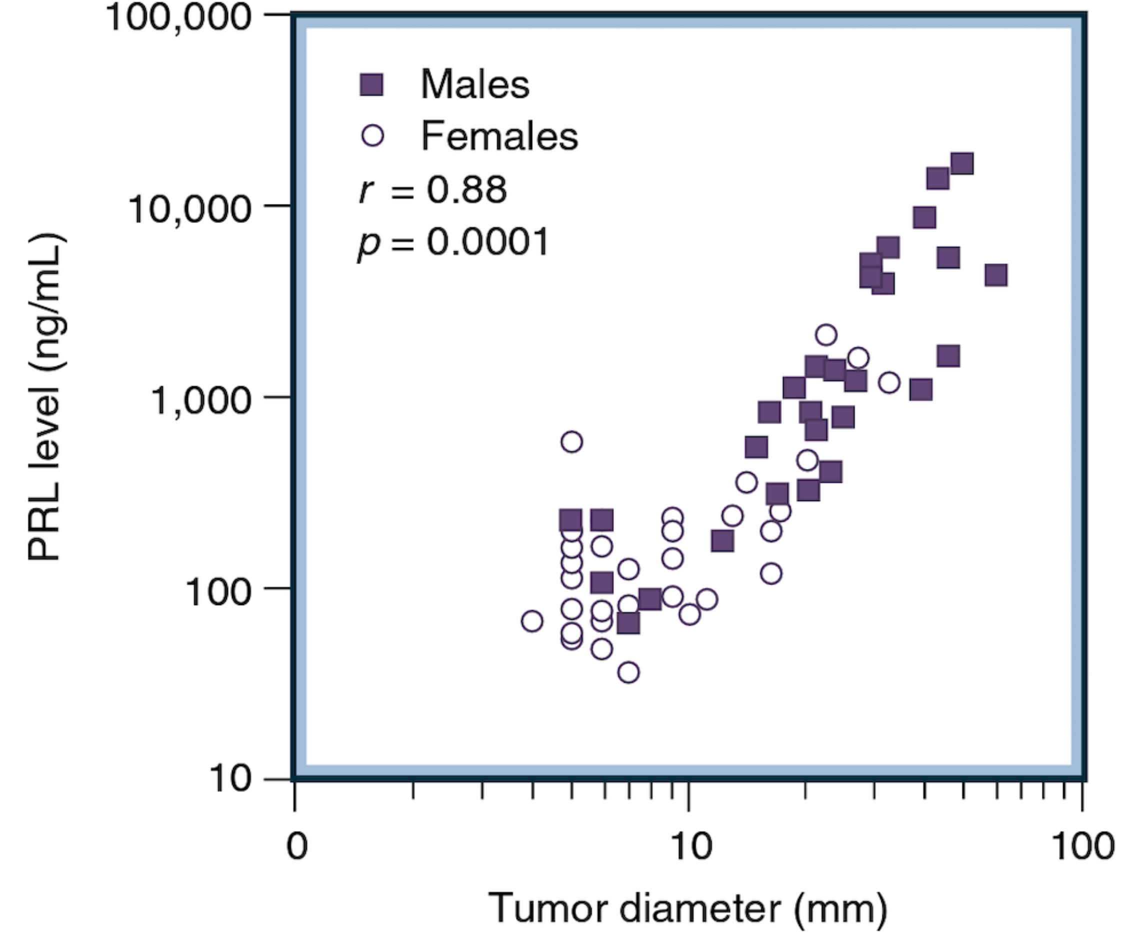


Image from Williams Textbook of Endocrinology 14th edition

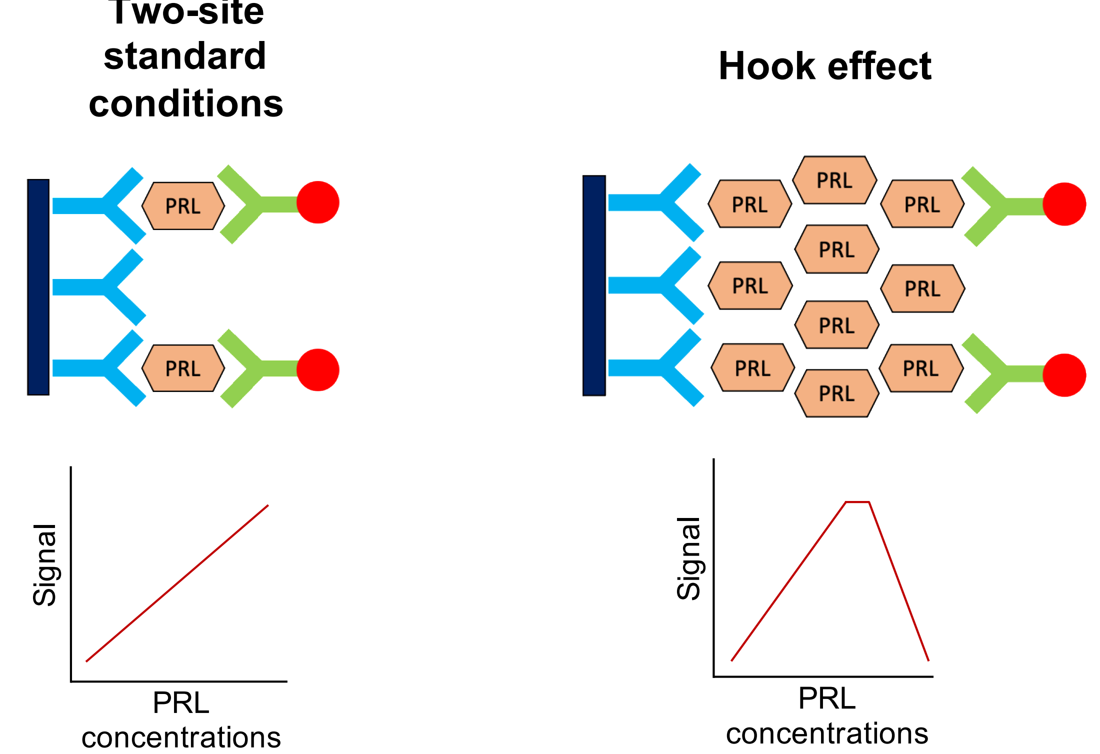
Size & Prolactin Levels in Prolactinomas

- Prolactinomas can present with any level of PRL elevation.
- PRL level >200 μg/L = strongly indicative of a PRL-secreting pituitary tumor
  - However, it could result from some drugs, e.g., metoclopramide, risperidone, and phenothiazines.
  - When suspecting drug-induced hyperprolactinemia → withhold medication for ≥3 days and retest PRL (if able to discontinue)
- PRL >500 μg/L = only observed in prolactinomas

Vilar L et al. J Endocrinol Invest 2008. PMID: 18560262; Arafah BM et al. J Clin Endocrinol Metab 1995; Melmed S et al. J Clin Endocrinol Metab 2011. PMID: 21296991

Hook Effect

- If the technique uses a single dilution
  - Extremely high PRL concentrations → falsely low value



Adapted from the pituitary 4th edition

Management of Prolactinoma

Goals

- Lower PRL levels
- Decrease tumor size
- Restore gonadal function

Knosp Classification

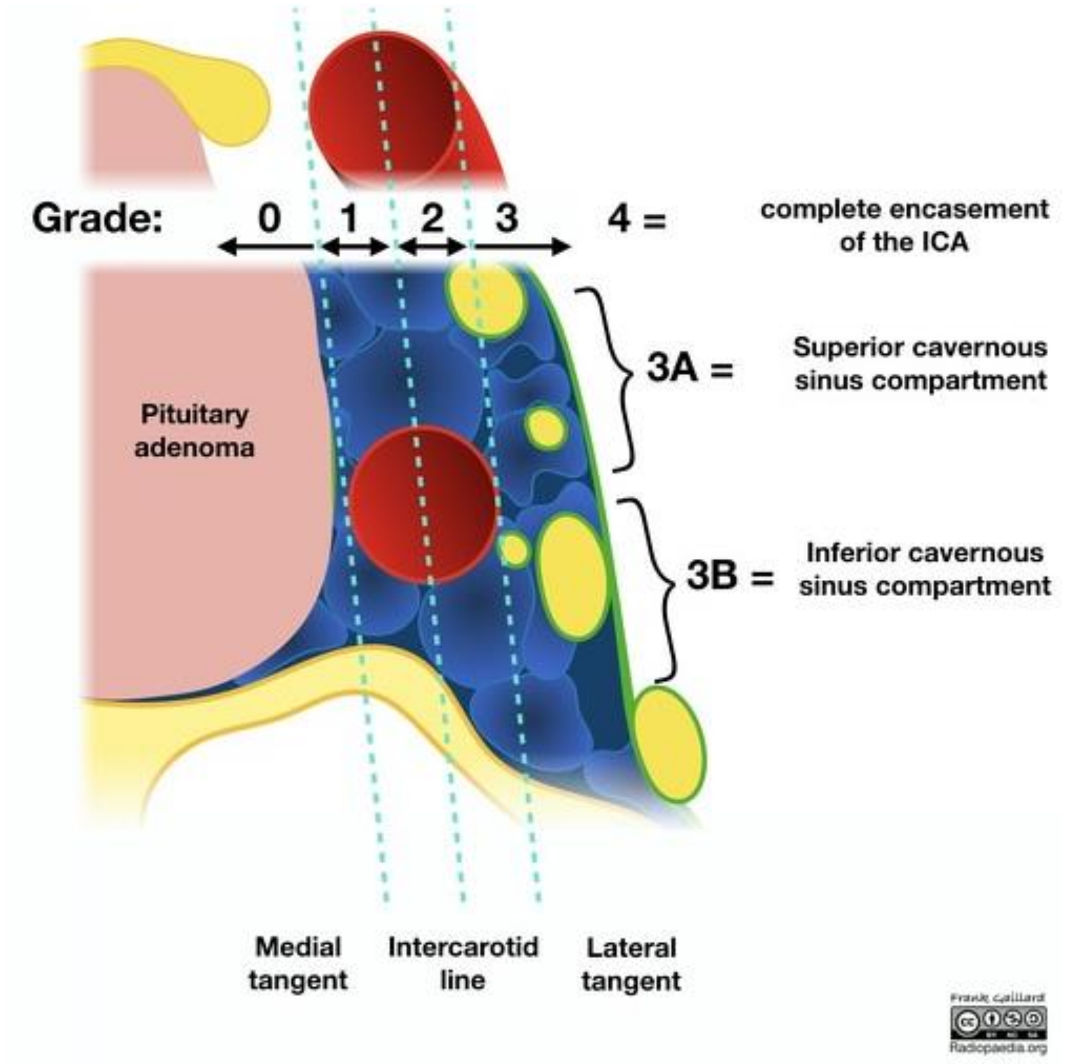


Image from https://radiopaedia.org/articles/knosp-classification-of-cavernous-sinus-invasion-by-pituitary-macroadenomas

Management of Prolactinoma

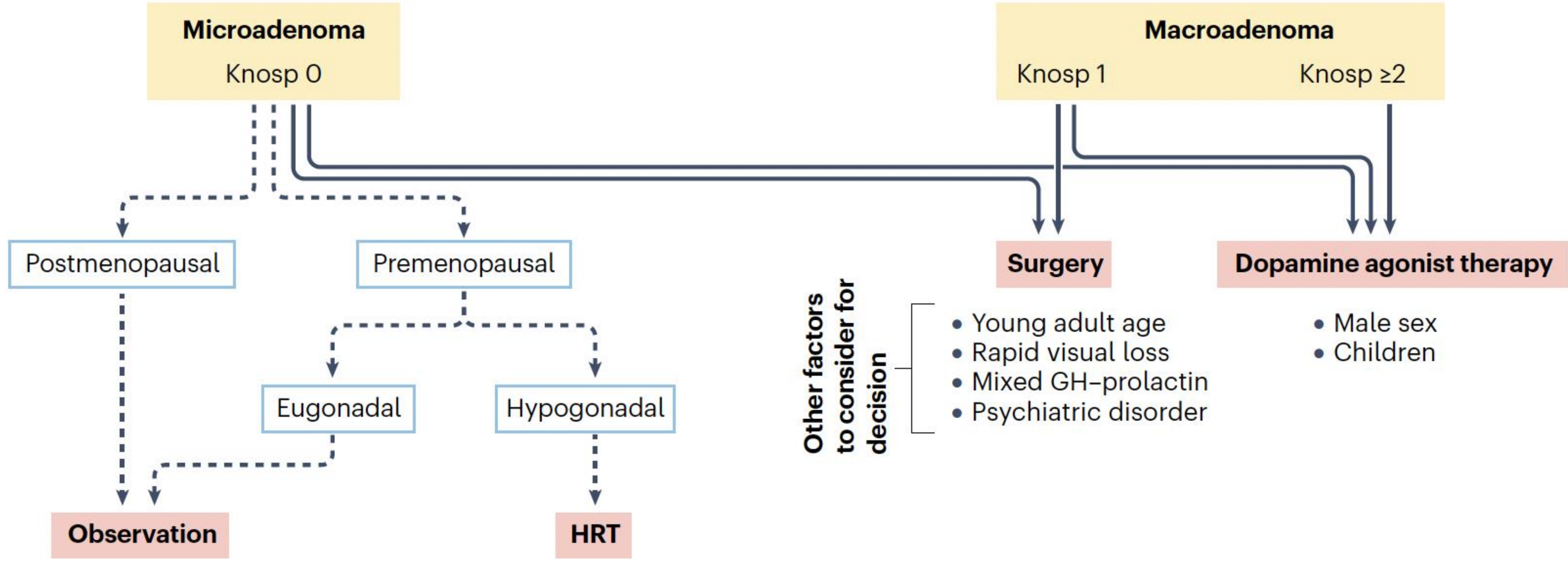


Image from Petersenn S et al. Nat Rev Endocrinol 2024. PMID: 37670148.

Surgery in Prolactinomas

- Transsphenoidal surgery can be offered to patients with
  - Drug intolerance
  - Dopamine agonist-resistant prolactinoma
  - It can be considered in women with large prolactinomas (that could potentially threaten vision during pregnancy)
  - CSF rhinorrhea

  - Pituitary apoplexy, Mixed GH-prolactin tumor (Pituitary Society 2023)

Microprolactinomas and well-circumscribed macroprolactinomas (Knosp grade 0 and 1) ** by experienced neurosurgeons

- Surgery by an expert pituitary neurosurgeon should therefore be discussed alongside dopamine agonist treatment as a first-line option in this subgroup of patients.

Pituitary Society 2023

Melmed S et al. J Clin Endocrinol Metab 2011. PMID: 21296991

Dopamine Agonist Treatment

- Bromocriptine
  - Starting dose: 1.25 mg/day
  - Dose range: 2.5-15 mg/day

- Cabergoline
  - Starting dose, e.g., 0.25 mg/day
  - Dose range: 0.5-3.5 mg/week
    - If long-term treatment with **high-dose cabergoline (>2.0 mg/wk)** is anticipated, the 2023 Pituitary Society Guideline recommends performing baseline echocardiography to detect any pre-existing valvular alterations.

Melmed S et al. J Clin Endocrinol Metab 2011. PMID: 21296991; Petersenn S et al. Nat Rev Endocrinol 2024. PMID: 37670148.

Side Effects of Dopamine Agonists

- Nausea occurs in up to 50% of patients
- Dizziness
- Nasal stuffiness
- Depression
- Digital vasospasm
- Psychosis or exacerbation of preexisting psychosis
- Hypersexuality and disordered impulse control

Administration at bedtime and/or with food may help improve tolerability

Summary: Dopamine Agonist Treatment

- Availability: Favor bromocriptine
- Efficacy: Favor cabergoline
- Tolerability: Favor cabergoline
- Cost: Favor bromocriptine

Other Concerns After Treatment

- CSF rhinorrhea
  - It occurred in up to 9% of patients with macroadenomas
  - It could occur spontaneously or after dopamine agonist treatment
  - Surgery is required
- Pituitary apoplexy
  - Rates of apoplexy in macroprolactinomas treated with dopamine agonists were not significantly higher than in untreated macroprolactinomas.

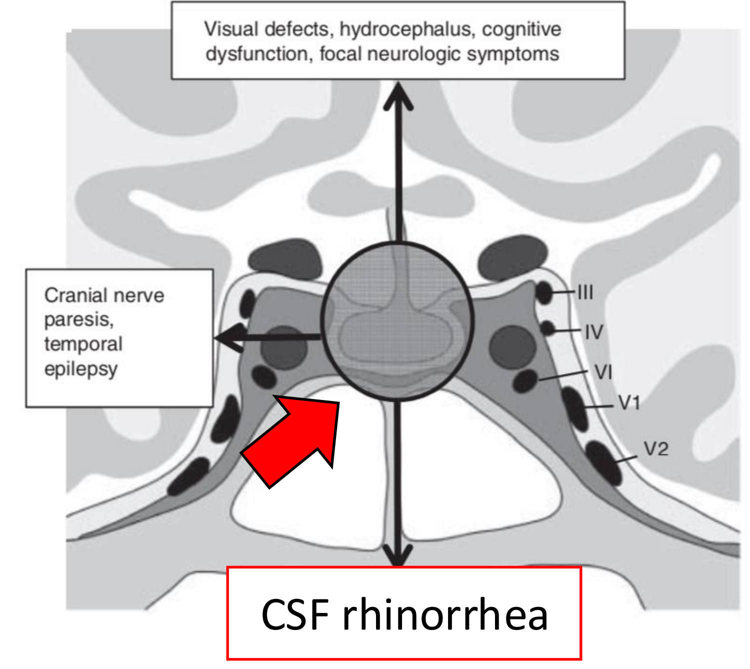


Image from Maiter D et al. Eur J Endocrinol 2014. PMID: 24536090.

Briet C et al. Endocr Rev 2015. PMID: 26414232; Honegger J et al. Pituitary 2020. PMID: 31853793; Lam G et al. Neurosurg Focus 2012. PMID: 22655691; Carija R et al. CNS Neurol Disord Drug Targets 2012. PMID: 23244423.

Follow Up

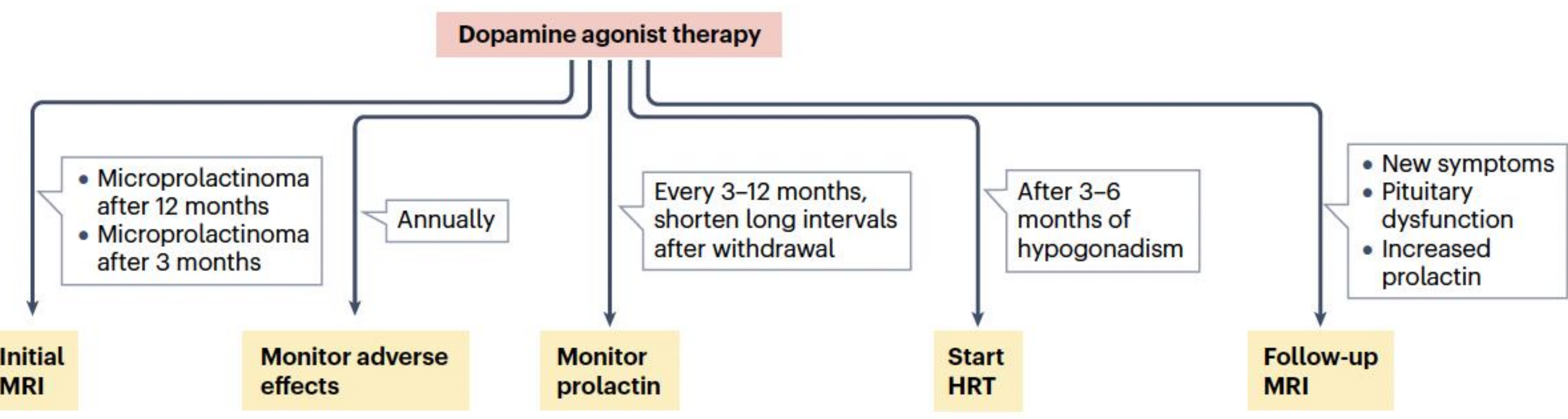


Image from Petersenn S et al. Nat Rev Endocrinol 2024. PMID: 37670148.

Prolactinoma: Summary

Periodic PRL measurement

- 1 month following therapy

Pituitary MRI

- After dopamine agonist treatment → ***repeat MRI in 1 year (3 months if macroprolactinoma)***
- If PRL continues to rise while on medication
- If new symptoms occur, e.g., headache, visual disturbances

Visual field

- In patients with macroadenomas at risk of impinging the optic chiasm

Assessment and management of comorbidities

- BMD in patients with >6 months of hypogonadism or with other risk factors for osteoporosis
- Pituitary trophic hormone reserve – hormonal deficiency, particularly in those with macroadenoma
- IGF1 – baseline in all cases
- MEN1 germline mutation screening – consider in patients with a family history of pituitary adenomas & in patients <30 years with pituitary macroadenoma

Melmed S et al. J Clin Endocrinol Metab 2011. PMID: 21296991; Petersenn S et al. Nat Rev Endocrinol 2023. PMID: 37670148.

When to Discontinue Medication

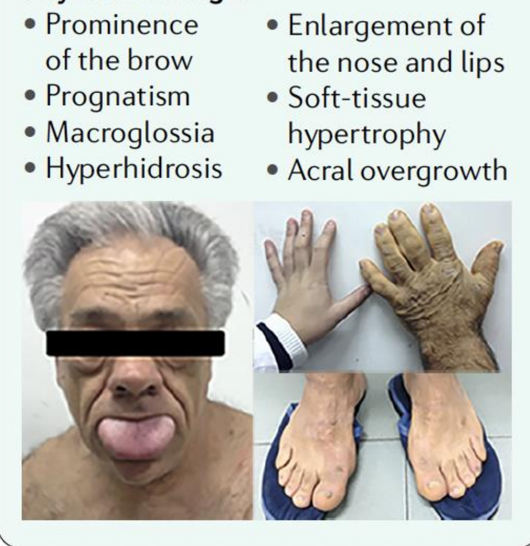
- During treatment, dopamine agonists can be tapered and discontinued in
  - Favorable predictors of successful withdrawal include **low maintenance doses of cabergoline**, treatment duration **>2 years,** and **substantial adenoma size reduction** (Pituitary Society 2023)
  - Patients who have been on treatment for **at least 2 years**, with **no longer PRL elevation & no visible tumor remnant on MRI** (Endocrine Society 2011)

- In women with microprolactinomas when;
  - Pregnancy
  - Menopause

Melmed S et al. J Clin Endocrinol Metab 2011. PMID: 21296991; Petersenn S et al. Nat Rev Endocrinol 2024. PMID: 37670148.

Acromegaly

มือเท้าใหญ่ คางยื่น ฟันไม่สบกัน หน้าเปลี่ยน ลิ้นใหญ่ จมูกใหญ่ นอนกรน ใส่แหวนไม่ได้ รองเท้าเปลี่ยนไซส์ มีติ่งเนื้อที่ลำตัว เสียงเปลี่ยน



Local tumour effects
- Headache
- Visual impairment
- Hyperprolactinaemia
- Hypopituitarism

Cardiovascular complications
- Hypertension
- Biventricular hypertrophy
- Cardiomyopathy
- Congestive heart failure
- Arrhythmias
- Valve disease

ความดันโลหิตสูง ประวัติ HF

Metabolic and endocrine complications
- Impaired glucose tolerance
- Diabetes mellitus
- Insulin resistance
- Dyslipidaemia
- Thyroid goitre

เบาหวาน ก้อนที่คอ คอโต

Respiratory complications
- Upper airway obstruction
- Ventilatory dysfunction
- Sleep apnoea
- Excessive snoring

Gastrointestinal complications
- Colonic polyps
- Dolichomegacolon

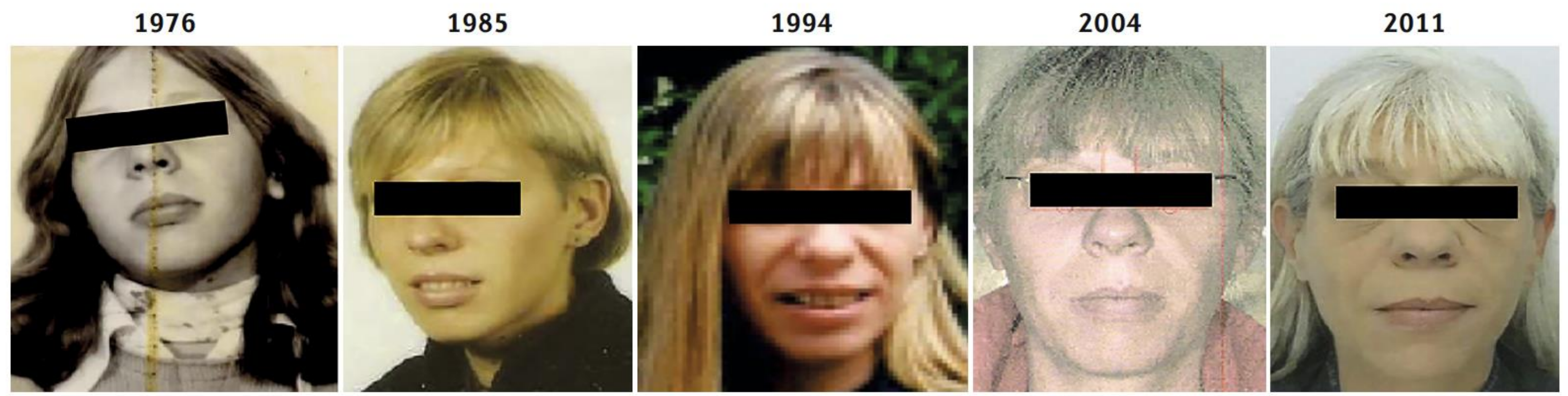
Skeletal system complications
- Increased articular cartilage thickness
- Arthropathy
- Carpal tunnel syndrome
- Paraesthesia
- Vertebral fractures

ปวดตามข้อ มีอาการ carpal tunnel syndrome

Reproductive disorders
- Menstrual disturbance
- Erectile dysfunction

Image from Colao A et al. Nat Rev Dis Primers 2019. PMID: 30899019.

ขอดูบัตรประชาชน หรือ ID card อื่นๆ

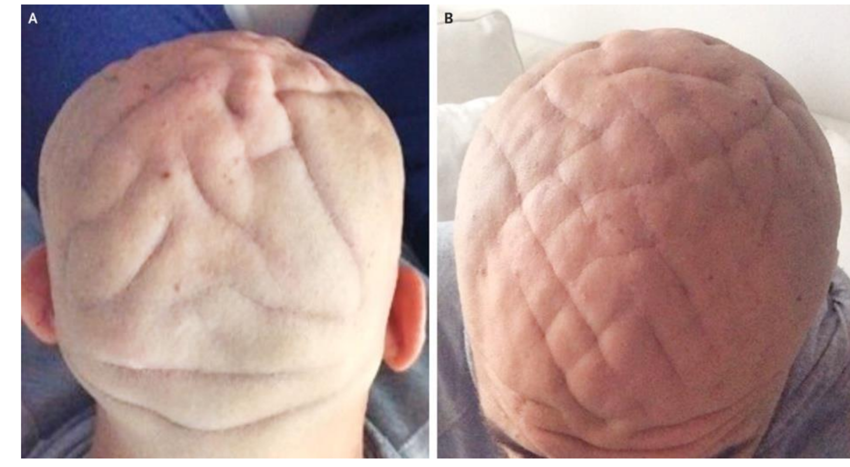


Change is progressive.

Image from Colao A et al. Nat Rev Dis Primers 2019. PMID: 30899019.

Acromegaly: Physical Examination

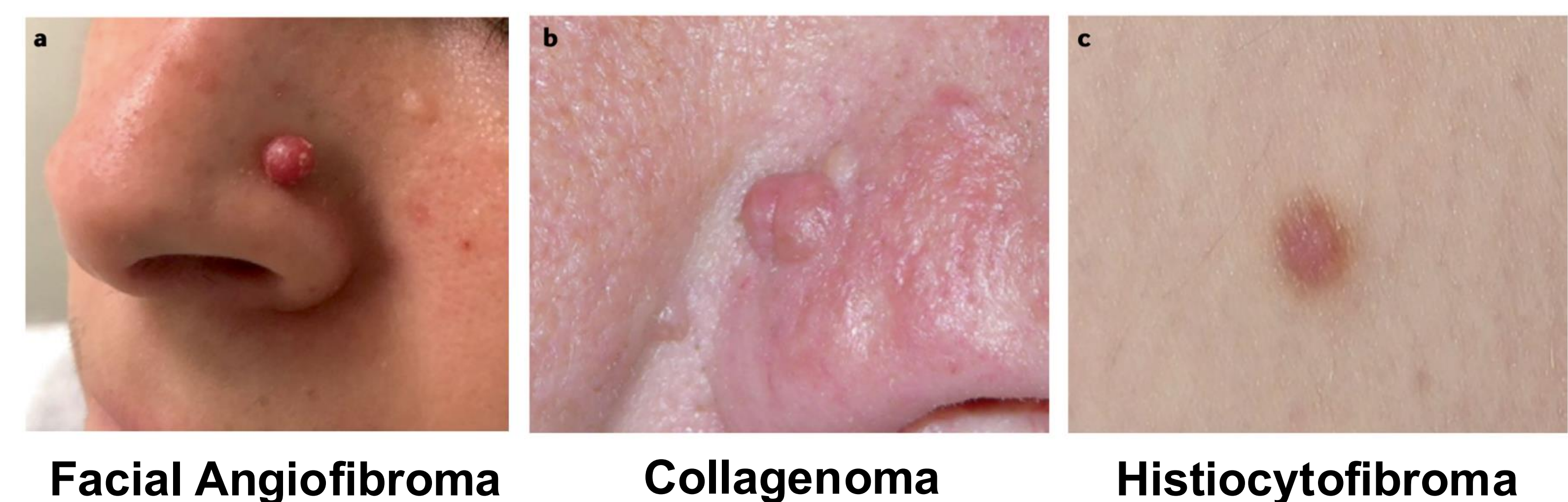
- วัด BP
- Visual field: VF defect, bitemporal hemianopia
- HEENT:
  - Cutis verticis gyrata
  - Coarse face, thick lip, big nose, macroglossia
  - Prominent supraorbital ridge, prognathism, malocclusion
  - Thyroid gland: enlargement, nodules
  - Mallampati
- Abdomen: hepatosplenomegaly
- Cardiovascular: heave/thrill, murmur, gallop
- Musculoskeletal: Spade-like hands and feet, Tinel/Phalen's test
- Skin: acanthosis nigricans, skin tag, oily skin
- Others, e.g., skin signs in MEN1 - lipoma, facial angiofibroma, collagenoma



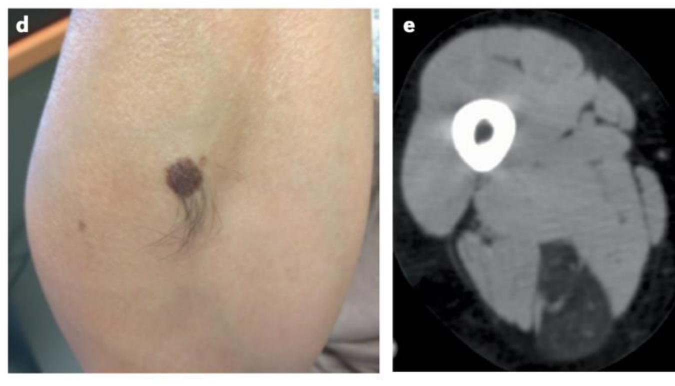
Cutis verticis gyrata

Image from Parolin M, Dassie F. N Engl J Med 2019. PMID: 31042829.

Skin Signs in MEN1



Facial Angiofibroma **Collagenoma** **Histiocytofibroma**



Lipoma

Image from Al-Salameh A et al. Nat Rev Endocrinol 2021. PMID: 33564173.

Etiology of Acromegaly

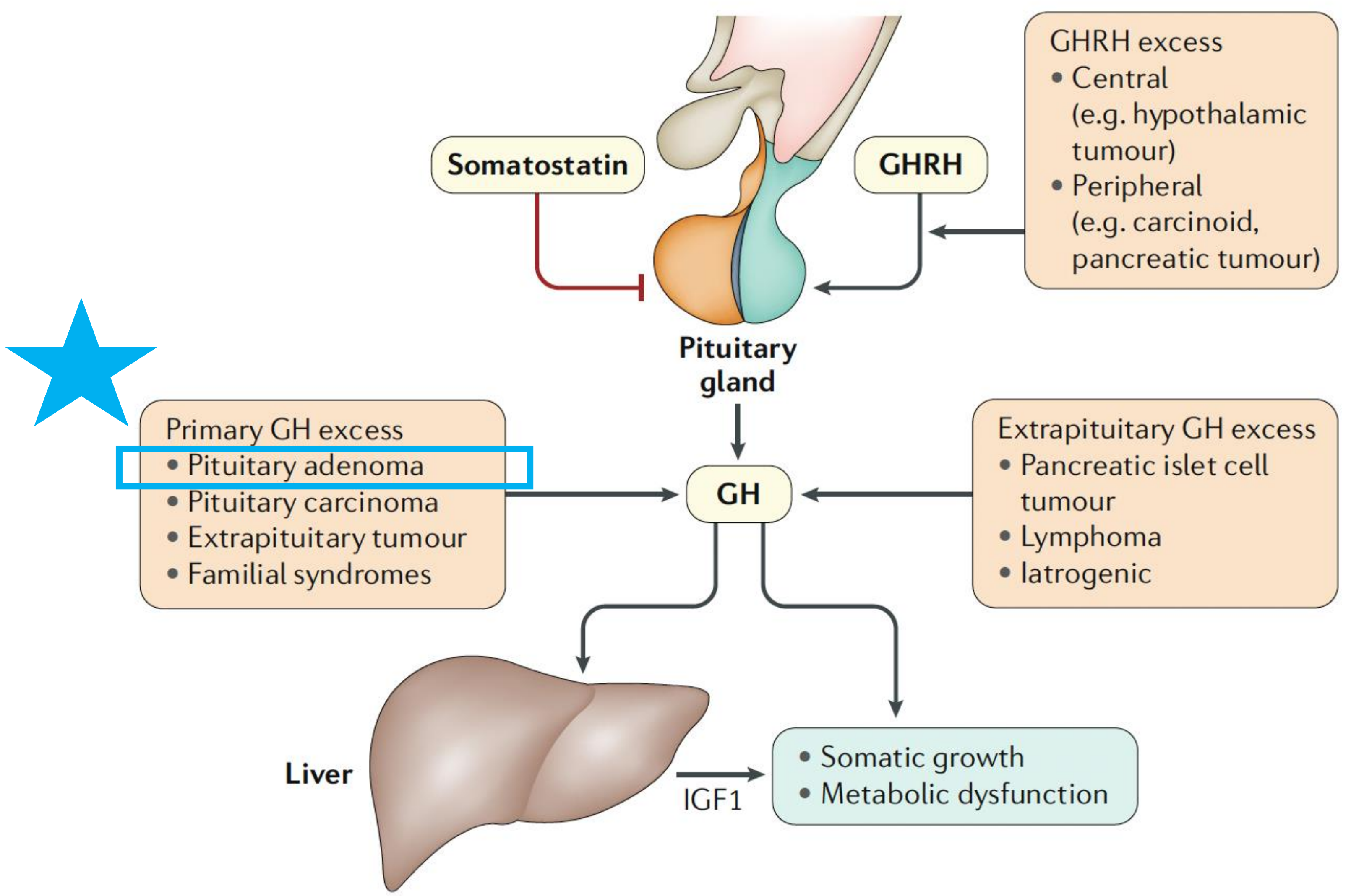


Image from Colao A et al. Nat Rev Dis Primers 2019. PMID: 30899019.

Criteria for Acromegaly Diagnosis

	Diagnosis	Therapeutic efficacy target
1st Acromegaly consensus [3]	IGF-I elevated for age and sex Confirm with random GH ≥ 0.4 µg/L *or* IGF-I elevated for age and sex Confirm with GH > 1 µg/L during OGTT	IGF-I normalized for age and sex GH < 1 µg/L during OGTT
7th Acromegaly consensus [4]	IGF-I elevated for age and sex *and* Random GH elevated	Random GH < 1 µg/L GH < 0.4 µg/L during OGTT
Endocrine society guidelines [5]	IGF-I elevated for age Confirm with GH > 1 µg/L during OGTT	IGF-I normalized for age Random GH < 1 µg/L
14th Acromegaly consensus (this publication)	IGF-I > 1.3 × ULN for age *and* Characteristic clinical signs of disease For equivocal results, IGF-I measurements can be repeated, and OGTT might additionally be useful	IGF-I normalized for age

GH growth hormone; *IGF-I* insulin-like growth factor I; *OGTT* oral glucose tolerance test; *ULN* upper limit of normal

For 75 gm OGTT – เจาะเลือดที่ 0, 60, 120 min

Image from Giustina A et al. Pituitary 2024. PMID: 37923946.

Other Assessment

- Hypertension
- Diabetes mellitus
- Echocardiography, EKG
- OSA
  - If suspected, a diagnostic evaluation should be performed prior to surgery
- Other pituitary hormones
  - Cortisol, FT4, TSH, Gonadotropins, PRL
- BMD, T-L spine X-ray
- Colonoscopy
- Thyroid ultrasonography if palpable thyroid nodules/other risk factors

Adapted from Giustina A et al. J Clin Endocrinol Metab 2020. PMID: 31606735.

Treatment

- Specific: Transsphenoidal surgery with tumor removal
- Supportive: Treatment of comorbidities, hormonal supplement (in patients with pituitary hormone deficiency)

Mutations in Acromegaly and Gigantism Syndromes

Syndrome	Affected gene	Function	Chromosomal locus	Acromegaly penetrance[a] (%)	Main clinical characteristics
Carney complex	*PRKAR1A*	Tumour suppressor	17q24.2	15	Skin pigmentation; cardiac and cutaneous myxomas; thyroid, testis and adrenal tumours; GH-cell hyperplasia or pituitary adenoma
Familial isolated pituitary adenomas	*AIP*	Tumour suppressor	11q13.2	30	Young familial invasive GH-secreting pituitary adenomas, often resistant to therapy
XLAG	*GPR101*	Oncogene	Xq26.3	100	XLAG due to somatotroph cell hyperplasia or pituitary adenoma
McCune–Albright	*GNAS1*[b]	Oncogene	20q13.32	20	Polyostotic fibrous dysplasia, café-au-lait spots and precocious puberty with GH and/or PRL excess
MEN 1	*MEN1*	Tumour suppressor	11q13.1	10	Pancreatic, pituitary and parathyroid gland tumours
MEN 4	*CDKN1B*	Tumour suppressor	12q13.1	Unknown	MEN-1-like, usually with GH-secreting pituitary adenomas
SDH complex deficiency syndrome	*SDHA*, *SDHB*, *SDHC* and *SDHD*	Tumour suppressor	5p15.33 (*SDHA*), 1p36.13 (*SDHB*), 1q23.3 (*SDHC*) and 11q23.1 (*SDHD*)	Very rare	Acromegaly with paraganglioma or pheochromocytoma

GH, growth hormone; MEN, multiple endocrine neoplasia; PRL, prolactin; SDH, succinate dehydrogenase; XLAG, X-linked acrogigantism. [a]Penetrance values are estimates because of the rarity of these syndromes. [b]Mutations in *GNAS1* are mosaic post-zygotic mutations. Data are taken from REFS[71,73,177].

Image from Colao A et al. Nat Rev Dis Primers 2019. PMID: 30899019.

Thank you

Questions are welcome

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