Mahidol University
Faculty of Medicine Ramathibodi Hospital

Endocrine Reviews

Thyroid and Adrenal Disorders

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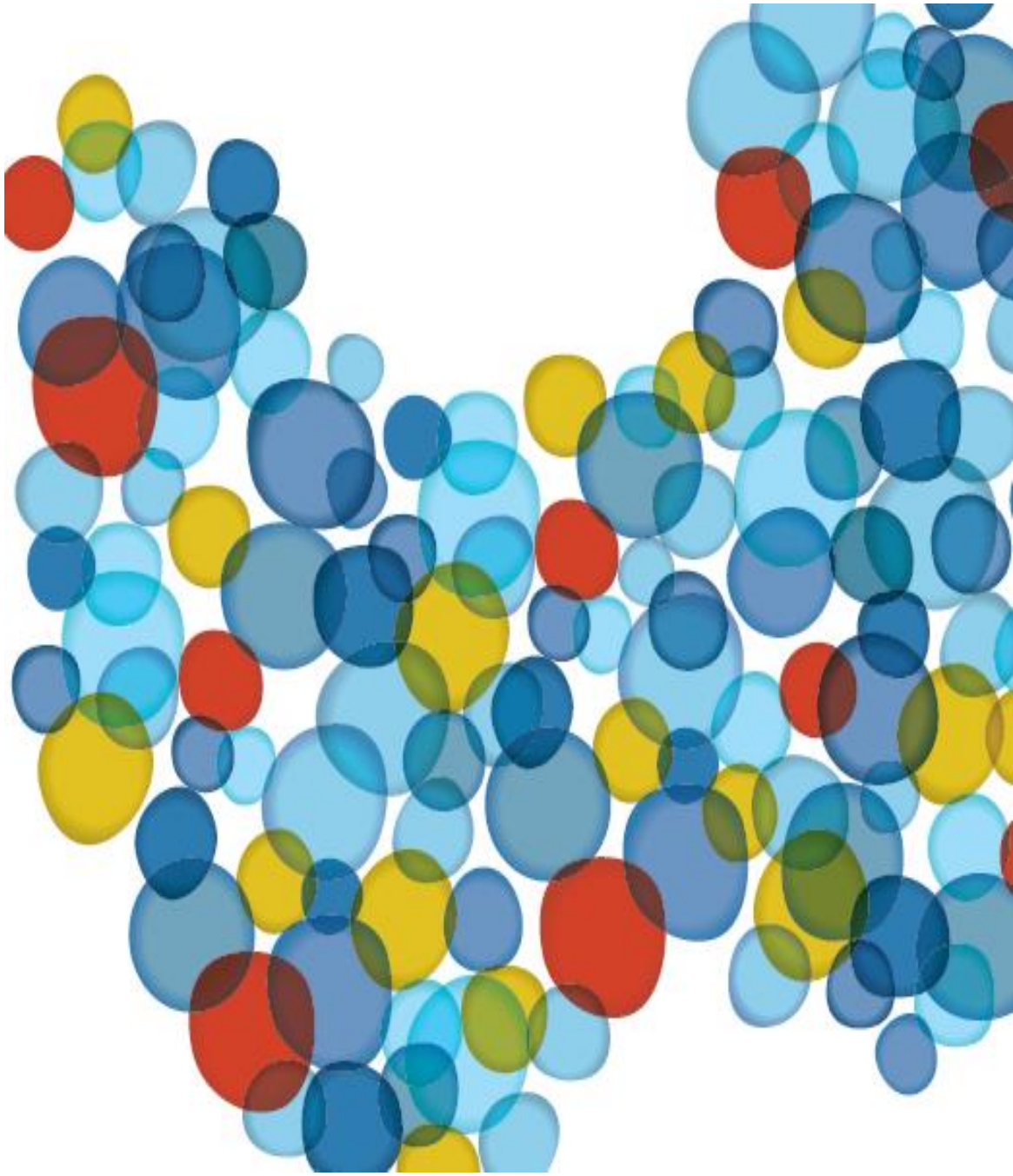
THYROID DISORDERS

- Thyroid Nodule
- Hyperthyroidism
- Hypothyroidism



Approach to thyroid nodule

AVOID screening for thyroid cancer in the general asymptomatic adults

1 Risk of thyroid malignancy

- Clinical risk factors
- USG thyroid
- FNA only in nodules with an intermediate-to-high clinical and risk of malignancy

2 Thyroid dysfunction?

- TSH measurement
- Usually euthyroid

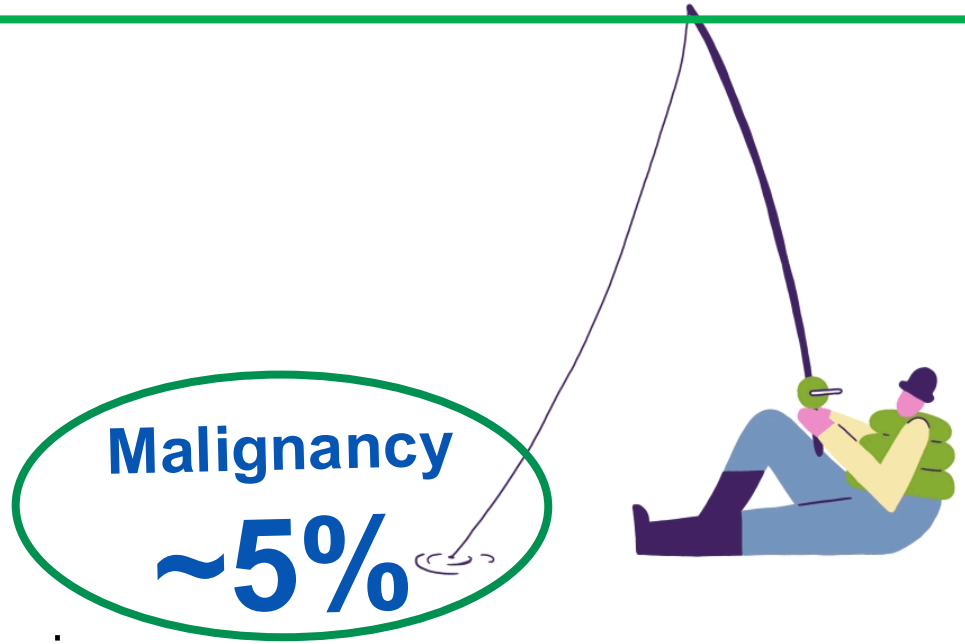
3 Compressive symptoms?

- Neck fullness
- Positional dyspnea
- Dysphagia
- Voice changes
- Neck imaging

Etiologies of thyroid nodule

1. Benign

- Thyroid follicular nodular disease
- Follicular adenoma, oncocytic adenoma
- Colloid cyst, simple cyst, hemorrhagic cyst
- Thyroiditis



2. Malignancy

- Follicular cell-derived carcinoma: papillary carcinoma,
  follicular carcinoma, oncocytic carcinoma, poorly differentiated carcinoma
- Anaplastic thyroid carcinoma
- C-cell-derived carcinoma: medullary thyroid cancer
- Other: primary thyroid lymphoma, sarcoma, teratoma,
  metastatic tumor: renal cell carcinoma, CA lung, CA breast, melanoma

Clinical Risk Factors for Thyroid Malignancy

Male, young age

Radiation exposure:

- Medical irradiation during childhood
- Accidental ionizing radiation exposure from fallout (childhood or adolescence)

Genetic factors:

- Family history of thyroid cancer
- Hereditary cancer syndromes (PTEN hamartoma tumor syndrome, familial adenomatous polyposis, DICER1 tumor predisposition, Carney complex, Werner syndrome)

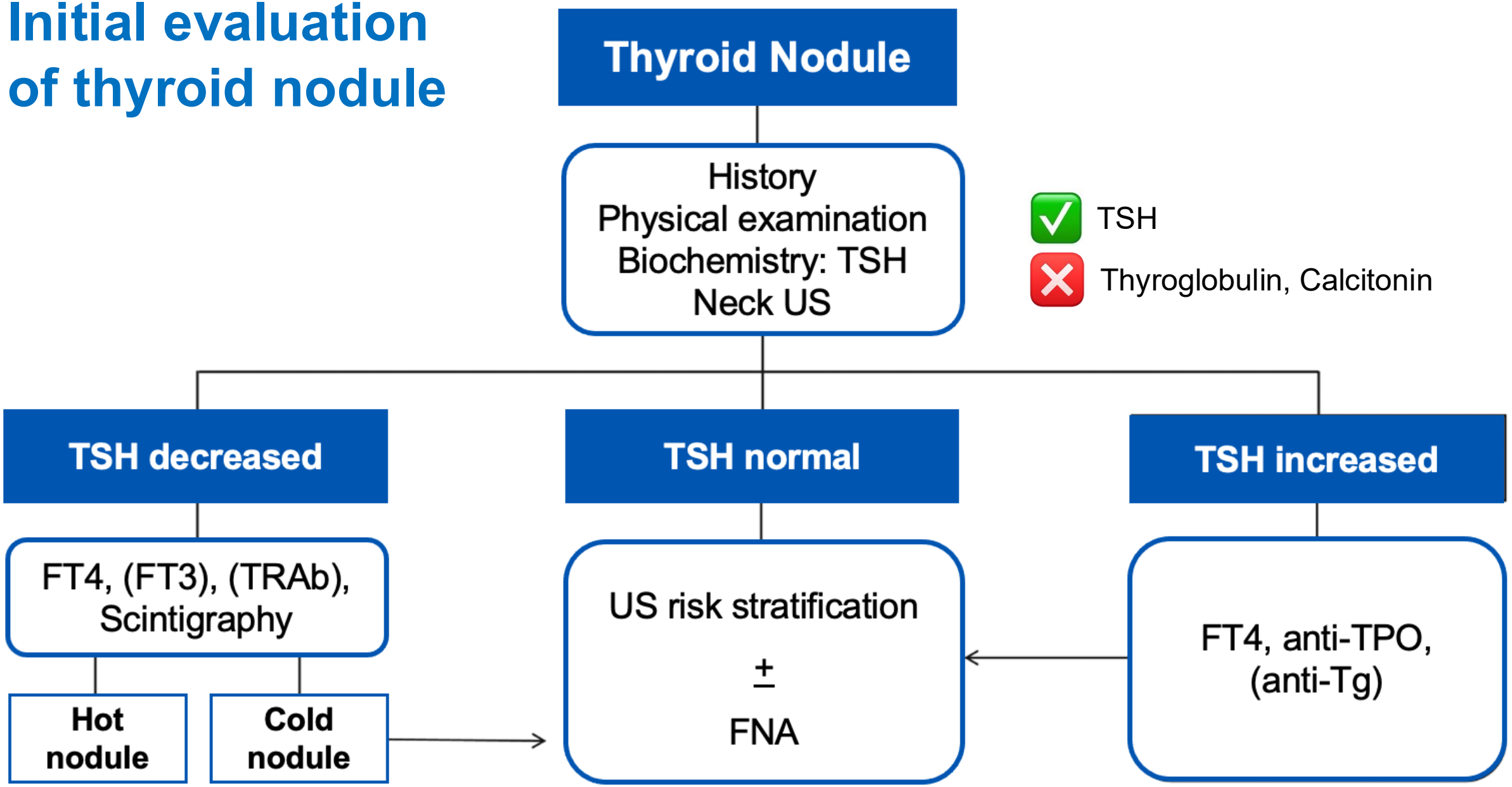
Nodule characteristics:

- Firm, fixed, or rapidly growing nodules
- Intraglandular location
  - Highest risk: isthmus
  - Lowest risk: lower third of a lobe
  - Intermediate risk: middle or upper pole of the lobe

"Not typically included in risk stratification but may guide shared decision-making."

Grani G et al. J Clin Endocrinol Metab. 2020;105(9):2869-2883.

Initial evaluation of thyroid nodule



Q1

A 55-yr-old woman: evaluation of hyperthyroidism Dx 1 week ago

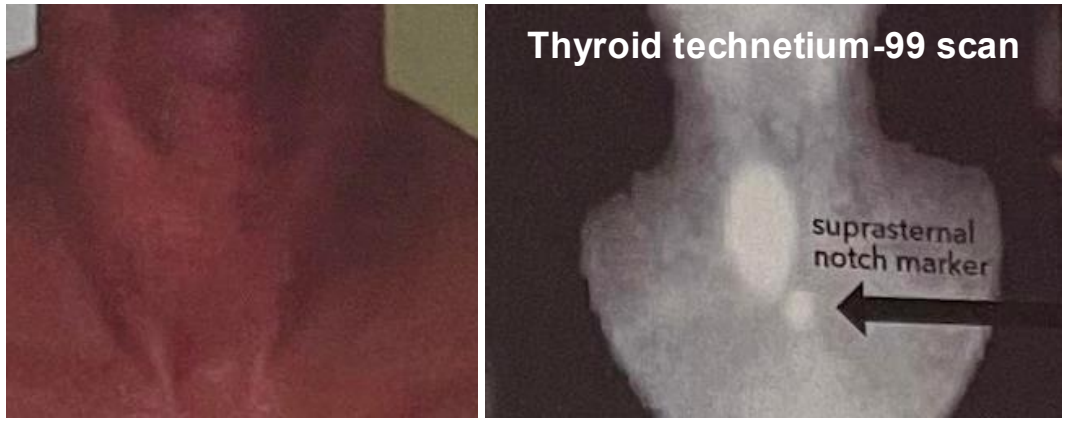
Palpable right thyroid nodule

TSH < 0.01 mU/L ↓

FT4 2.1 ng/dL ↑

TT3 210 ng/dL ↑

Methimazole and atenolol were prescribed.



Uptake at 24 hr = 30% (N 14-30%)

Which of the following is the most appropriate management?

A. NSAIDS

B. Thyroglobulin level

C. FNA thyroid nodule

D. Radioactive iodine

Answer:
D. Radioactive iodine

Dx toxic adenoma

Thyroid US with
survey of the cervical lymph nodes
should be performed in
ALL patients with
known or suspected thyroid nodules.

Thyroid US is
NOT routinely recommended
for asymptomatic subjects

Role of Thyroid Ultrasound

Palpable nodule

- Confirmation of a sonographically identifiable nodule corresponding to the palpable abnormality
- Detection of additional nonpalpable nodules for which FNA may be indicated
- Determination of accuracy of FNA by palpation
- Identification of the sonographic characteristics of the thyroid nodule(s)

Normal thyroid examination

- Prior history of H&N irradiation
- Family history of thyroid cancer, including PTC

2017 ACR: ACR-TIRADS

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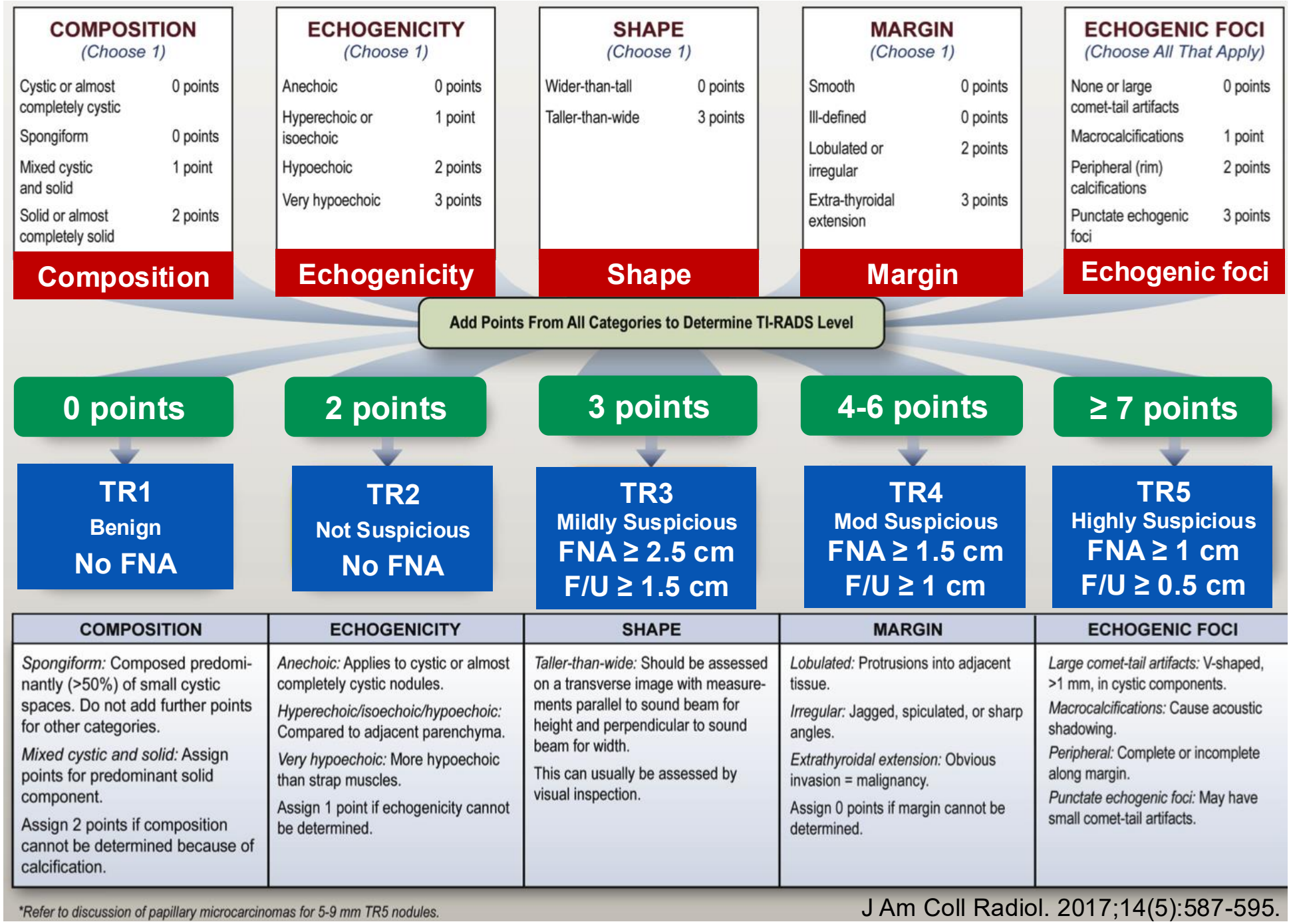
EXCEPTIONS

- FDG avid nodule
- Suspicious cervical lymph nodes
- Preoperative for hyperparathyroidism
- Nodules adjacent to RLN/trachea
- Symptomatic nodules
- Mummified cysts: restructured benign collapsed thyroid nodule (S/P FNA, PEI)
- Clinical risk factors: MEN type 2, radiation in childhood, family history
- Referrer and patient preference
- Age and comorbidities

Follow-up Intervals

- TR5: q 1 yr for 5 years
- TR4: 1, 2, 3, and 5 years
- TR3: 1, 3, and 5 years
- TR1 & 2: No FNA or F/U



COMPOSITION	ECHOGENICITY	SHAPE	MARGIN	ECHOGENIC FOCI
Spongiform: Composed predominantly (>50%) of small cystic spaces. Do not add further points for other categories. *Mixed cystic and solid:* Assign points for predominant solid component. Assign 2 points if composition cannot be determined because of calcification.	*Anechoic:* Applies to cystic or almost completely cystic nodules. *Hyperechoic/isoechoic/hypoechoic:* Compared to adjacent parenchyma. *Very hypoechoic:* More hypoechoic than strap muscles. Assign 1 point if echogenicity cannot be determined.	*Taller-than-wide:* Should be assessed on a transverse image with measurements parallel to sound beam for height and perpendicular to sound beam for width. This can usually be assessed by visual inspection.	*Lobulated:* Protrusions into adjacent tissue. *Irregular:* Jagged, spiculated, or sharp angles. *Extrathyroidal extension:* Obvious invasion = malignancy. Assign 0 points if margin cannot be determined.	*Large comet-tail artifacts:* V-shaped, >1 mm, in cystic components. *Macrocalcifications:* Cause acoustic shadowing. *Peripheral:* Complete or incomplete along margin. *Punctate echogenic foci:* May have small comet-tail artifacts.

*Refer to discussion of papillary microcarcinomas for 5-9 mm TR5 nodules.

J Am Coll Radiol. 2017;14(5):587-595.

Q2

A 65-yr-old woman: F/U Hashimoto thyroiditis Rx with LT4

- Thyroid exam: enlarged thyroid gland, Rt > Lt,

  mobile **2-cm nodule** in the lower pole; no palpable cervical adenopathy

- Normal TSH

Which of the following is the most appropriate diagnostic test to perform next?

A. US neck

B. CT scan of the neck

C. FNA thyroid nodule

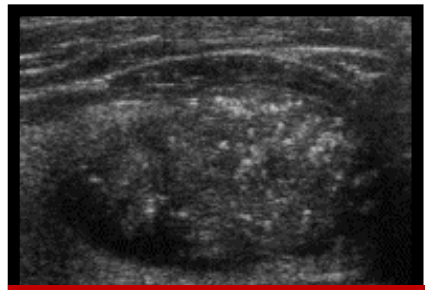
D. Thyroid uptake and scan

Answer:
A. US neck

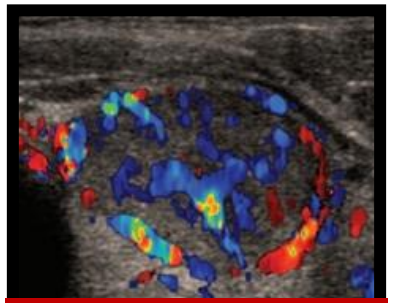
US can confirm the presence of thyroid nodules palpated on examination and based on findings help to determine if FNA is needed to assess for malignancy

Sonographic Features Associated with Thyroid Cancer

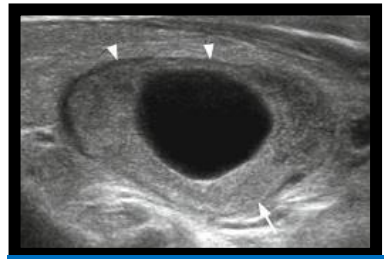
	Sensitivity	Specificity
Microcalcification	44%	89%
Hypoechoic	81%	53%
Solid	86%	18%
Tall > wide	48%	92%
Poorly defined margins	55%	79%
Absence of halo	66%	54%
Intranodular vascularity	62%	77%



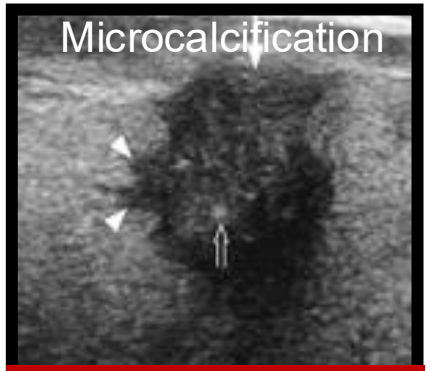
Microcalcification



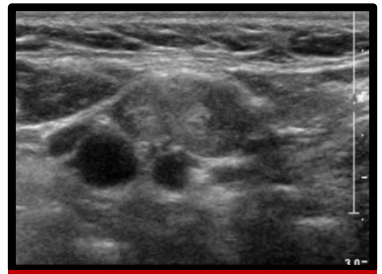
Intranodular vascularity



Halo



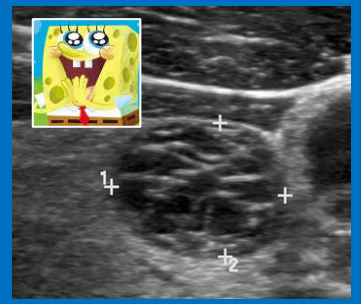
Hypoechoic
Poorly defined margins
Tall > wide



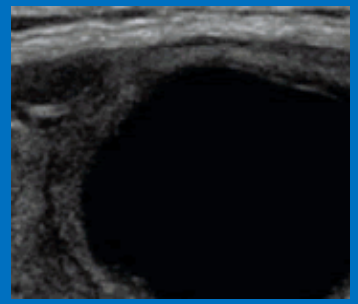
Cervical node metastasis

Microcalcification represents psammoma bodies in PTC

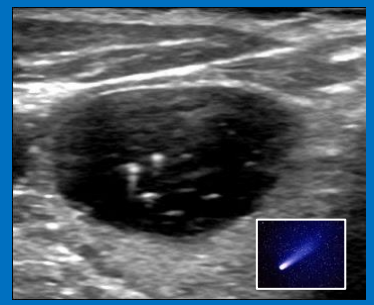
Sonographic Features of Benign Thyroid Nodules



Spongiform



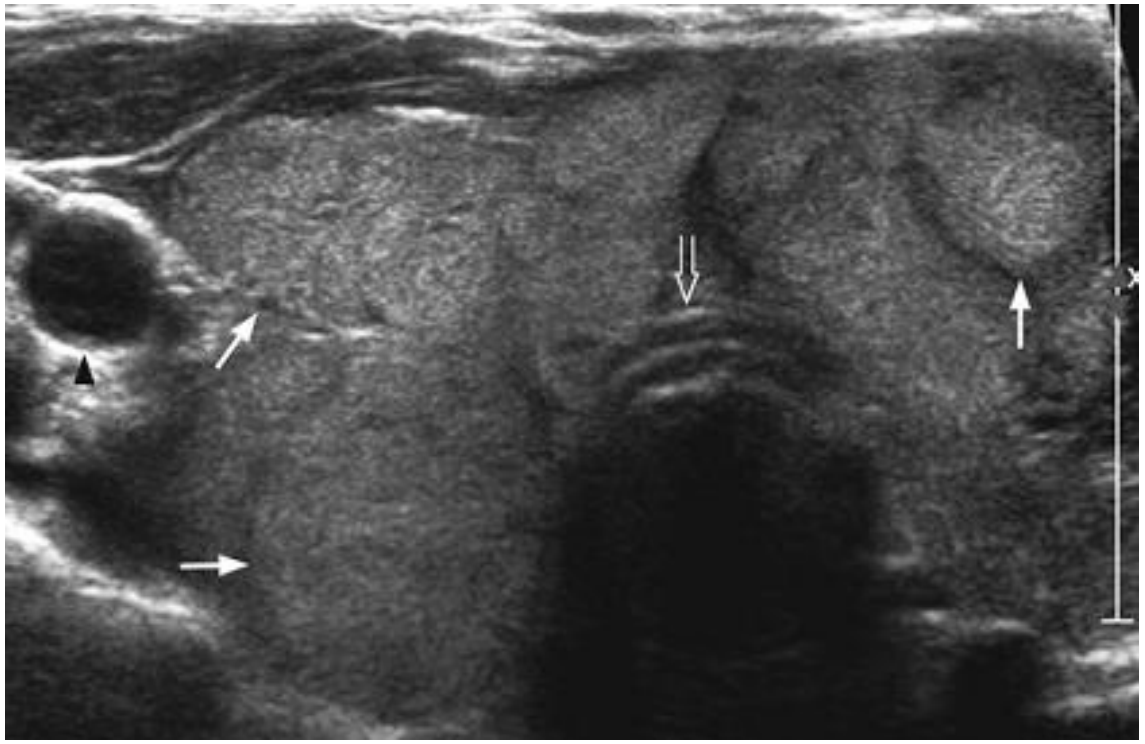
Pure cyst



Comet-tail

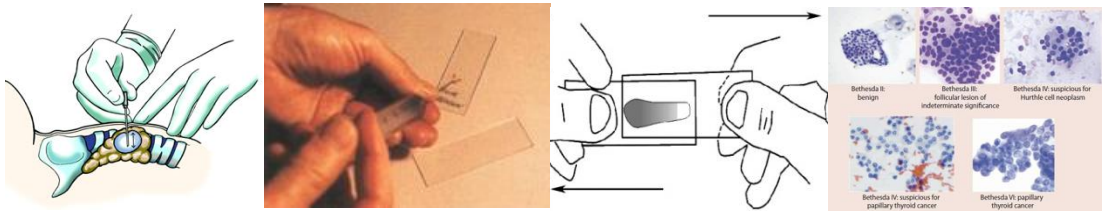
Comet-tail artifact represents "Benign" colloid nodule

Multiple Nodules



- When multiple nodules ≥ 1 cm are present, FNA based upon US pattern
- If multiple sonographically similar low or very low suspicion pattern nodules, the likelihood of malignancy is low and it is reasonable to FNA the largest nodule (>2 cm) and observe others

Recommend FNA for <u>no more than 2 nodules</u>
with the highest point scores that warrant FNA



2023 Bethesda system for reporting thyroid cytopathology

Diagnostic category	Risk of Malignancy Mean % (range)	Usual management
I. Nondiagnostic	**13** (5-20)	Repeat FNA with US guidance
II. Benign	**4** (2-7)	Clinical and US F/U
III. AUS	**22** (13-30)	Repeat FNA, molecular testing, Dx lobectomy, or surveillance
IV. FN	**30** (23-34)	Molecular testing, Dx lobectomy
V. Suspicious for malignancy	**74** (67-83)	Molecular testing, lobectomy or near-total thyroidectomy
VI. Malignancy	**97** (97-100)	Lobectomy or near-total thyroidectomy

AUS, atypia of undetermined significance; Dx, diagnostic; F/U, follow-up
FN, follicular neoplasm; FNA, fine-needle aspiration; US, ultrasound

Ali SZ, VanderLaan PA. The Bethesda System for Reporting Thyroid Cytopathology: Definitions, Criteria, and Explanatory Notes, 3rd ed. Springer: New York, NY, USA; 2023.

MANAGEMENT OF BENIGN THYROID NODULE

- Observe
- Radioactive iodine
- Surgery
- Minimally invasive technique

- Percutaneous ethanol injection
- Radiofrequency ablation
- Laser thermal ablation
- Microwave ablation
- High frequency ultrasonography

Management of differentiated thyroid cancer

Options for small, low-risk papillary thyroid carcinoma

- Active surveillance
- Lobectomy
- Minimally invasive interventions

Q3

A 46-yr-old man with Hx of thyroid nodule for 2 years

- USG: 2-cm left upper pole isoechoic solid nodule without microcalcification or irregular margin, no lymphadenopathy

  = low suspicion for malignancy
- FNA: benign

F/U 2 years

Physical exam: 2-cm left upper pole thyroid nodule, firm, mobile, no LN enlargement
TSH 2.0 mIU/L (N)

Which of the following is the most appropriate next step in management?

A. Repeat FNA

B. LT4 initiation

C. Thyroid scan & uptake

D. USG thyroid

Answer: D. USG thyroid

2015 ATA guidelines: F/U USG

High-suspicion nodules: 6-12 months

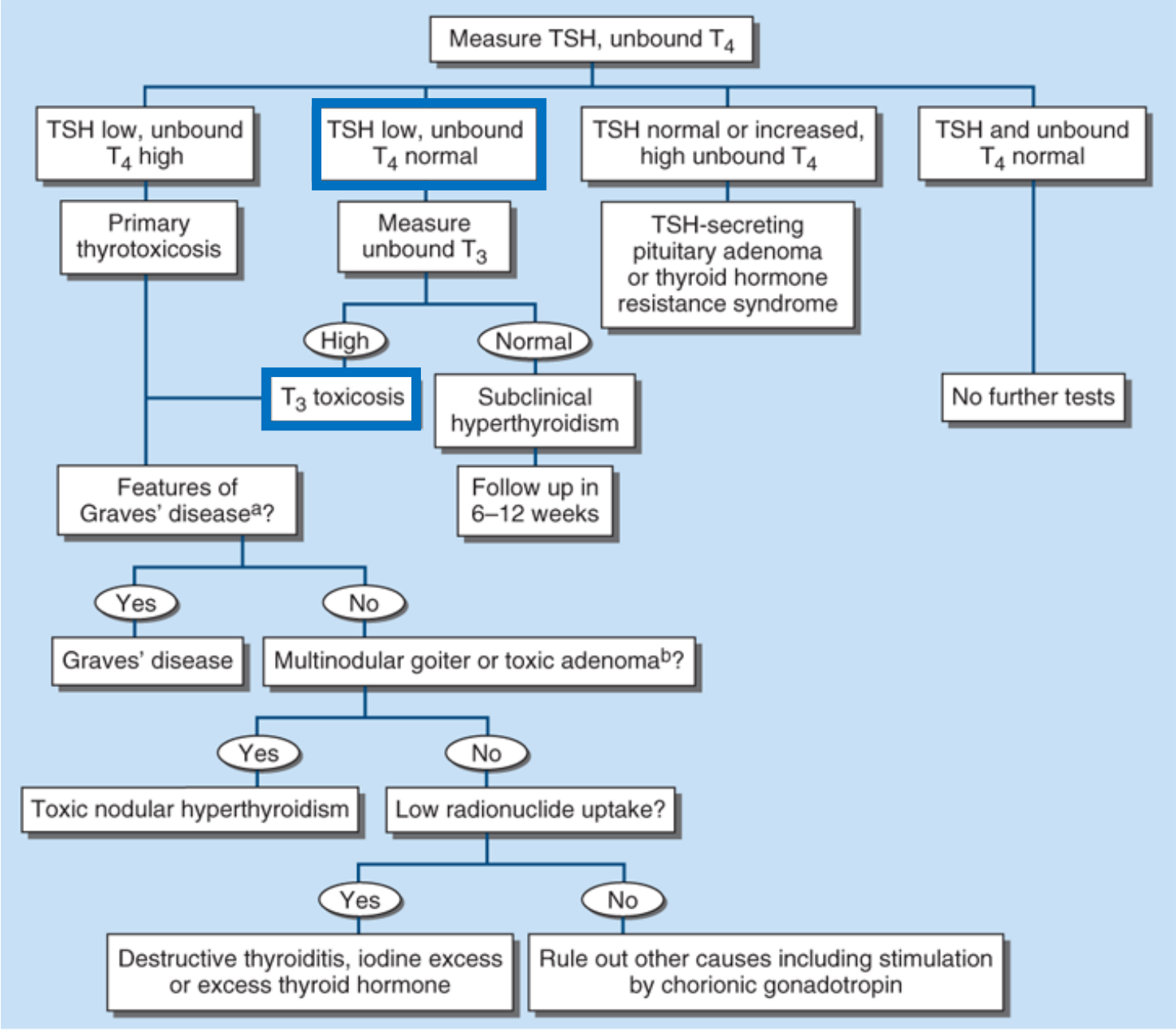
Intermediate- and low-suspicion nodules: 12-24 months

Very low-suspicion nodules: > 24 months

THYROTOXICOSIS

Determining the underlying cause of thyrotoxicosis is essential for guiding management

Etiologies	Pathophysiology	TSH	Thyroid uptake	Tg	Clues
Graves' disease	TSH receptor Ab	↓	↑	↑	GO, TRAb, goiter, bruit, fam Hx, autoimmune
Toxic MNG	Autonomous secretion	↓	↑	↑	MNG
Toxic adenoma	Autonomous secretion	↓	↑	↑	Size > 3 cm
Struma ovarii	Ovarian teratoma (+thyroid tissue)	↓	↑ at ovary	↑	Abd pain, mass, ascites
Iodine excess	Jod-basedow phenomenon	↓	↓	↑	Hx contrast, amiodarone
Subacute thyroiditis	Acute release of thyroid hormone	↓	↓	↑	Painful thyroid, ESR
hCG-secreting tumor	hCG binds with TSH receptor	↓	↑	↑	hCG level
Factitious	Exogenous thyroid hormone	↓	↓	↓	Rx w cholestyramine
TSHoma	TSH-secreting pituitary adenoma	↓/N/↑	↑	↑	MRI pituitary



Source: Longo D, Fauci A, Kasper D, Hauser S, Jameson JL, Loscalzo J, Holland S, Langford C: Harrison's Principles of Internal Medicine, 22nd Edition

T3 toxicosis

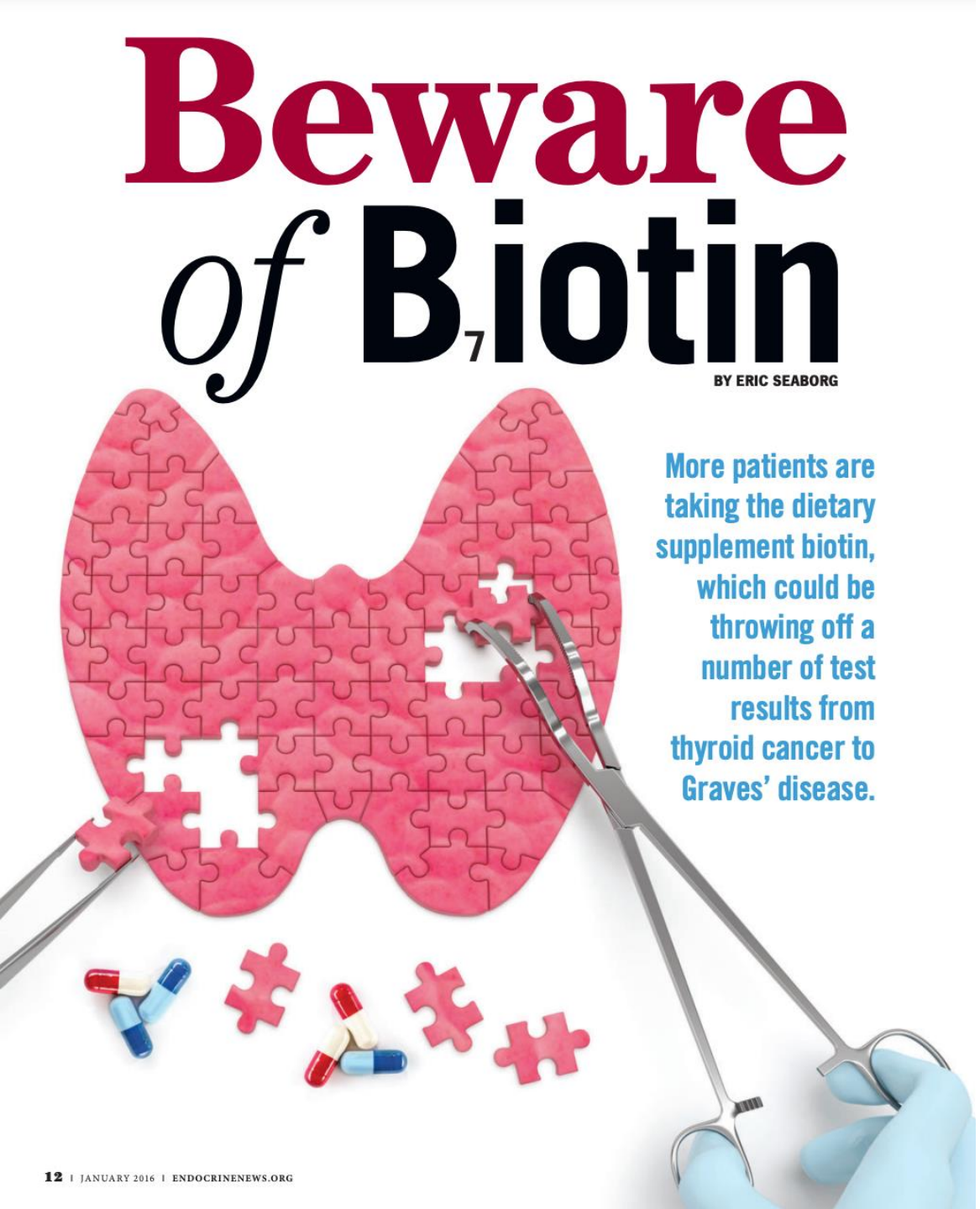
Prevalence:
3.5-5.6% (general clinic[1,2])
16% (thyroid clinic[3])

- Early hyperthyroidism; Graves' disease, toxic MNG
- Iodine deficiency area
- During treatment of Graves' disease

T4 toxicosis

- Hyperthyroidism with nonthyroidal illness
- Drug effects: LT4, amiodarone

1. Sriphrapradang C, Bhasipol A. Ann Med Surg 2016.
2. Panchavinnin P et al. J Med Assoc Thai. 2018;101(8):1055-9.
3. Snabbon T et al. J Med Assoc Thai 2004;87 Suppl2:S19-21



"Biotin" problem

- Biotin in human serum is a potential interfering factor for **streptavidin-biotin-based assays**
- Biotin in patient samples can cause falsely high or fasely low results
- Immunoassay-based laboratory results

- ACTH
- AFP
- Anti TPO
- Anti-TG
- Ca125
- Ca15-3
- Ca19-9
- CEA
- Cortisol
- C-peptide
- DHEAS
- Digoxin
- Estradiol
- Folate
- Free PSA
- FSH
- FT3
- FT4
- Beta HCG
- Hs TnT
- IgE
- Insulin
- LH
- Progesterone
- prolactin
- PSA
- PTH
- SHBG
- Testosterone
- Total B12
- TSH

↑ T3, T4

↓ TSH

↑ TRAb

Stop taking biotin for **at least 2 days before** thyroid testing

Q4

Due to an outbreak of thyrotoxicosis in the prison,

you are the internist assigned to investigate the cause.

Several male prisoners

Palpitation, weight loss, fatigue, muscle weakness

↓TSH, ↑FT4, ↑FT3

Low radioactive iodine uptake

Low thyroglobulin levels

Which of the following is the most likely diagnosis?

A. Iodine excess

B. Graves disease

C. Subacute thyroiditis

D. Factitious thyrotoxicosis

Answer:
D. Factitious thyrotoxicosis

- Hamburger thyrotoxicosis
- Exposure to exogenous thyroid hormone in frozen meat

(Pattarawongpaiboon C et al. BMJ Nutr Prev Health. 2023;6(2):318-325.)

Q5

A 32-yr-old woman: palpitation, heat intolerance for 2 weeks

First trimester of pregnancy

Pulse rate 110/min; fine tremor

Thyroid: nontender and symmetrically and diffusely enlarged

TSH <0.01 mU/L, ↑FT4 5.3 ng/dL

Which of the following is the most appropriate diagnostic test?

A. Thyroid scan & uptake

B. Thyroid-stimulating immunoglobulin

C. Thyroid ultrasonography

D. Total T3 levels

Answer:
B. Thyroid-stimulating immuoglobulin

TSH receptor antibody

Q6

A 29-yr-old woman: abnormal TFTs

GA 26 wk pregnancy

Lack of weight gain during pregnancy, palpitation, anxiety, insomnia

No famHx of thyroid or autoimmune disease

Exam: pulse 98/min, thin woman, mild tremor, lid lag, small goiter, no exophthalmos

↑ TSH 6.5 mU/L, ↑ FT4 2.6 ng/dL

Which of the following is the most likely diagnosis?

A. Gestational thyrotoxicosis

B. Graves disease

C. Hypothyroidism

D. TSHoma

Answer:
D. TSHoma

Inappropriate TSH secretion

Raised thyroid hormones {(free) T4 &/or (free) T3}
Non-suppressed TSH (within or above reference interval)

- **Review: thyroid status, intercurrent illness, medications**
- **Investigate for lab assay interference**

Resistance to thyroid hormone-beta		TSHoma
present in ~90%	**Affected family members**	absent
mutation in ~90%	***THRB* sequencing**	no mutation
normal	**SHBG / ICTP**	raised (occ. normal)
normal	**ASU / ASU:TSH molar ratio**	raised (or normal)
preserved / exaggerated	**TSH response to TRH**	absent / blunted
(near) full suppression	**L-T3 suppression test**	no / limited suppression
no response	**Response to depot SRL trial**	normalise T4&T3 in ≥80%
no adenoma (incidentaloma in ~10%)	**Pituitary MRI (± molecular PET imaging)**	adenoma (occasionally occult)

Adapted from 2024 European Thyroid Association Guidelines on diagnosis and management of genetic disorders of thyroid hormone transport, metabolism and action

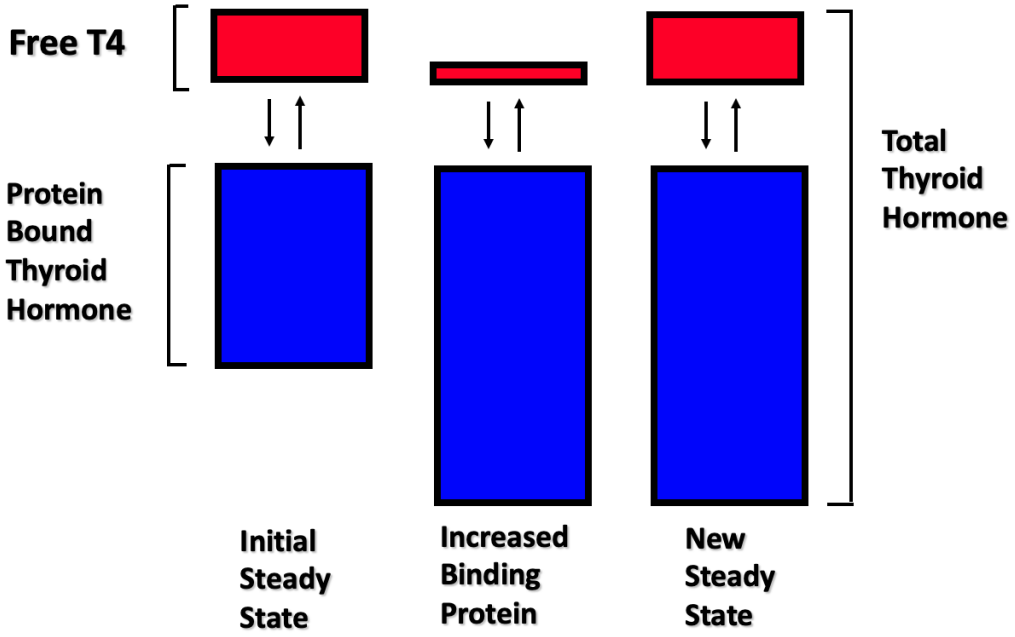
Factors effect thyroxine-binding globulin (TBG)

↑
- Estrogen, hyperestrogenemic states; pregnancy
- Tamoxifen, oral contraceptives
- Opiate, 5FU, clofibrate, perphenazine
- Infectious and chronic active hepatitis, biliary cirrhosis
- Acute intermittent porphyria
- HIV infection
- Small cell carcinoma
- Genetic factors

↓
- Androgen
- Large doses of glucocorticoid
- L-asparaginase
- Active acromegaly
- Malnutrition
- Major systemic illness
- Nephrotic syndrome
- Genetic factors

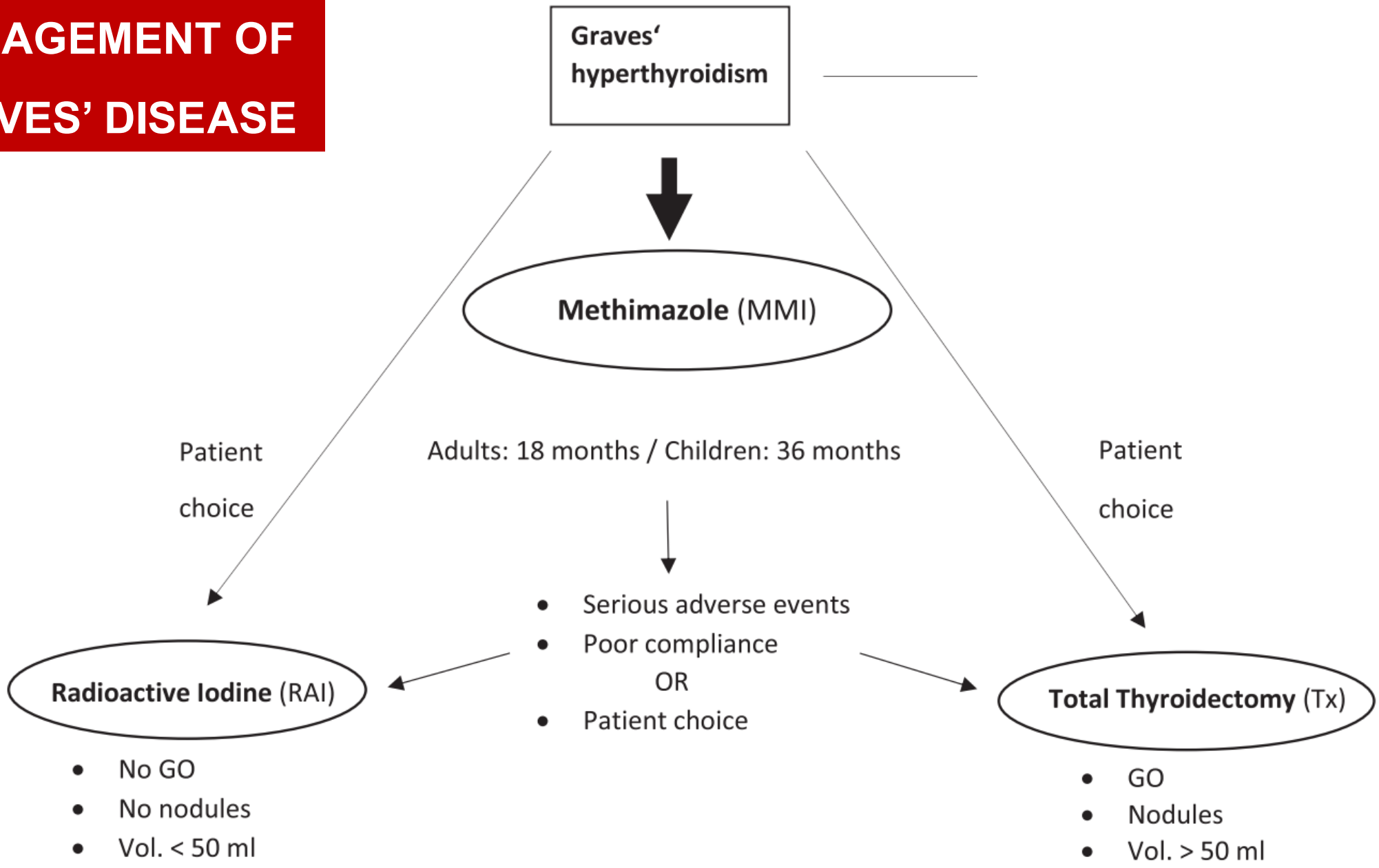
Euthyroid hyperthyroxinemia

- TBG excess
- Familial dysalbuminemic hyperthyroxinemia (FDH)
- Anti-T4 antibody
- ↓T4 deiodination: amiodarone, high dose propranolol
- Assay artifact
- Acute psychosis, high altitude, amphetamine



DeGroot LJ, Stanbury JB: The Thyroid and its diseases 4th ed, Wiley, 1975

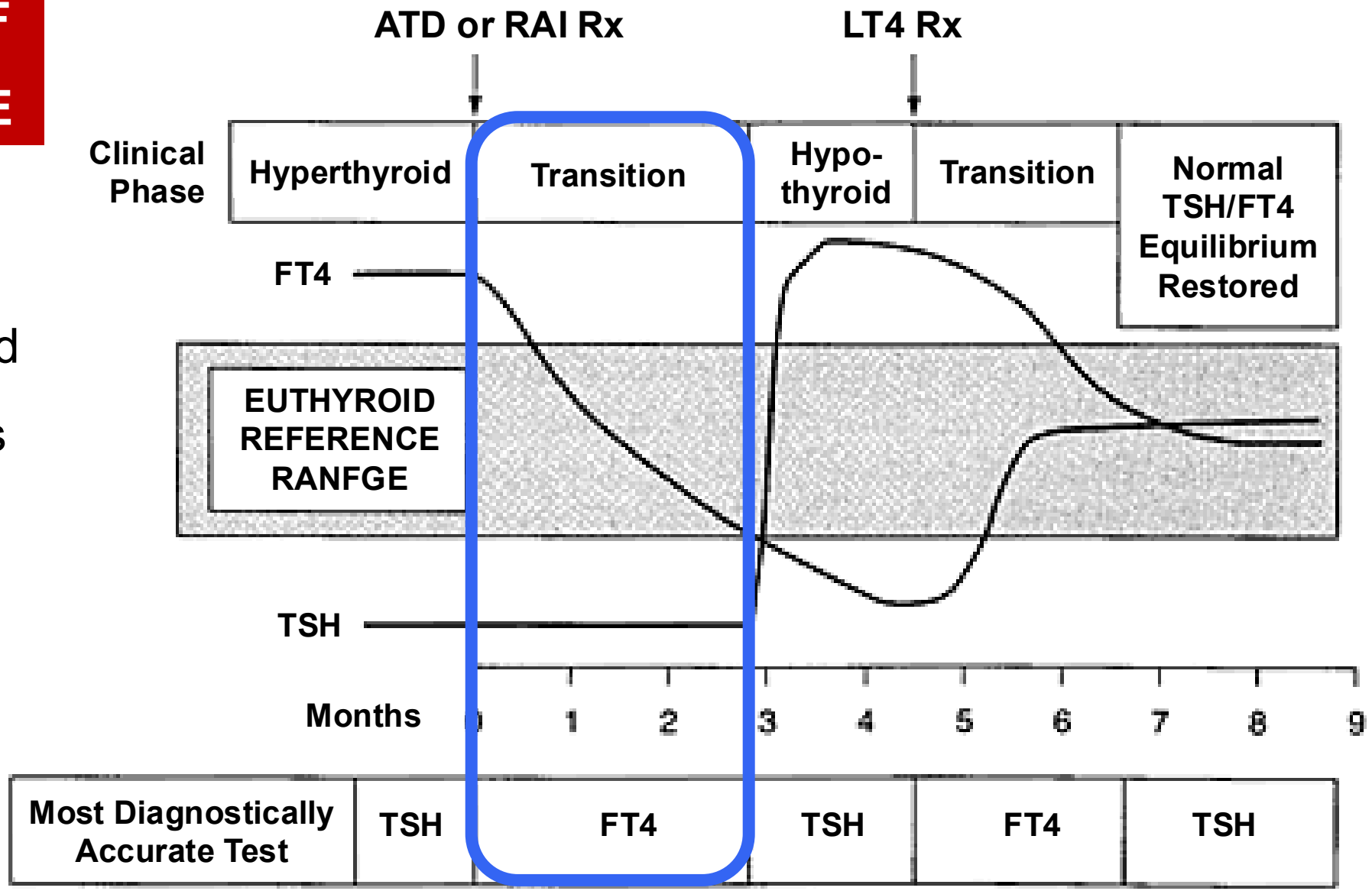
MANAGEMENT OF GRAVES' DISEASE



Kahaly GJ. J Clin Endocrinol Metab. 2020;105(12):3704-3720.

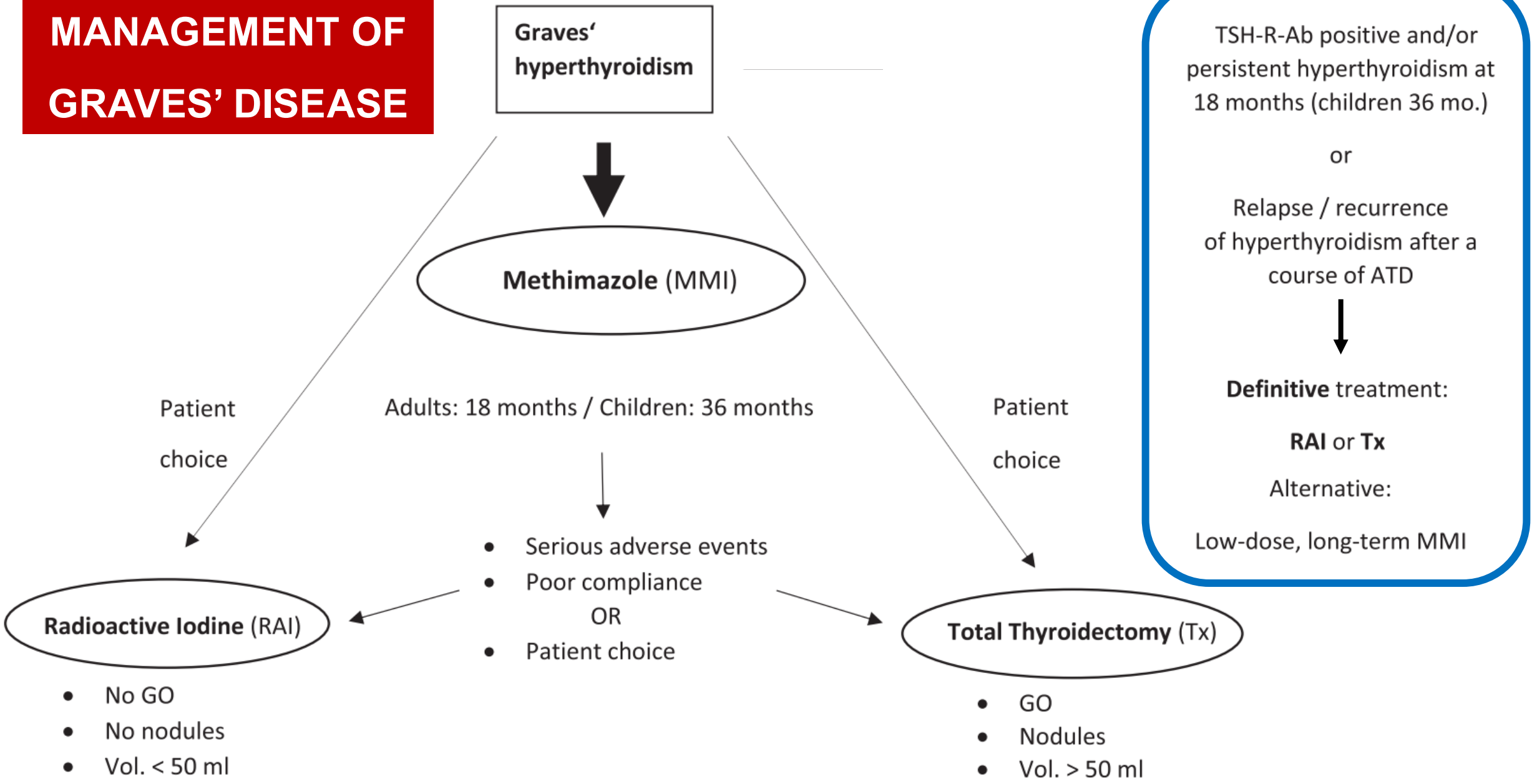
MANAGEMENT OF GRAVES' DISEASE

- TSH levels often remain suppressed for several months
- Not a sensitive index of early Rx response



Baloch Z et al. Thyroid. 2003; 13:1-126.

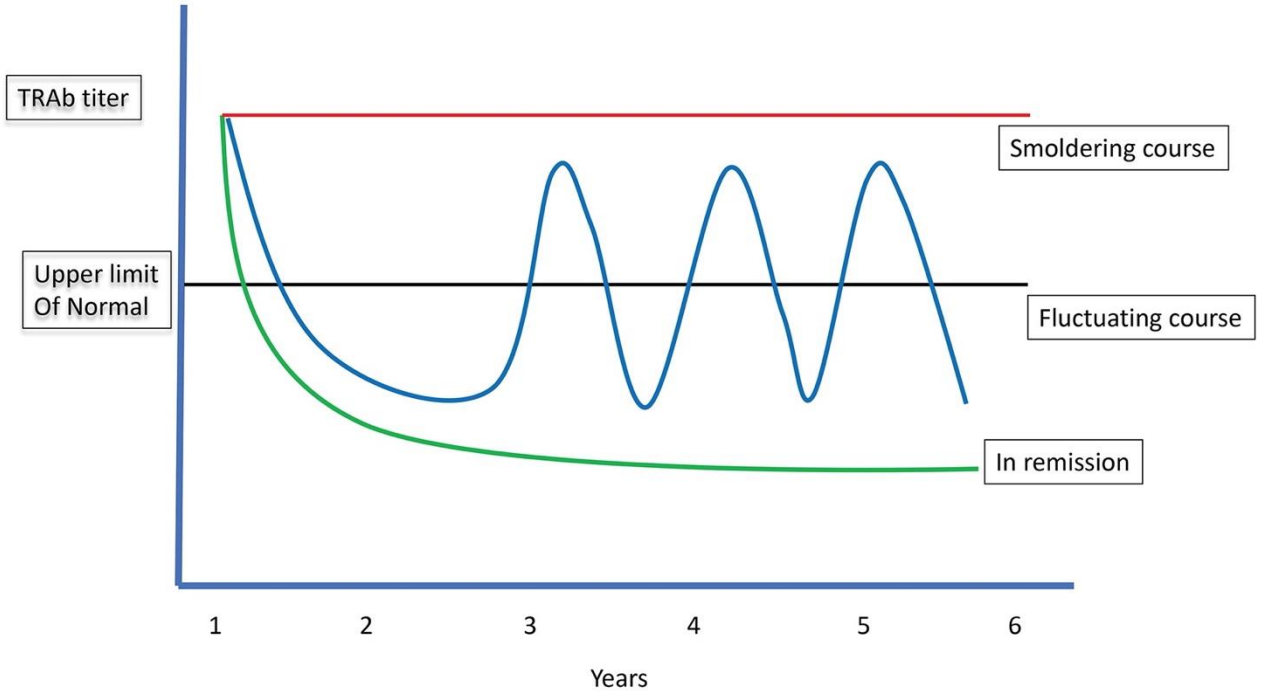
MANAGEMENT OF GRAVES' DISEASE



Kahaly GJ. J Clin Endocrinol Metab. 2020;105(12):3704-3720.

Long-term MMI for Graves' Disease

TRAb Status in Graves' Disease



- Relapse of hyperthyroidism is common after stopping conventional 12–18 months of Rx.
- Long-term MMI Rx is effective and safe for maintaining euthyroidism.
- Studies show ≥ 5 years of ATD treatment leads to remission in most Graves' hyperthyroidism patients.

Azizi F et al. J Clin Endocrinol Metab. 2024;109(10):e1881-e1888.

GRAVES' DISEASE

Side Effects of Antithyroid Drugs

Minor

Common (1-5%)

- Urticaria or other rash
- Arthralgia
- Fever
- Transient leukopenia

Uncommon (<1%)

- GI upset
- Abnormal smell and taste
- Arthritis

Major

STOP THE DRUG
DO NOT
SWITCH/↓DOSE

Rare (0.2-0.5%)

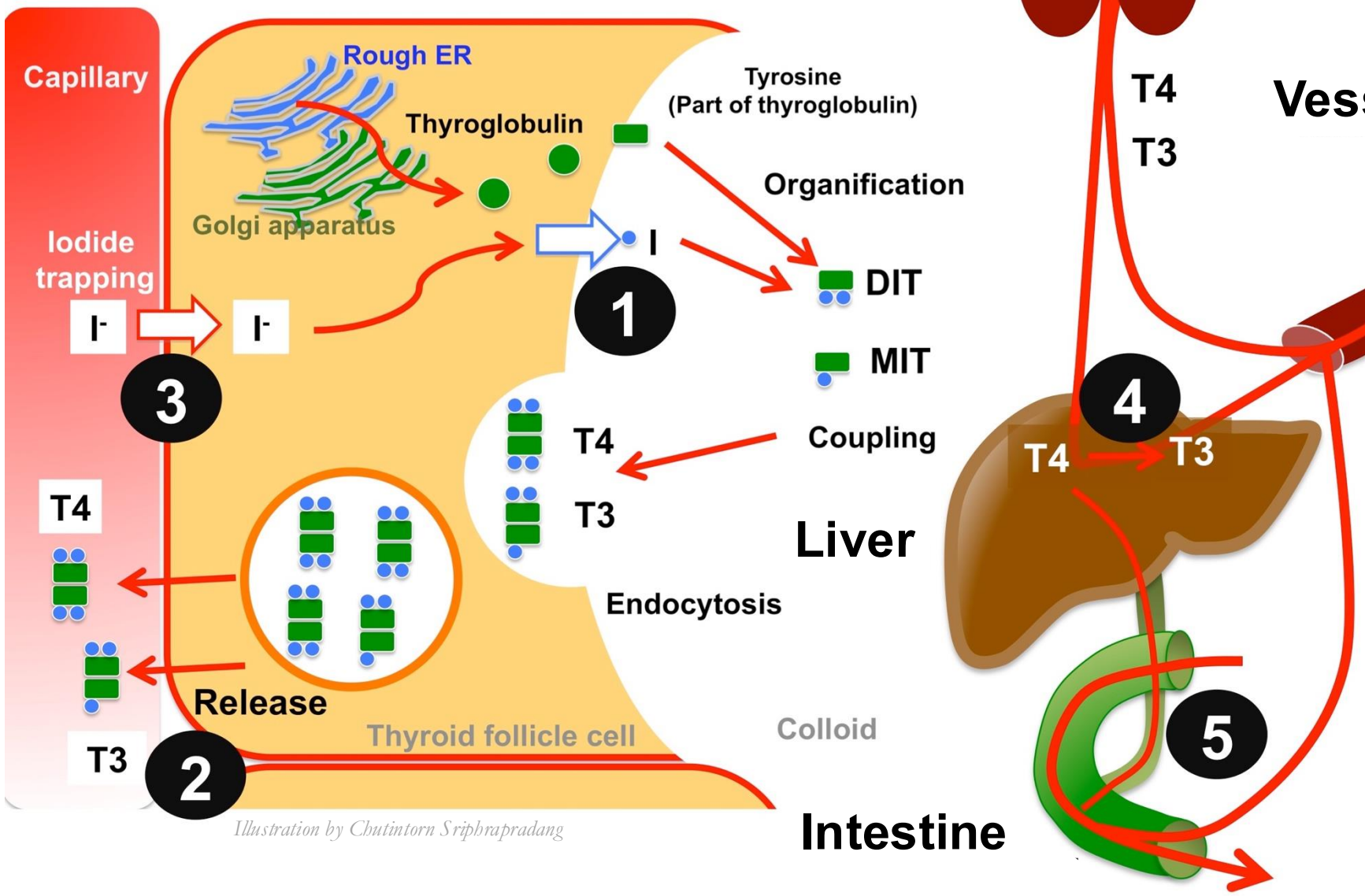
- Agranulocytosis

Very rare (<0.1%)

- Aplastic anemia
- Thrombocytopenia
- Toxic hepatitis (PTU)
- Cholestatic jaundice (MMI)
- Vasculitis, lupus-like, ANCA+ (PTU)
- Hypoprothrombinemia (PTU)
- Hypoglycemia (MMI, anti-insulin Ab)
- Pancreatitis (MMI) NEW

Thionamide and nonthionamide for management of thyrotoxicosis

THYROID HORMONE SYNTHESIS

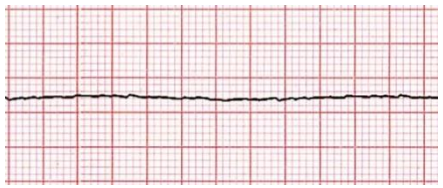


Large dose of inorganic iodide

- Inhibits thyroid hormone release:
- More rapid action than ATD, corticosteroid
- Wolff-Chaikoff effect

1. Thionamide, lithium
2. Inorganic iodide, lithium
3. Perchlorate
4. High dose PTU, high dose propranolol, corticosteroid
5. Cholestyramine
6. Plasma exchange

AVOID USE BETA-BLOCKER in frank heart failure → CV collapse!



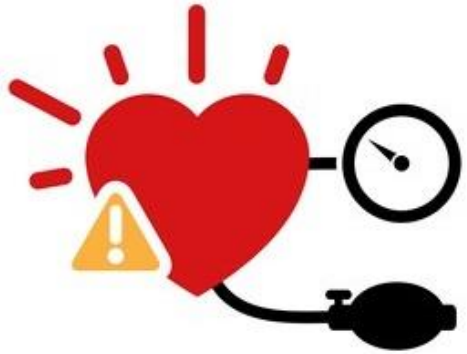


Table 1. Reported Cases of β-Blocker–Induced Circulatory Collapse in Patients With Thyroid Storm.

Study	Patient	Thyroid Disease	Evidence of HF[a]	β-Blocker and Dose	Type of Circulatory Collapse	Post–β-Blockade TTE	Hospital Course After Episode of Circulatory Collapse
Yamashita et al[16] (2015)	62, female	Grave's disease; thyroid storm	LVEF of 30%	Bisoprolol (dose not reported)	Hypotensive	Not reported	Bisoprolol was discontinued after the hypotensive episode and the patient remained tachycardic. Lindolol chloride was initiated for HR control and did not cause further drops in SBP. HR was successfully controlled and TTE after stabilization of HR showed LVEF of 55%. Tachycardia recurred and patient underwent thyroidectomy after which was discharged home in stable condition.
Vijayakumar et al[17] (1989)	85, female	Multinodular goiter; thyroid storm	History of HF (details not reported)	Propranolol 4 mg IV, 20 mg PO	Hypotensive with atrial fibrillation	Not reported	Resuscitation with, atropine, adrenaline, and dobutamine was initiated. Persistent AF and tachycardia after propranolol discontinuation was accompanied by acute limb ischemia. Esmolol infusion was initiated and carefully titrated for HR control and dobutamine was continued for BP support. 36 hours later, the patient was hemodynamically stable and underwent total thyroidectomy and right-sided AKA and was discharged in stable condition.
Ngo and Tan[20] (2006)	32, male	Grave's disease; thyroid Storm	CXR shows cardiomegaly with mild congestion	Propranolol 10 mg PO	Hypotensive with atrial flutter	LVEF of 25% with severe TR and MR	No further dose of propranolol was administered. Patient underwent successful cardioversion for atrial flutter and was put on inotropic support along with intra-aortic balloon pump. Patient stabilized after resuscitative measures and was discharged in stable condition.
Narechania et al[21] (2015)	27, female	Grave's disease; thyroid Storm	CXR shows cardiomegaly	Metoprolol (dose not reported)	Cardiac arrest (PEA)	Global LV dysfunction with severe MR and TR	Successful resuscitation with chest compressions and epinephrine (no further details reported).
Eleftheriou et al[22] (2010)	39, female	Thyroid storm	LVEF of 35%	Propranolol 2 mg IV	Cardiac arrest	LVEF of 15%	CPR initiated with no response. Diagnosis of cardiogenic shock was made and attempt of Extracorporeal cardiovascular support with ECMO was not successful. Patient subsequently developed multi-organ failure and expired 5 days later.
Fraser et al[23] (2001)	52, female	Thyroid storm	LVEF of 35%	Sotalol 1 mg/kg IV	Cardiac arrest	Global impairment of LV function	CPR initiated with successful return of pulse. Patient remained hypotensive requiring vasopressor and inotropic support to maintain blood pressures. 24 hours later patient was hemodynamically stable and was discharged on day 10 of admission. Repeat TTE 6 weeks later revealed LVEF within normal range.
Boccalandro et al[24] (2003)	48, female	Grave's disease; thyroid storm	S3, JVD, bilateral crackles, hepatomegaly, hepatojugular reflex	Propranolol 40 mg PO	Hypotensive	LVEF <20%, 4-chamber dilation, MR and TR	Supportive care with hemodynamic stability within 24 hours (no further details reported).
Ashikaga et al[25] (2000)	50, female	Grave's disease; thyroid storm	Not reported	Propranolol (dose not reported)	Hypotensive	Four-chamber dilation with reduced LV function	Propranolol was D/C. Vasopressor and inotropic therapy were initiated with successful hemodynamic stabilization and improvement in cardiac index. Predischarge TTE was normal. Patient discharged in stable condition.
Dalan and Leow[15] (2007)	43, female	Thyroid storm	No reported evidence	Propranolol 20 mg PO	Cardiac arrest (asystole)	LVEF 60% with dilated atria	Propranolol was D/C. CPR with successful return of pulse. Vasopressor initiated for BP control and patient recovered (no further details reported).
	43, female	Thyroid storm	LVEF of 45%, atrial dilation, TR	Propranolol 20 mg PO	Cardiac arrest (asystole)	Not reported	Propranolol therapy D/C. CPR and vasopressor support with initial improvement. Patient developed a second episode of cardiac arrest and consequently expired.

J Investig Med High Impact Case Rep. 2017;5(4):2324709617747903.

Q7

- A 68-yr-old man: shortness of breath, palpitation, difficulty sleeping, 5-kg wt loss
- Hx HF, AF on metoprolol, lisinopril, amiodarone, dabigatran

- Exam: afebrile, BP 140/80, irregular P 102/min, RR 24/min, brisk DTR, fine tremor, bilateral lid lag, no goiter
- Lab: TSH < 0.01 mU/L, ↑ FT4 3.1 ng/dL, ↑ TT3 190 ng/dL, undetectable TRAb
- US: normal thyroid size & parenchyma, no vascularity on color flow Doppler

In addition to ↑ metoprolol dose,
which of the following is the most likely initial management?

A. Discontinue amiodarone

B. Begin methimazole

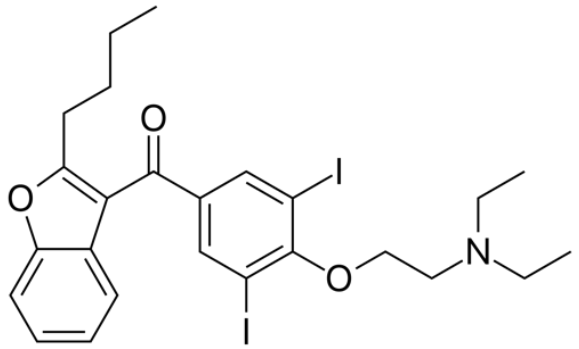
C. Begin prednisone

D. Thyroid scintigraphy with uptake

Answer: C. prednisone

- AIT type 2
- However, I would like to suggest to treat both type 1 & 2 AIT in case of heart disease

Amiodarone



200-mg amiodarone

~ 75 mg of iodine

~ 7 mg of free iodine

Normal I requirement

0.15-0.30 mg/d

- **Liposolubility:** prolonged storage in high conc. in fat and muscle
- **Very long $T_{1/2}$** 60-142 days: adverse effects can occur and persist long after stop the drug

High incidence of adverse side effects

- Pulm toxicity, cardiac QT prolongation, photosensitivity, blue skin discoloration, corneal microdeposits, optic neuropathy, hepatic enz elevation, thyroid disorder

Mechanisms of amiodarone induced thyroid disorder

Iodine related mechanisms

Wolff – Chaikoff effect

Inhibition of iodine organification

↓

Reduced production T3, T4, increased TSH

↓

Escape effect → T4, T3, TSH return to normal

Frequently in normal thyroid

Fail to escape → Hypothyroidism remains

Frequently in Hashimoto disease

Jod-Basedow effect

Excess of iodine substrate

↓

Uncontrolled overproduction of thyroid hormones

↓

Hyperthyroidism (Type1)

Frequently in Graves disease, endemic goiter, toxic multinodular goiter, thyroid adenoma

Mechanisms not related to iodine

Cytotoxic thyroid effect

↓

Destructive thyroiditis

↓

Hyperthyroidism (Type 2)

Amiodarone inhibits D2 deiodinases

↓

Decreasing T4 to T3 conversion

↓

Reduction in serum T3 level

Inhibition of T3 binding to its nuclear receptor

↓

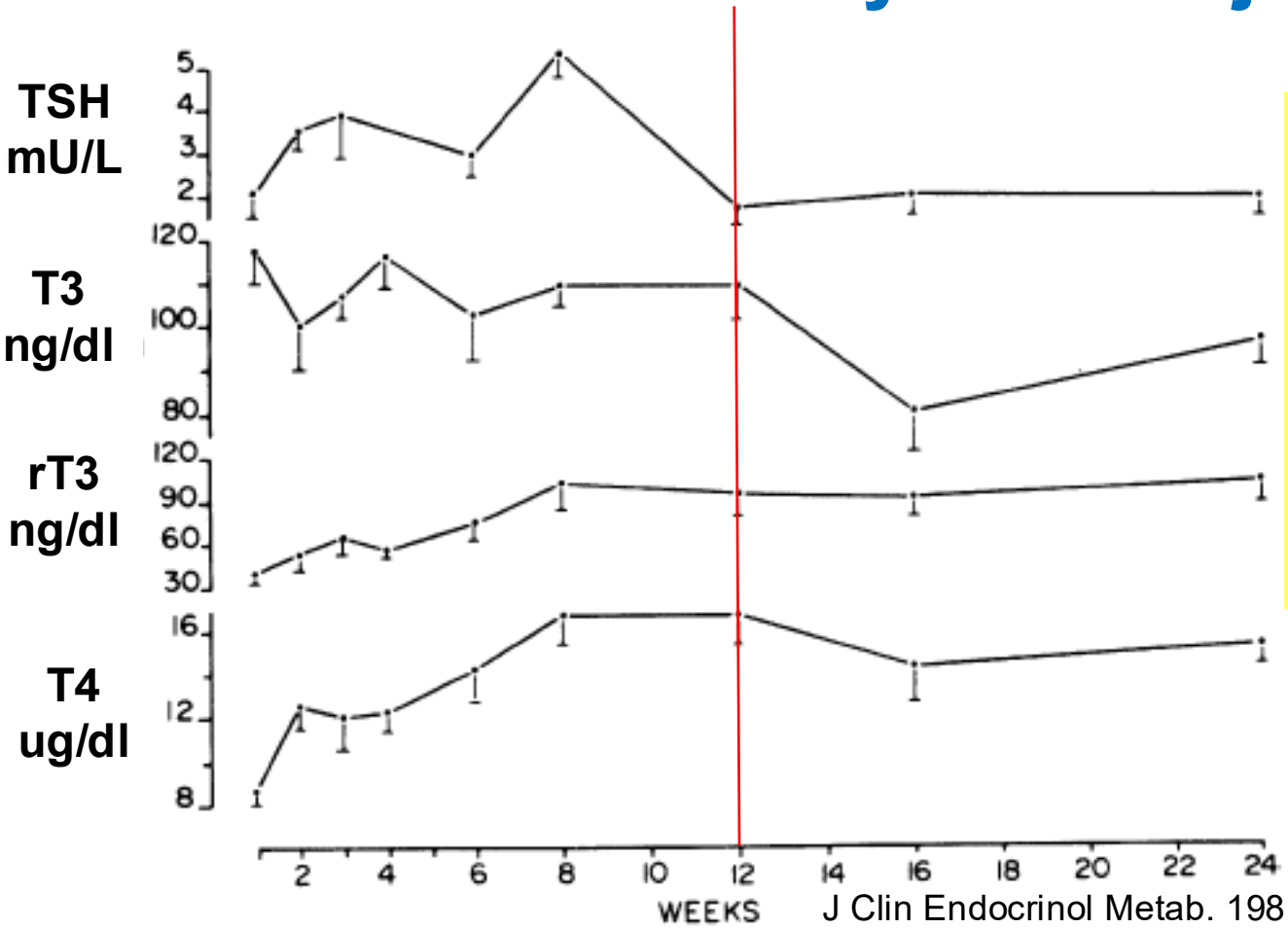
Reduced hormone action.

Ylli D et al. J Clin Endocrinol Metab. 2021; 106(1):226-236.

Effects of amiodarone on TFTs in euthyroid subjects

In a euthyroid subject with a normal thyroid gland, amiodarone administration will result in:

- Slight ↑ TSH, T4, FT4, rT3 in the 1st Mo of Tx
- Normalize in the following 3 to 6 Mo



J Clin Endocrinol Metab. 1981;53:997–1001.

Due to deiodinase inhibition

- Serum T3 will remain ↓
- Typically below the ref range

Thyroid hormone	Acute effects (≤3 mos)	Chronic effects (≥3 mos)
Total and free T4	↑ 50%	Remains ↑ 20-40% of baseline
T3	↓ 15-20%, remains in low-normal range	Remains ↓ 20%, remains in low-normal range
rT3	↑ >200%	Remains ↑ >150%
TSH	↑ 20-50%, transient, generally remains <20 mU/L	Normal

AIT 1 vs AIT 2

↓ TSH; ↑ FT4; N or ↑FT3/T3

The absolute levels of FT4 and FT3 at presentation have no discriminatory value between AIT 1 and AIT 2, although they tend to be higher in AIT 2

	AIT 1	AIT 2
Underlying thyroid abnormalities	Yes	Usually no[a]
Colour-flow Doppler sonography	Increased vascularity	Absent hypervascularity
Thyroidal RAIU	Low/normal/increased[b]	Suppressed
Thyroid autoantibodies	Present if AIT is due to Graves disease	Usually absent[c]
Onset time after starting amiodarone	Short (median 3 months)	Long (median 30 months)
Spontaneous remission	No	Possible
Subsequent hypothyroidism	No	Possible
First-line medical treatment	Antithyroid drugs[d]	Oral glucocorticoids
Subsequent definitive thyroid treatment	Generally yes	No

RAIU, radioiodine uptake. [a] A small goitre may be present. [b] In iodine-replete areas RAIU is always suppressed. [c] Anti-thyroglobulin and anti-thyroid peroxidase antibodies do not allow a diagnosis of AIT 1. [d] Antithyroid drugs (thionamides) may be associated (for a few weeks) with sodium perchlorate.

Novel biomarker:

- **Beta-glucuronidase:** lysosomal enzyme released into the ECF during inflam (↑ AIT2)

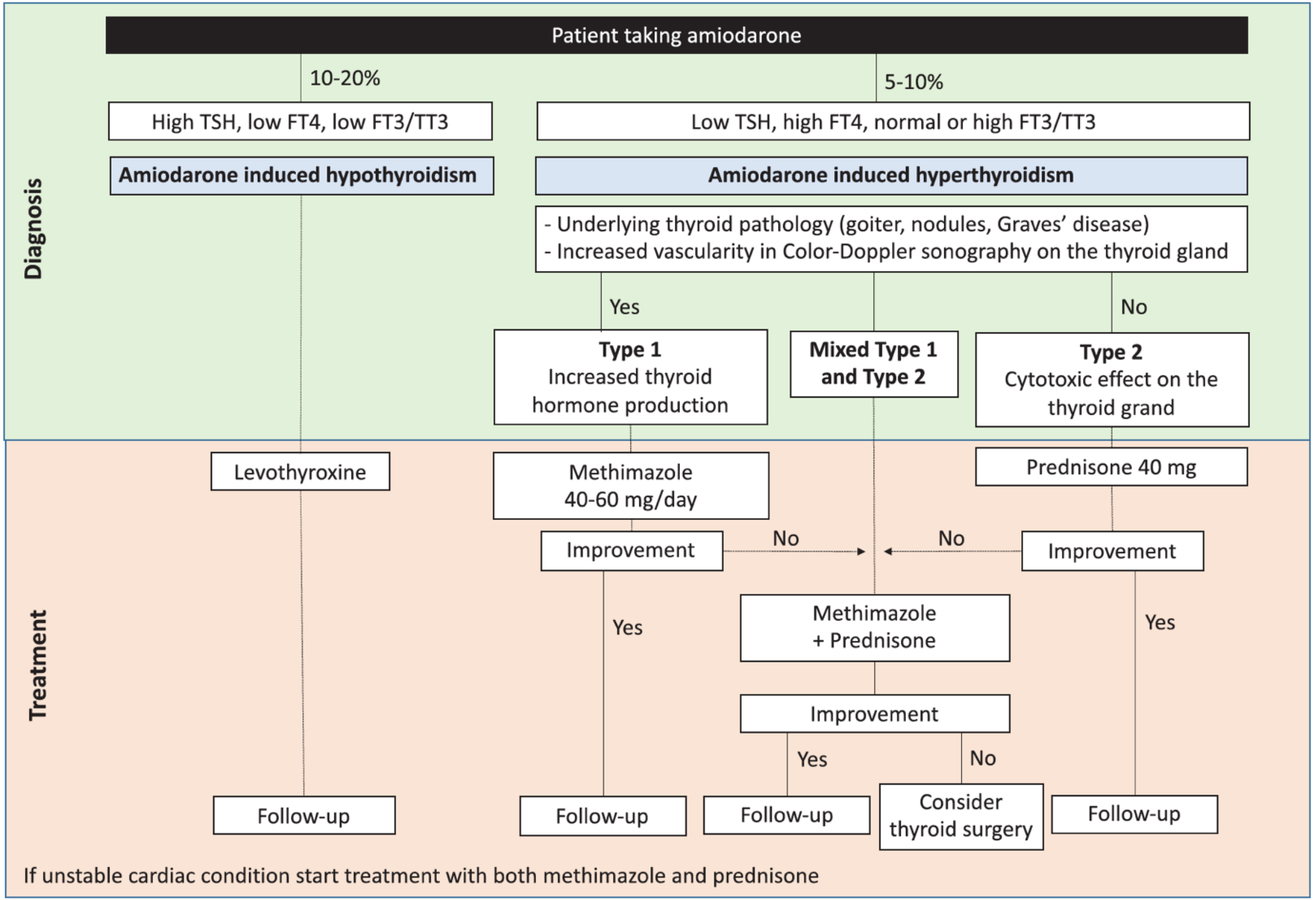
Markantes GK et al. Eur Thyroid J. 2019;8(4):215-220.

Advantages and disadvantages of amiodarone withdrawal in patients with AIT

Disadvantages	Advantages
Efficient drug for life-threatening arrhythmias	Amiodarone and its metabolites have a long half-life, making an immediate exacerbation of cardiac symptoms unlikely
Cardiac protective properties: antagonistic effect on β-adrenergic receptors, inhibition of T_4 deiodination, blockade of T_3 binding to thyroid hormone receptors	Greater chance of achieving euthyroidism and delivering definitive thyroid treatment (particularly radioiodine) at an earlier stage
Amiodarone and its metabolites have a long half-life; thus, discontinuation might be useless, at least in the short term	Continuation of the drug in AIT 2 is associated with a delayed restoration of euthyroidism and a higher chance of recurrence

- If amiodarone is withdrawn, MMI should be continued until urine I levels return to normal (6-18 Mo)
- If in the future amiodarone needs to be reintroduced, close monitoring is fundamental
  - 75% of patients restarting amiodarone treatment risk having another episode of AIT
  - Need definite Tx (I-131) when pt can be weaned off amiodarone (and normalized urine I level)

Markantes GK et al. Eur Thyroid J. 2019;8(4):215-220.



Ylli D et al. J Clin Endocrinol Metab. 2021; 106(1):226-236.

HYPOTHYROIDISM

- Etiologies: Hashimoto's thyroiditis, Post Sx/RAI, drug (amiodarone, lithium)
- Always evaluate Hypo in bilat CTS, dementia
- ↑ LDL, ↑ CK, anemia, hypoNa, ↑ PRL
- Suspected central hypothyroidism → check cortisol before initiate LT4

LT4 replacement: dose 1.6 ug/kg/day, once daily; before meal

  - $T_{1/2}$ 7 days: F/U TSH at 4-6 weeks after start LT4 then q 3-6 → 6-12 months
  - Old age, CAD risk: start low and slowly titrate up
  - Pregnancy: 25-30% ↑dose prepregnancy dose

Q8

- A 56-yr-old man: palpitation, fine tremor, difficulty sleeping over the past month
- Hypothyroidism from S/P thyroidectomy 6 Mo ago
- Takes LT4 on an empty stomach with a cup of coffee every morning
- 2 Mo ago Dx with hypogonadism, Rx testosterone

	2 months ago	Today
TSH (mU/L)	**1.5**	**0.08**
Free T4 (ng/dL)	**1.1**	**1.4**

- His current meds: LT4, testosterone IM, calcium carbonate, omeprazole

Which of the following is the most explanation of TFT results?

A. Calcium carbonate

B. LT4 with coffee

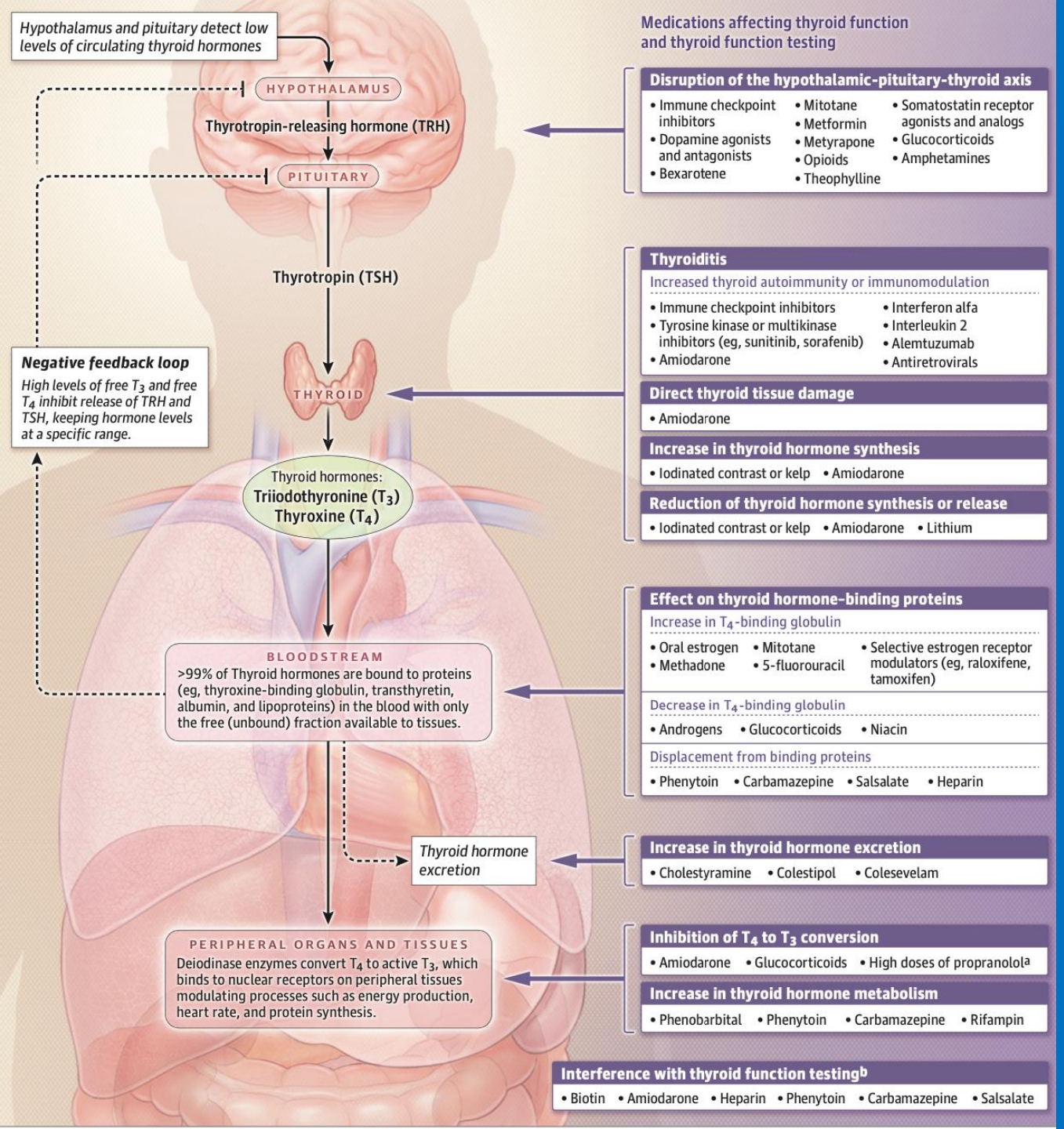
C. Omeprazole

D. Testosterone

Answer: D. Testosterone

Testosterone→ ↓TBG

→ ↑metabolically active free T4



Medications affecting thyroid function or interfering with thyroid function testing

Chaker L, Papaleontiou M. JAMA. 2025 Sep 3. doi: 10.1001/jama.2025.13559. Online ahead of print.

Medications that may interfere on with LT4 therapy

Absorption	$CaCO_3$, ferrous sulfate, $Al(OH)_3$, sucralfate, PPI soy, coffee, milk gastritis, celiac disease	Concomitant use to be avoided
TBG	estrogen*, androgen	TFT to be monitored
Metabolism	tyrosine kinase inhibitors, phenobarbital, phenytoin, carbamazepine, rifampin, sertraline	TFT to be monitored

$Al(OH)_3$, aluminum hydroxide; TBG, thyroxine-binding globulin
*Transdermal estrogen does not increase TBG concentrations

Q9

- A 75-yr-old woman: weight gain for 6 months
- No additional symptoms (fatigue, cold intolerance, constipation)

- Pulse rate 82/min
- BMI 26 kg/m^2
- Normal thyroid exam
- TSH ↑ 9 mU/L, FT4 1 ng/dL (N)

Which of the following is the most appropriate management?

A. Initiate LT4

B. Measure T3 level

C. Repeat TFT in 6-8 weeks

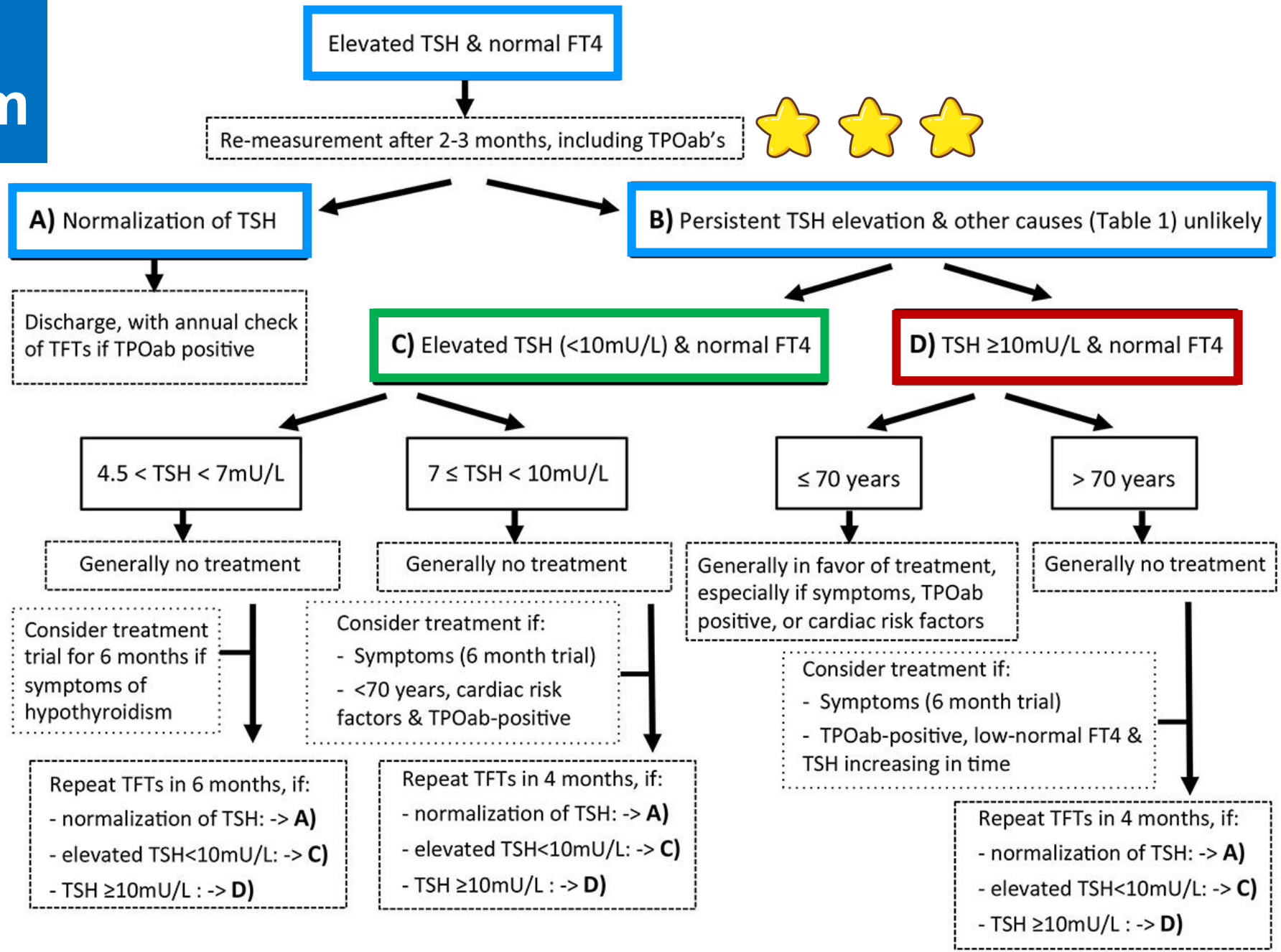
D. No additional management

Answer:
C. Repeat TFT in 6-8 weeks

Subclinical hypothyroidism

Subclinical Hypothyroidism

- Progression to overt hypothyroidism
- Risk of CVD
- TSH > 10: LT4 Rx
- TSH 4.5-10: controversial
  - ✓ Patient age
  - ✓ Degree of TSH elevation
  - ✓ Symptoms
- Dose 25-50 ug/d



resident360.nejm.org

Q10

- A 74-yr-old woman: @ER decreased responsivenss
- Hx S/P total thyroidectomy and stopped her meds at some time unknown

- T 34.1 c, BP 80/45, P 46/min, RR 10/min, O_2 sat 92%
- Arousable with painful stimuli, periorbital edema, bipedal edema, Na 129

Which of the following is the essential initial step in the management?

A. Administer IV T3

B. Active rewarming

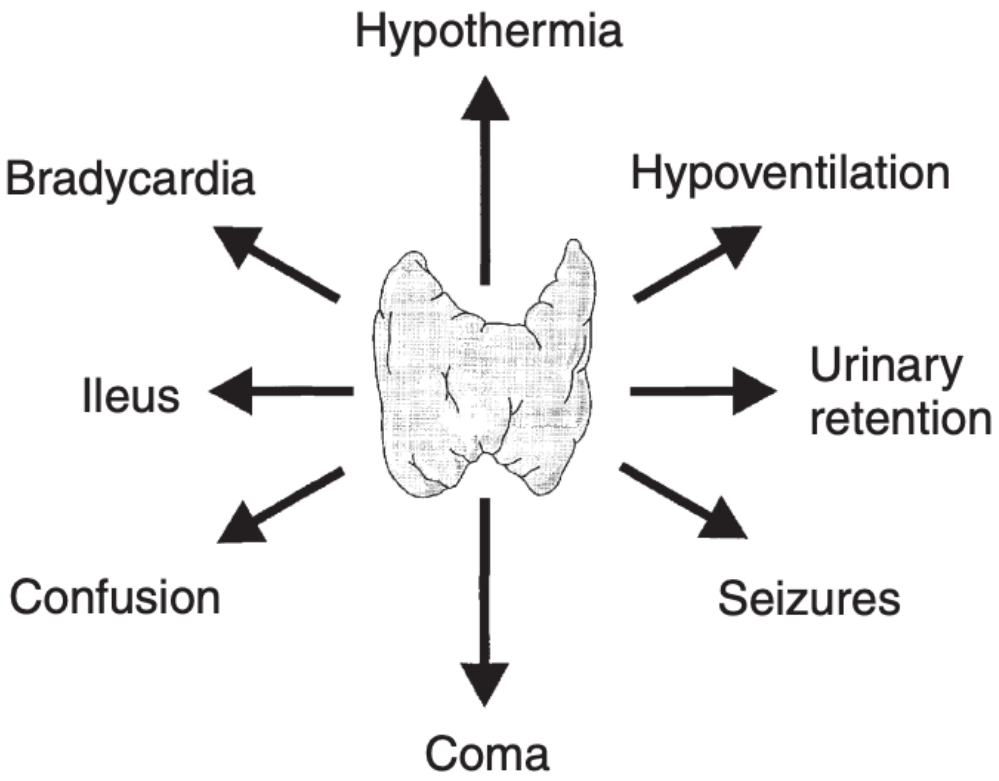
C. Adminster norepinephrine

D. Administer IV hydrocortisone

Answer:
D. IV hydrocortisone

Myxedema coma

Myxedema Coma



Treatment of myxedema coma

Thyroid Hormone Replacement (Rapid)
Levothyroxine 200–300 mcg IV over 5 minutes, or
Triiodothyronine 5–10 mcg IV every 6–12 hours, then
Levothyroxine 50–100 mcg daily PO or IV

Glucocorticoid Therapy (Stress Doses for 2–3 Days)
Hydrocortisone 200 mg daily, or
Methylprednisolone 40 mg daily, or
Prednisone 50 mg daily, or
Dexamethasone 7.5 mg daily

Support Circulation, Oxygenation and Ventilation
IV fluids
Oxygen
Mechanical ventilation (if needed)
Passive rewarming (if severely hypothermic)

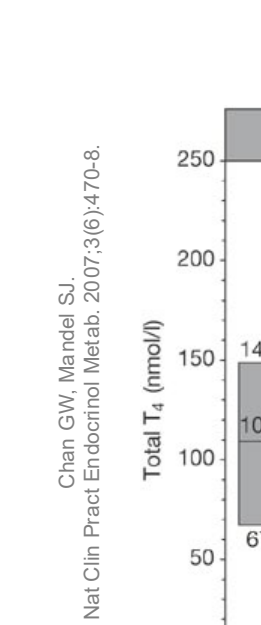
Treat Precipitating Cause (critically important)

IV, Intravenous; *PO,* oral.

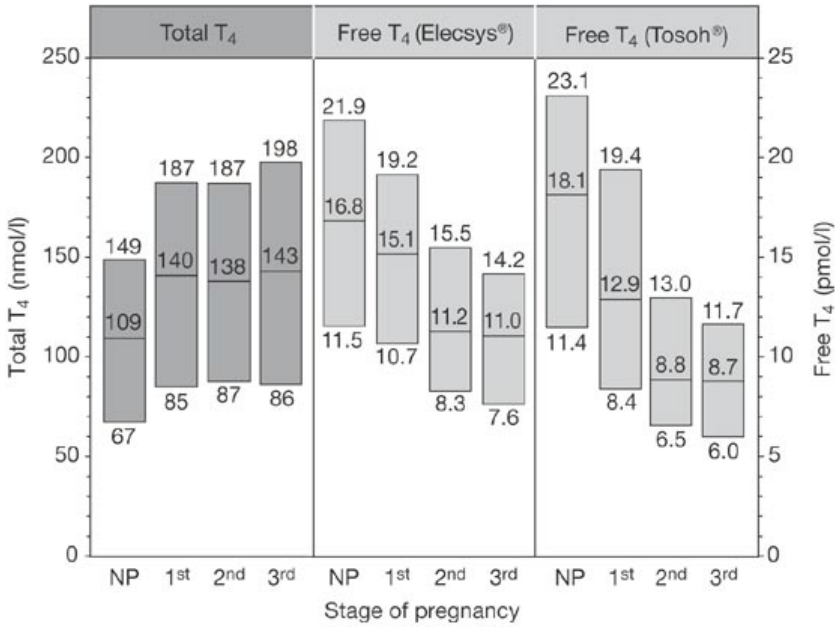
Endocrine Secrets, 7th edition (2020)

Physiologic changes in pregnancy

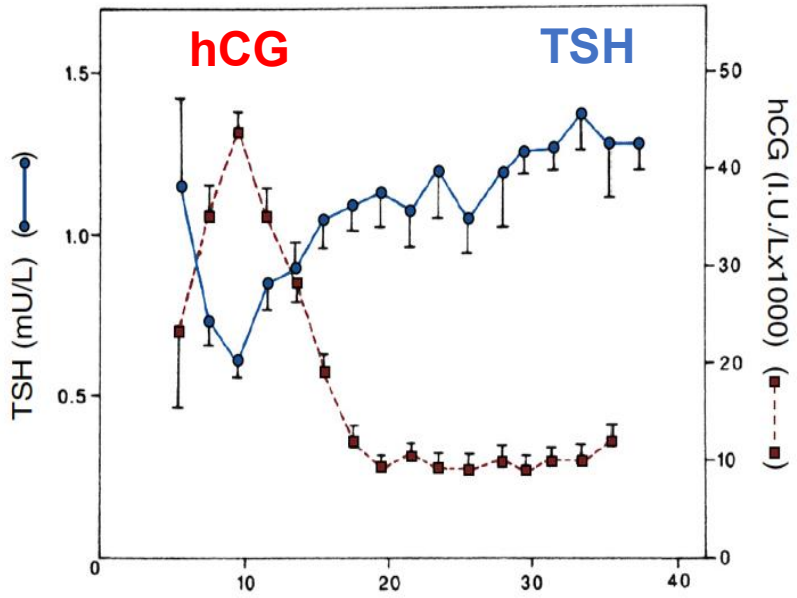
Physiologic changes	Thyroid function test changes
↑ Thyroxine-binding globulin (↑ estrogen)	↑ Total T4 and total T3
First trimester hCG elevation	↑ Free T4 and ↓ TSH
↑ Plasma volume	↑ T4 and T3 pool size
↑ Type III 5-deiodinase due to increased placental mass	↑ T4 and T3 degradation (resulting in requirement for increased hormone production)
Thyroid enlargement (in some women)	↑ Serum thyroglobulin
↑ Iodine clearance	↓ Hormone production in iodine-deficient areas
Immunological changes	↓ thyroid antibody levels



Chan GW, Mandel SJ.
Nat Clin Pract Endocrinol Metab. 2007;3(6):470-8.



GA (weeks)	Recommended test(s)
0-7	FT4
8-16	FT4, TT4
17-40	TT4 (pregnant range = 1.5 x nonpregnant range)



GA	TSH levels (mIU/L)
Population-based, trimester-specific reference ranges	
7-12 weeks	0.1-4
2nd & 3rd trimester	0.5-4

Gestational thyrotoxicosis vs Graves disease

	GT	GD
TRAb	No	Yes
Thyrotoxic symptoms	mild	variable
Stigmata of GD	none	may be present
T3:T4 ratio	<20:1	>20:1
N/V	Yes	No

GT: persistent hyperthyroidism after GA 18 wk requires evaluation for an alternate Dx

Pre-existing Graves disease in pregnancy

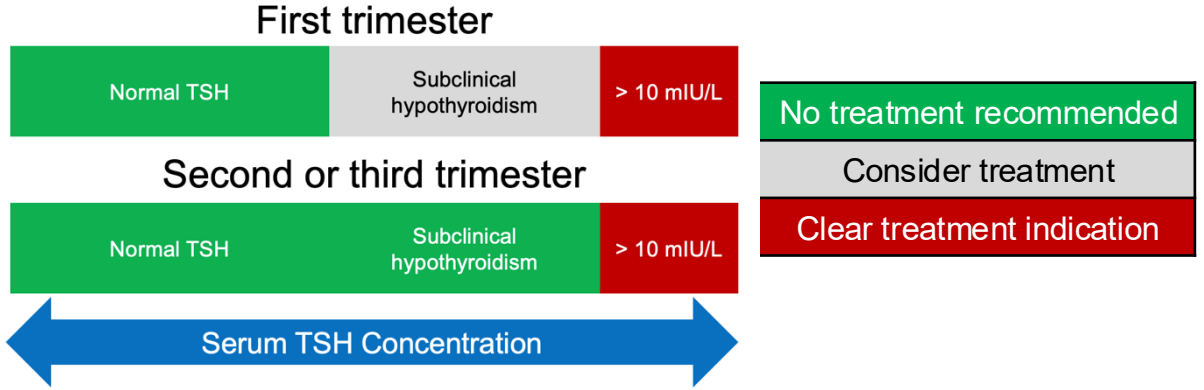
- Switch from MMI to PTU as soon as pregnancy is confirmed (concern MMI embryopathy) **OR**
- Discontinue MMI with careful TFT monitoring (MMI 5-19 mg/d Rx for 12-18 Mo with normal TFT & neg TRAb)
- Lowest dose, keep FT4 high N
- Cessation of ATD in the 3rd trimester if TSH not suppressed and undetectable TRAb

Risk of iodine deficiency: I supplement 150 ug/d

Hypothyroid pregnant woman

- Preconception: TSH < 2.5
- ↑ LT4 dose 30% as soon as pregnancy is confirmed
- Postpartum: returning LT4 to preconception dose

Subclinical hypothyroidism treatment



Thyroid nodule ~ nonpregnant patients

- Non-aggressive PTC: may delay Sx until delivery

Assessment of Fetal and Neonatal Graves Disease Risks

Measurement of TSH Receptor Ab

All women with history of Graves disease

↓

Early pregnancy

TRAb positive ↘ ↘ TRAb negative

Fetal thyroid function begins ~18 weeks gestation.

Risk of fetal Graves disease

GA 18-22 wk

No need to F/U

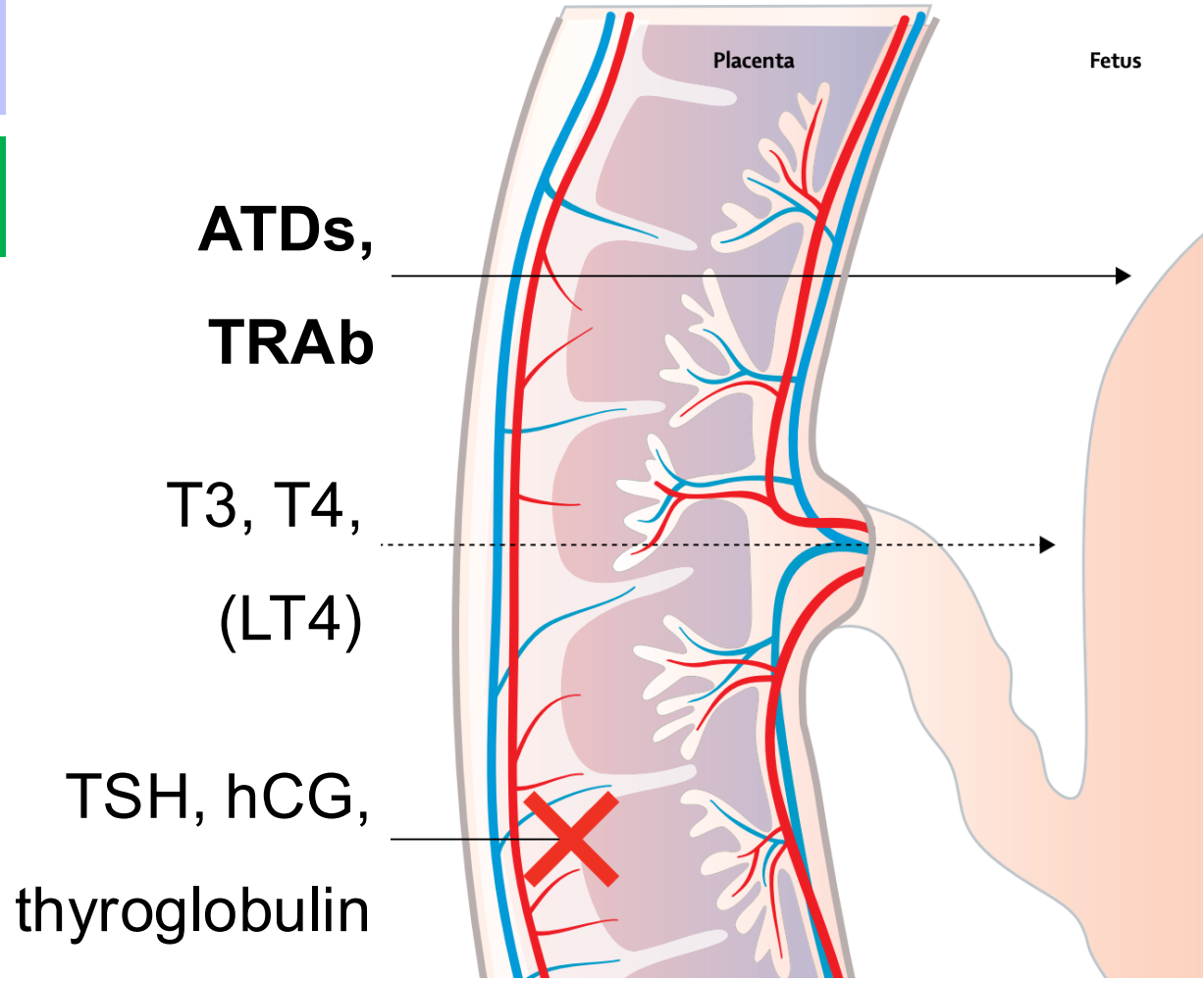
TRAb positive ↘ ↘ TRAb negative

Risk of neonatal Graves disease

GA 30-34 wk

No need to F/U

TRAb > 3xULN: high risk



ATD = antithyroid drug

Leo SD, Pearce EN. Lancet Diabetes Endocrinol. 2018;6:575-86.

INVESTIGATIONS IN THYROID DYSFUNCTION

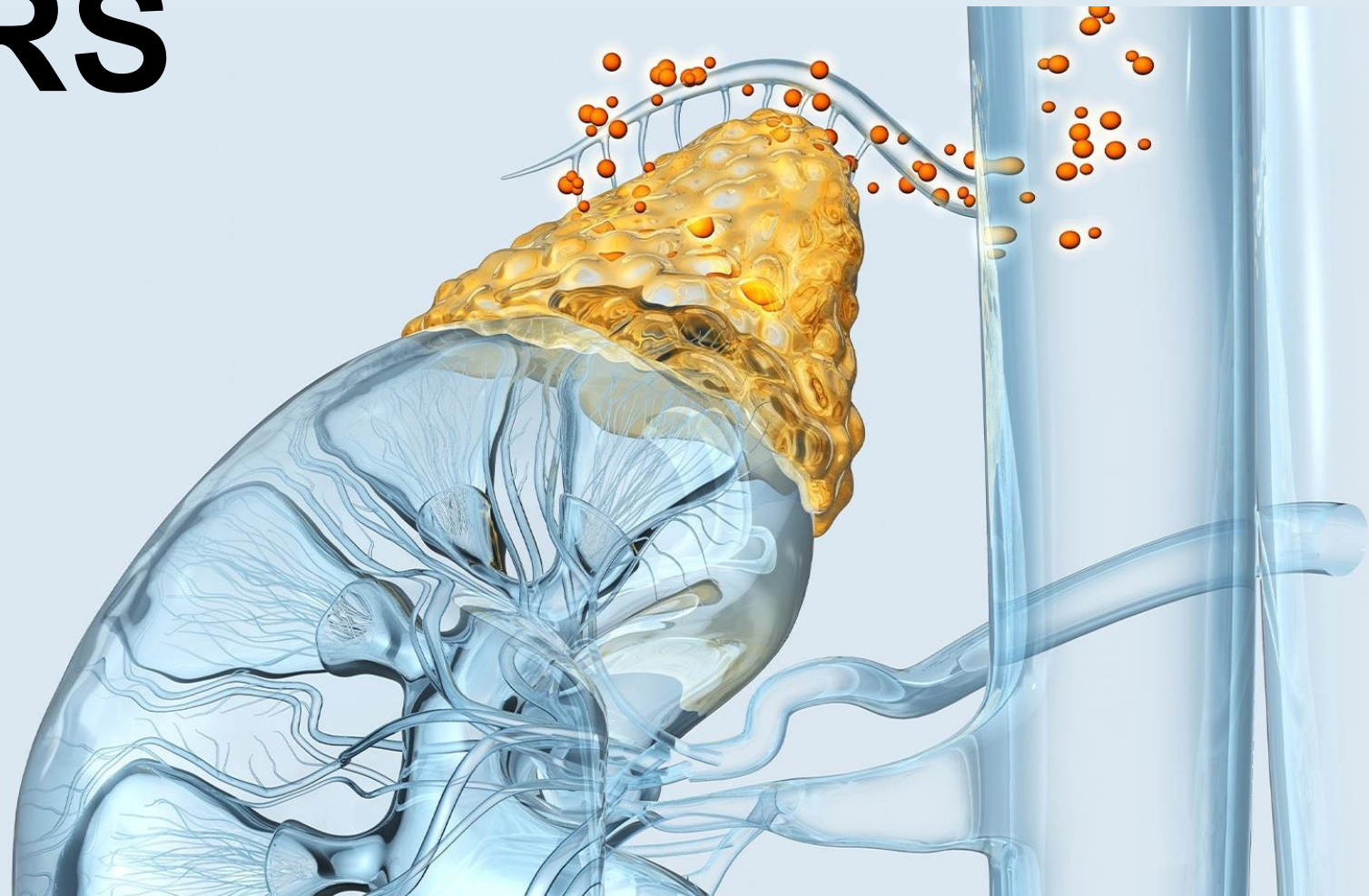
SCREENING	**TSH**
HYPERTHYRODISIM	**TSH FT4 (FT3/TT3)** **W/U Graves'disease: TRAb**
HYPOTHYRODISIM	**TSH FT4** **W/U Hashimoto: anti-TPO (± anti-Tg)** **Central hypo: FT4**

FREE DOWNLOAD

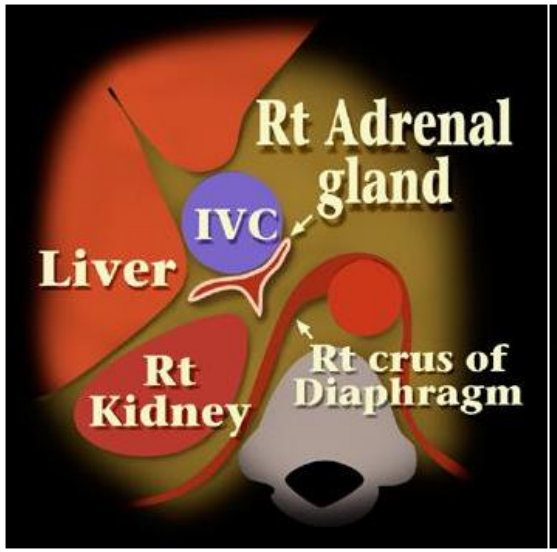
Available at
thaiendocrine.org

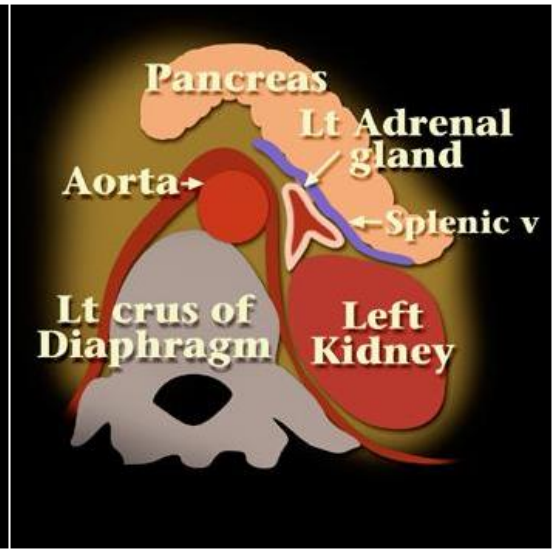
ADRENAL DISORDERS

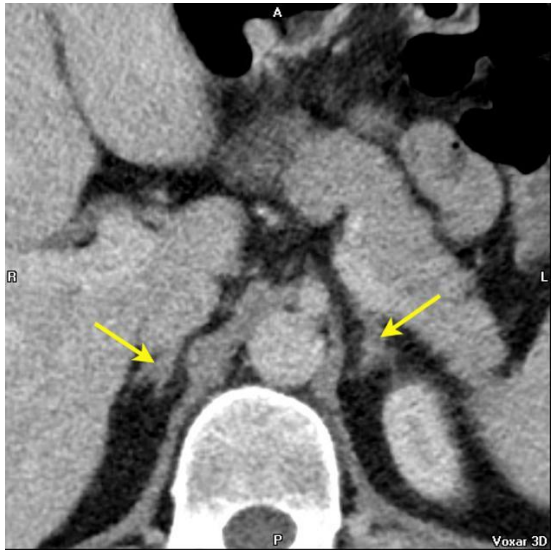
- Incidentaloma
- Cushing syndrome
- Primary aldosteronism
- Pheochromocytoma
- Adrenal insufficiency

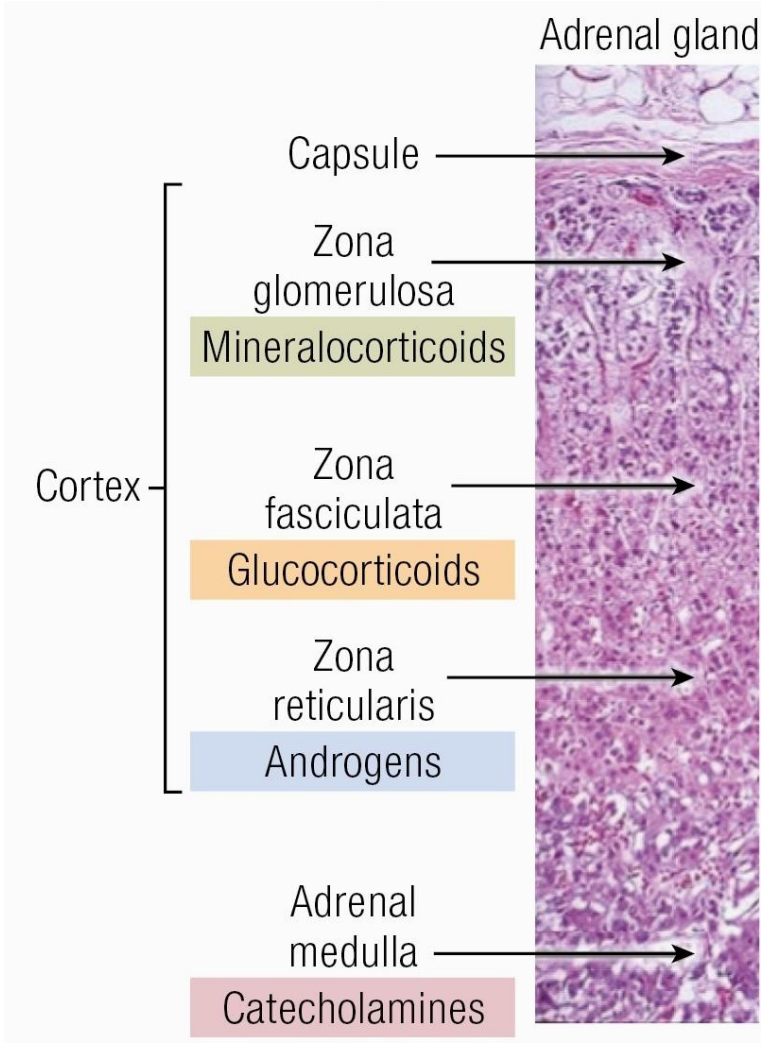


Normal Adrenal Glands









Adrenal glands lie superior and anteromedial to the kidneys.

- The Lt adrenal gland lies more anteromedial than superior when compares to the Rt adrenal gland.

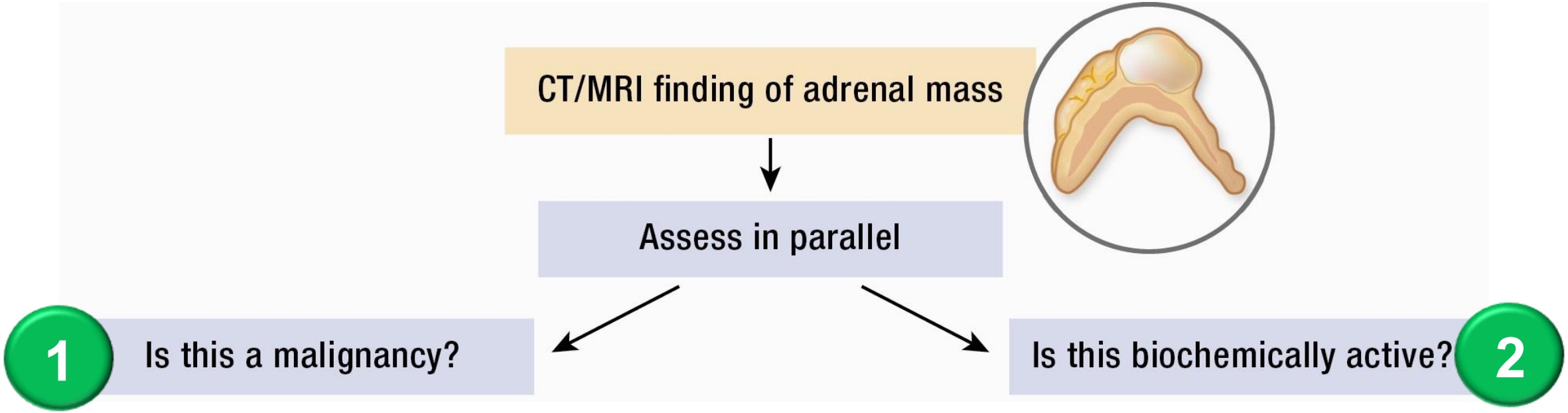
Shape: inverted V or Y, triangular

Size: should not be thicker than the adjacent crus of diaphragm.

Adrenal Incidentaloma

- Common, ~2% general population
- > 7% age > 70 yrs
- Rare in age < 40 yrs

- ~2%: adrenocortical cancer
- Up to 10%: autonomous secretion of adrenal hormones



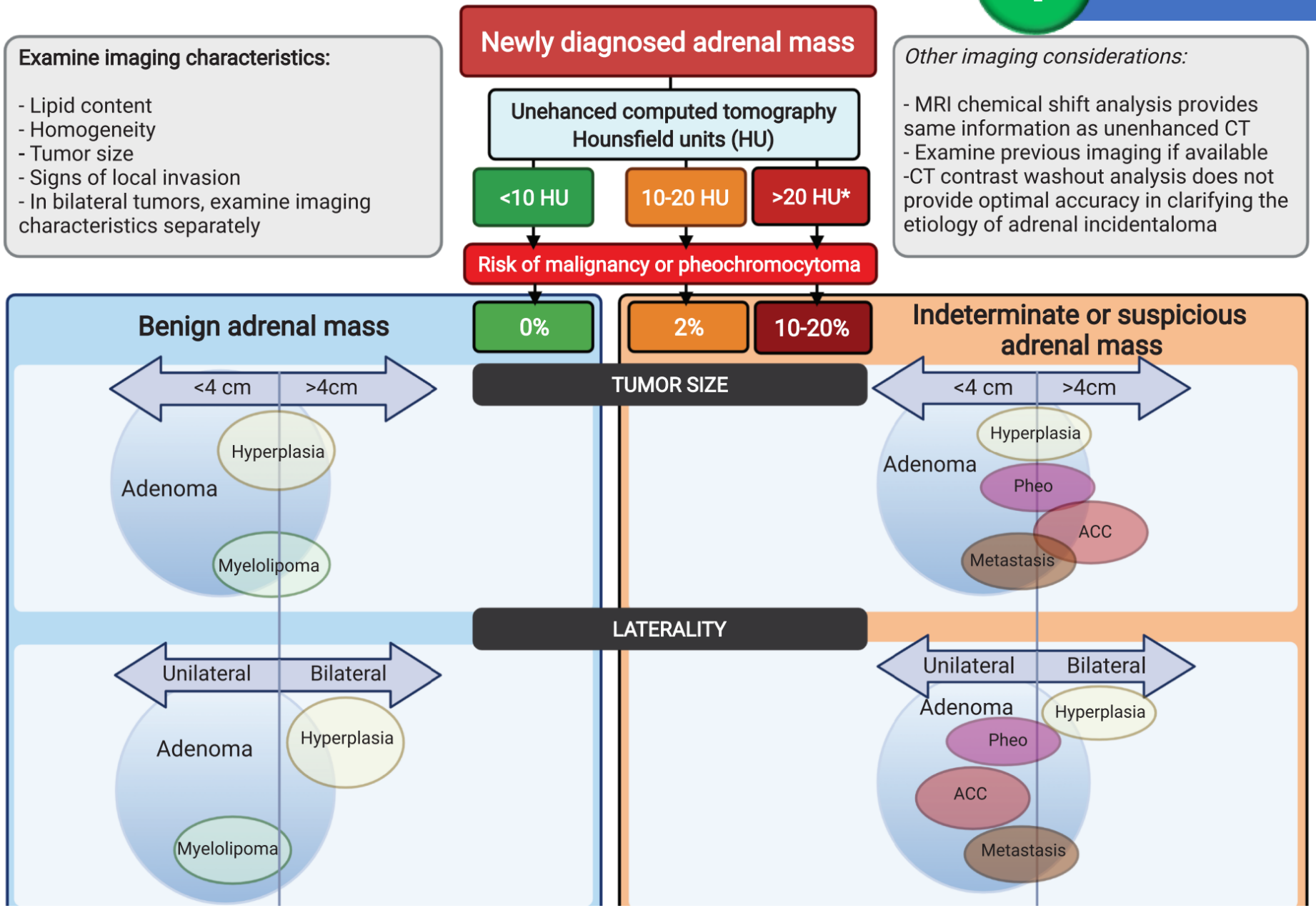
Sherlock M et al. Endocr Rev. 2020;41(6):775-820.

Adrenal Incidentaloma

1 Is this a malignancy?

Examine imaging characteristics:

- Lipid content
- Homogeneity
- Tumor size
- Signs of local invasion
- In bilateral tumors, examine imaging characteristics separately



Other imaging considerations:

- MRI chemical shift analysis provides same information as unenhanced CT
- Examine previous imaging if available
-CT contrast washout analysis does not provide optimal accuracy in clarifying the etiology of adrenal incidentaloma

BENIGN

Size <4 cm

HU <10

Homogenous density

INDETERMINATE/ SUSPICIOUS FOR MALIGNANCY

Size >4 cm

HU >10

Heterogeneous

Hypervascularity

Bancos I, Prete A. J Clin Endocrinol Metab. 2021;106(11):3331-3353.

Unenhanced CT

Any size and homogeneous **AND** HU ≤10	Homogeneous **AND** HU 11-20 **AND** tumor <4 cm	Homogeneous HU 11-20 tumor ≥4 cm **or** Homogeneous HU >20 tumor <4 cm **or** Heterogeneous tumor <4 cm	Homogeneous HU >20 tumor >4 cm **or** Heterogeneous tumor >4 cm
No further imaging required	Additional imaging (or interval imaging in 12 months)	MDT meeting and consider proceeding swiftly to additional imaging (or immediate surgery)	MDT meeting and consider proceeding swiftly to surgery (or further imaging FDG-PET/CT)
		Uncharacterized (continuing indeterminate mass)	In case of: no surgery
		Interval imaging in 6-12 months (non contrast CT/MRI)	Interval imaging in 6-12 months (non contrast CT/MRI)

Favoring a benign adrenal lesion:

- Contrast-enhanced washout CT scanning (>60% absolute washout, delayed scan at 15 min)
- Loss of signal intensity on out-phase MRI chemical shift imaging
- Absent FDG uptake on FDG-PET (or uptake < that of liver)

2 Is this biochemically active ?

Risk of malignancy or pheochromocytoma

Benign adrenal mass — 0%

- Work up for
  - Mild autonomous cortisol secretion (1-mg overnight DEX suppression test)
  - Primary aldosteronism if HT ± hypoK
  - **Not needed:** catecholamine excess
- Consider undiagnosed congenital adrenal hyperplasia (17-OH-progesterone) in large and bilateral myelolipomas

2% 10-20% Indeterminate or suspicious adrenal mass

- Work up for
  - Mild autonomous cortisol secretion
  - Primary aldosteronism if HT ± hypoK
  - **Catecholamine excess**
- **If clinical suspicion of ACC: DHEA-S, sex steroids**
- Work up for 1º adrenal insufficiency (morning cortisol and ACTH) in patients with bilateral adrenal masses (adrenal metastases/lymphomas/infection)

- **If clinical suspicion of Cushing syndrome:** 24-hr UFC, salivary cortisol

2 Is this biochemically active ?

Laboratory workup

- **All patients:** 1 mg-DST, cutoff cortisol 1.8 ug/dL
- **If hypertension/hypoK:** renin, aldosterone, K^+, Cr
- **If HU >10:** plasma or urine metanephrines
- **If clinical suspicion of Cushing syndrome:** 24-hr urine free cortisol, salivary cortisol
- **If bilateral masses:** 17-OH-progesterone
- **If clinical suspicion of bilateral adrenal metastases:** morning cortisol and ACTH
- **If clinical suspicion of ACC:** steroid precursor/steroid profiling, DHEA-S, androstenedione, testosterone, estradiol

Bancos I, Prete A. J Clin Endocrinol Metab. 2021;106(11):3331-3353.

Benign adrenal incidentaloma

1-mg Dexamethasone Suppression Test

Serum cortisol
< 1.8 ug/dL

Serum cortisol
≥ 1.8 ug/dL

Exclude overt
Cushing syndrome

No autonomous cortisol secretion

**No treatment and
no follow-up**

Mild autonomous cortisol secretion (MACS)

Comorbidities potentially attributable to cortisol

YES

MACS confirmed?
ACTH independency?:
ACTH, DHEA-S level
Consider specific Rx

MACS: If surgery, need steroid cover periop period

NO

Monitor for development of comorbidities potentially attributed to cortisol

BP, diabetes, BMD

Indications for FNA…Almost Never!

Main indications for adrenal biopsy:

- Suspected malignant adrenal tumors other than ACC (adrenal metastasis, sarcoma, lymphoma)
- Infectious etiology of the adrenal mass (fungal, tuberculosis)

Only if **ALL** of the following criteria are met:

- The lesion is not conclusively benign on imaging criteria
- The lesion is hormonally inactive with pheo excluded
- Outcome will affect therapeutic strategy

Q11 A 61-yr-old woman: W/U diverticulitis and found adrenal incidentaloma

- CT: a 3.5-cm left adrenal mass, 17 HU, absolute contrast washout of 80% at 10 min
- No HT, normal serum Cr and electrolytes, 1-mg DST < 1.8 ug/dL

Which of the following is the most appropriate test to perform next?

A. Adrenal biopsy

B. Adrenalectomy

C. Screening for 1^{o} aldosteronism

D. Repeat abdominal CT at 12 months

Answer: D. Repeat CT

1-mg overnight DEX test (UFC not sensitive)

HT and/or hypoK → PA evaluation

Hyperandrogenism → DHEAS

Q12

A 51-yr-old woman: adrenal incidentaloma

- CT: 2.5-cm right adrenal mass, 6 HU
- HT Dx 2 yrs ago
- Perimenopause: sweating, hot flush
- Med: HCTZ, doxazosin
- BP 142/90, P 90/min, BMI 33
- No Cushingoid appearance
- 1-mg DST: cortisol 8 ug/dL
- ARR 13, plasma metanephrines WNL

Which of the following is the most likely diagnosis?

A. Pheochromocytoma

B. Primary aldosteronism

C. Mild autonomous cortisol secretion

D. Non-hormone-secreting adrenal adenoma

Answer:
C. MACS

Q13

A 45-yr-old woman: bloating and constipation

- CT: 5-cm right adrenal mass, 42 HU, absolute contrast washout 38% at 10 min
- Test for pheo, MACS: neg
- Unremarkable medical history, no med

Which of the following is the most appropriate next step in management?

A. Adrenal biopsy

B. Adrenalectomy

C. Mitotane therapy

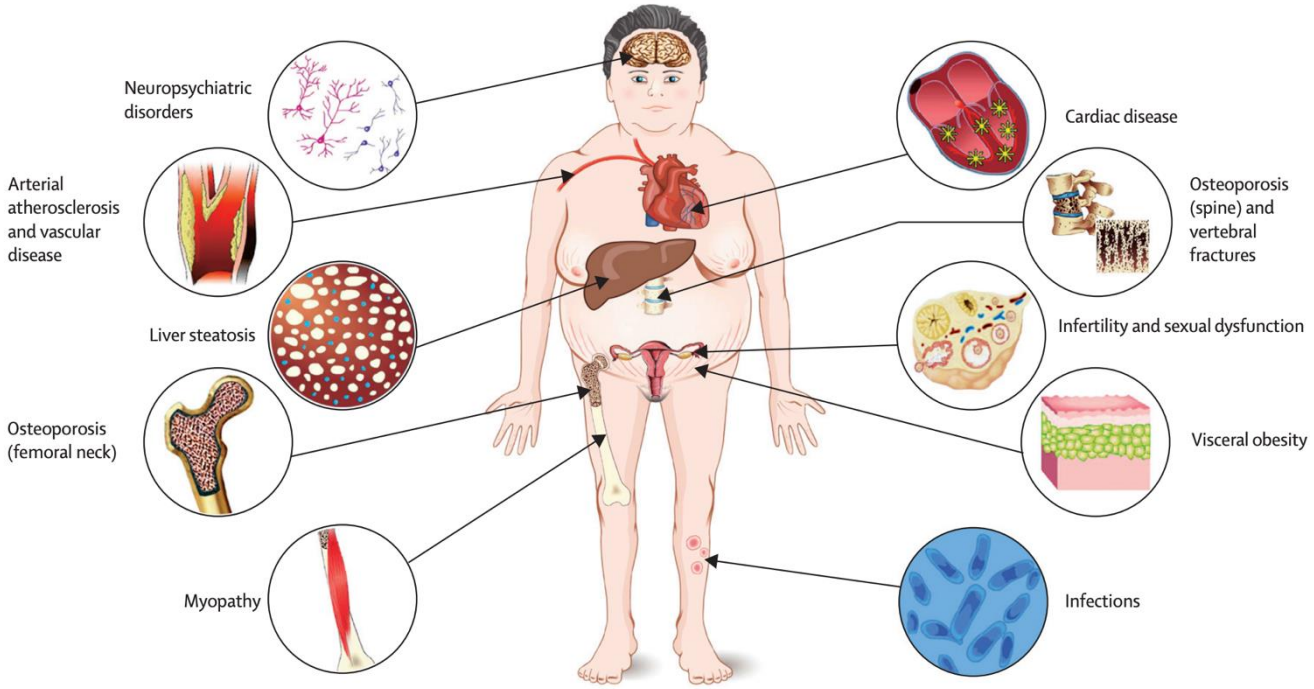
D. Repeat CT at 6 months

Answer: B. Adrenalectomy

Adrenalectomy is recommended for adrenal incidentaloma with radiologic features that suggest increased risk of an adrenal malignancy (size > 4 cm, density > 10 HU, and absolute contrast washout <50% at 10 min)

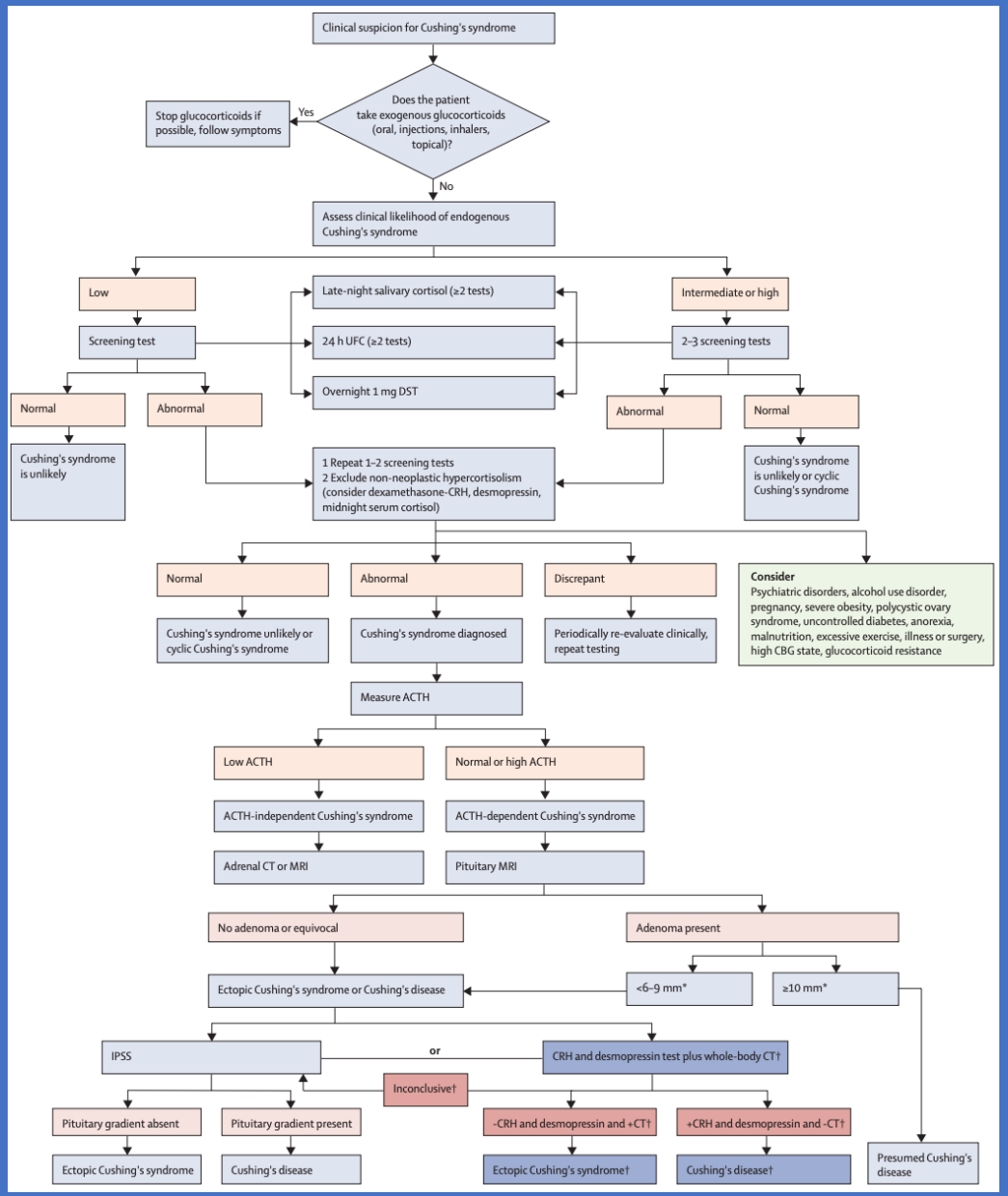
ACC → Sx **Metastasis → Bx**

Cushing Syndrome

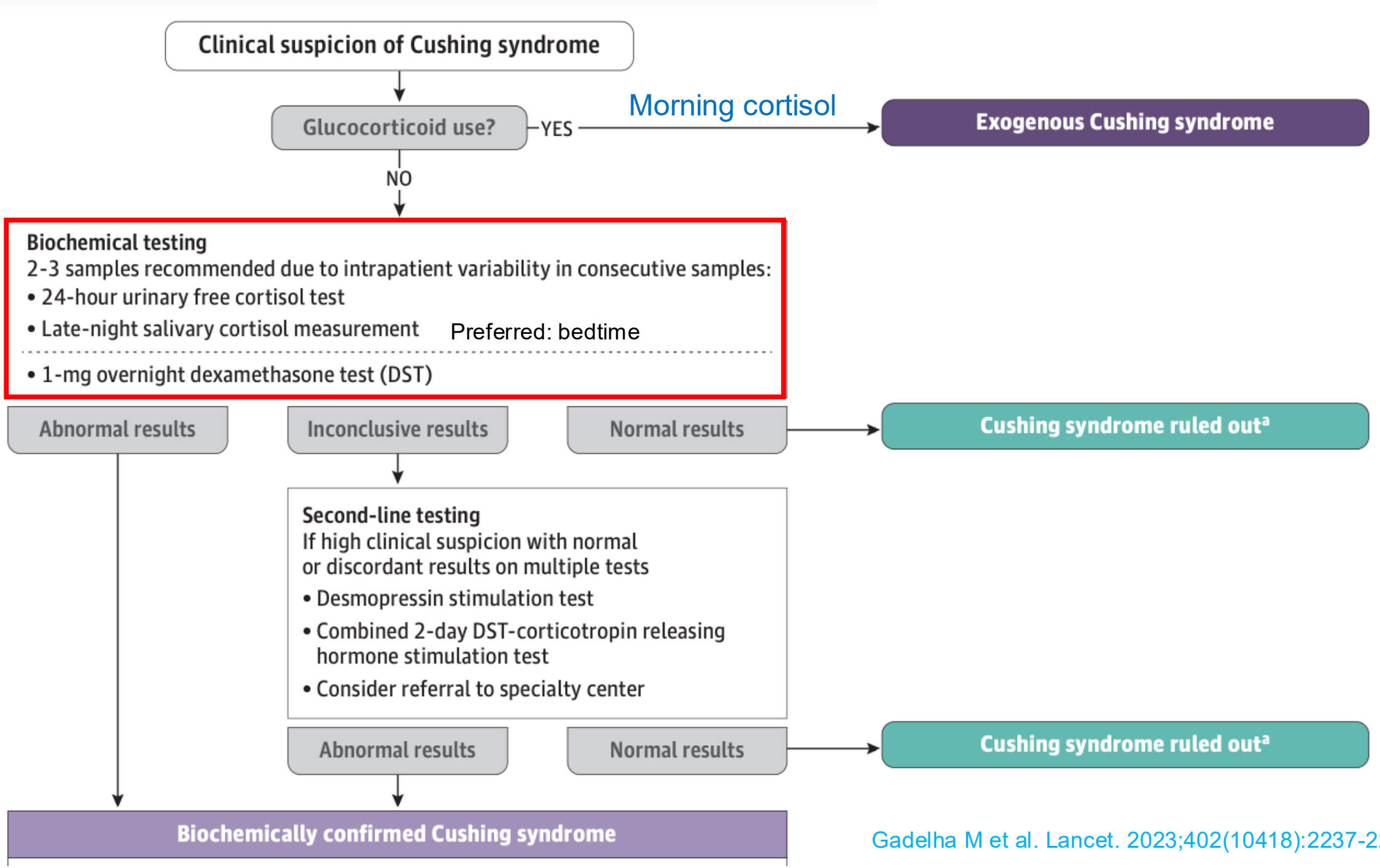


Check-list of complications	→	Preventive and curative treatments

- Phlebitis/Thromboembolism ? → Preventive/curative anticoagulation
- Hypertension ? → PO/IV antihypertensive
- Hyperglycemia ? → Antidiabetic drugs/insulin infusion
- Infection ? → Appropriate antibiotics
- Pneumocystosis ? → Preventive sulfamethoxazole trimethoprim
- Hypokalemia ? → IV potassium/MR antagonist
- Nutritional status ? → Renutrition
- Steroid psychosis ? → Sedatives and lower cortisol levels urgently

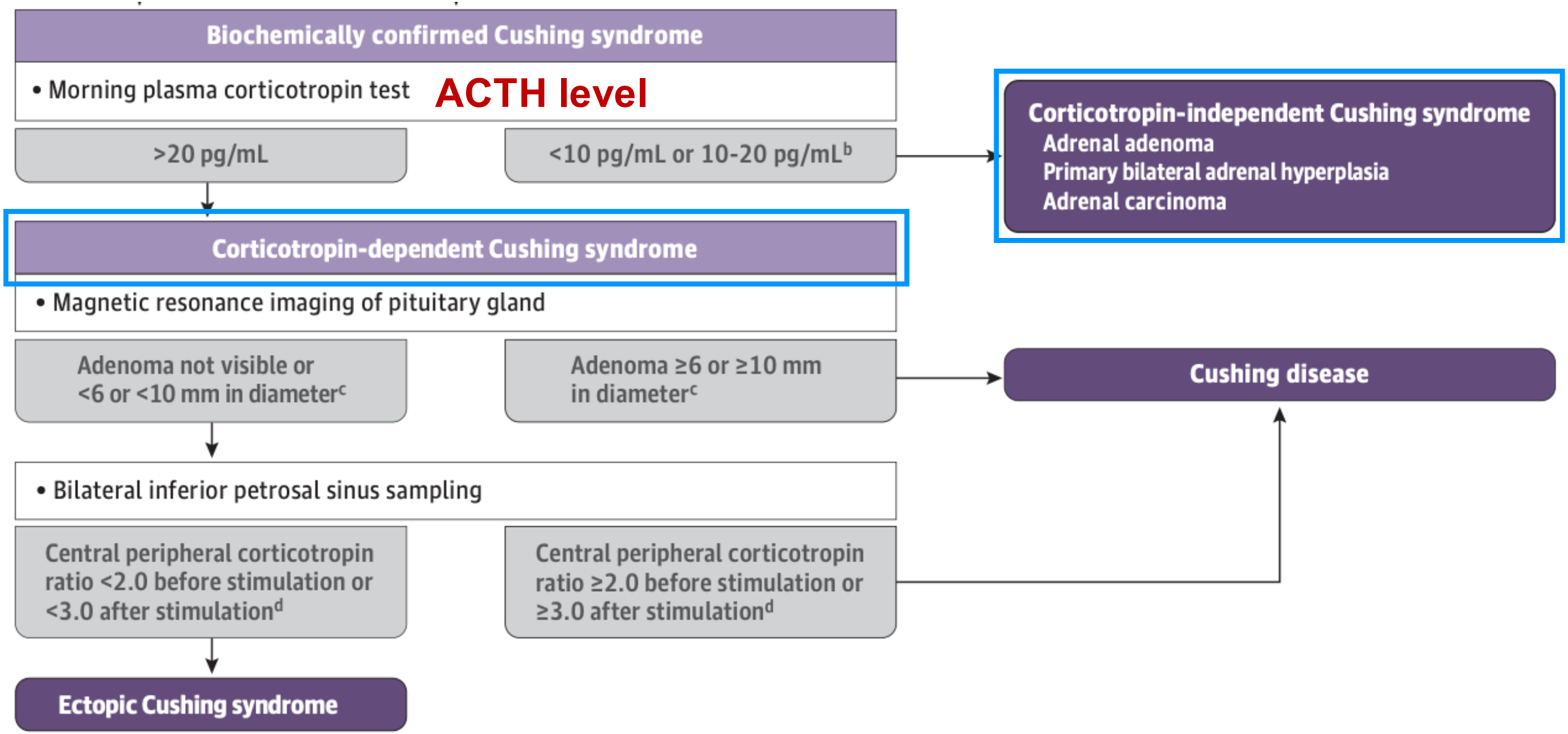


Consensus on diagnosis and management of Cushing's disease: a guideline update. Lancet D&E 2021;9:847-75.



Gadelha M et al. Lancet. 2023;402(10418):2237-2252.

[continued]



Gadelha M et al. Lancet. 2023;402(10418):2237-2252.

Q14

A 48-yr-old woman: 6-Mo hx of 9-kg weight gain

- Easy bruising
- Newly Dx T2DM Rx with metformin
- Normal BP, BMI 38, central obesity, wide violaceous striae on abdomen
- Elevated 24-h urine free cortisol and late-night salivary cortisol levels

Which of the following is the most appropriate Dx test to perform next?

A. Abdominal CT

B. ACTH level measurement

C. 8-mg DEX suppression test

D. Inferior petrosal sinus sampling

Answer:
B. ACTH level

Q15

A 48-yr-old woman: 1-yr hx of 11-kg weight gain

- Easy bruising, fatigue
- **Nigh shift worker**
- Underlying HT, T2DM
- Meds: lisinopril, **estradiol**, aspirin, metformin
- BP 142/88, BMI 34, central obesity, no striae, no prox m weakness

Which of the following is the most appropriate next step in evaluation?

A. Late-night salivary cortisol

B. Morning serum cortisol

C. 1-mg overnight DST

D. 24-h UFC

Answer: D. 24-h UFC

Night shift worker → reverse diurnal cortisol

Estrogen → ↑ CBG → ↑ cortisol

Cushing Caveats and restrictions for tests used to screen for hypercortisolism

All tests	False positive	Cross-reactivity with metabolites or synthetic GCs (immunoassays)	
	False negative	Cyclic CS	
UFC	False positive	Incorrect collection Fluid intake > 4 L/d Pregnancy Pseudo-CS	Carbamazepine or fenofibrate (HPLC) Drugs inhibit-cross-reactivity with metabolites or synthetic GCs (licorice, carbenoxolone)
	False negative	Incorrect collection GFR < 50 ml/min	Mild CS
1 mg-DST	False positive	Elevated CBG (pregnancy, estrogen therapy) Decreased DEX absorption	Drugs increasing DEX metabolism by CYP3A4 enzyme (barbiturates, phenytoin, carbamazepine, rifampicin) Pseudo-CS
	False negative	Impaired liver or renal function	Drugs inhibiting DEX metabolism by CYP3A4 enzyme (itraconazole, ritonavir, fluoxetine, diltiazem, cimetidine)
Bed time salivary cortisol	False positive	Incorrect collection Blood contamination Oral diseases	Nocturnal or shift workers Drugs inhibiting the 11beta-HSD2 enzyme (licorice, carbenoxolone)

CBG = cortisol binding globulin; CS = Cushing syndrome, DEX = dexamethasone,
DST = dexamethasone suppression test, GC = glucocorticoid, GFR = glomerular filtration rate, HSD = hydroxysteroid dehydrogenase

Adapted from Nieman LK et al. Nat Rev Dis Primers. 2025;11(1):4.

Q16

A 38-yr-old woman: 9-mo hx of oligomenorrhea, ↑ facial & body hair

- Deeper voice, frontal hair loss
- Unremarkable medical history, no med
- Normal vital signs, BMI 28
- Coarse dark hair @ chin and chest
- Total testosterone ↑ 97 ng/dL, DHEAS ↑ ↑ ↑ 910 ug/dL

Which of the following is the most appropriate Dx test to perform next?

A. Abdominal CT

B. Adrenal vein sampling

C. Pelvic MRI

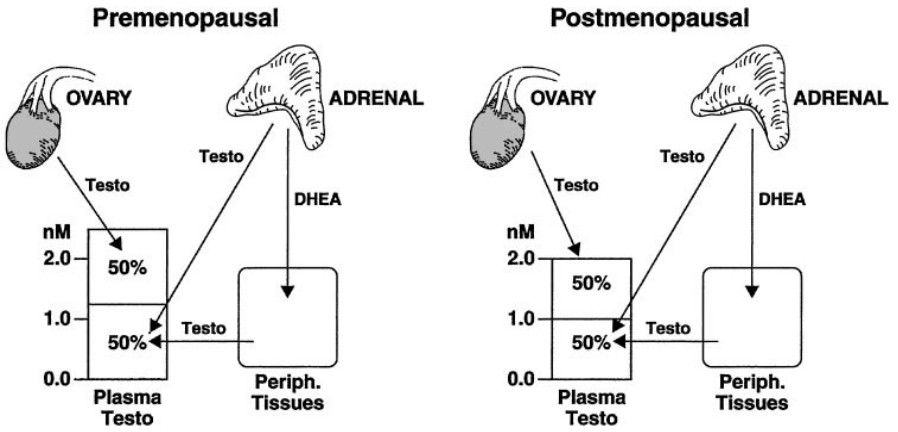
D. Pelvic US

E. Pituitary MRI

Answer: A. Abdominal CT

Androgen-secreting adrenal tumor

- ✓ Rapid-onset hirsutism, virilization
- ✓ The major source of DHEAS is the adrenal gland



Q17

A 52-yr-old woman: 1-yr hx of 7-kg weight gain

- Easy bruising, HT, worsening DM
- Hx of depression, anxiety
- Meds: metformin, lisinopril
- BP 155/97, P82, Cushingoid appearance
- ↑ 24-h UFC 205 ug/d; LNSC 298 mg/mL (<100), ACTH < 5 pg/mL

Which of the following is the most likely cause of hypercortisolism?

A. Adrenal tumor

B. Bronchial carcinoid

C. Pituitary tumor

D. Psychiatric illness

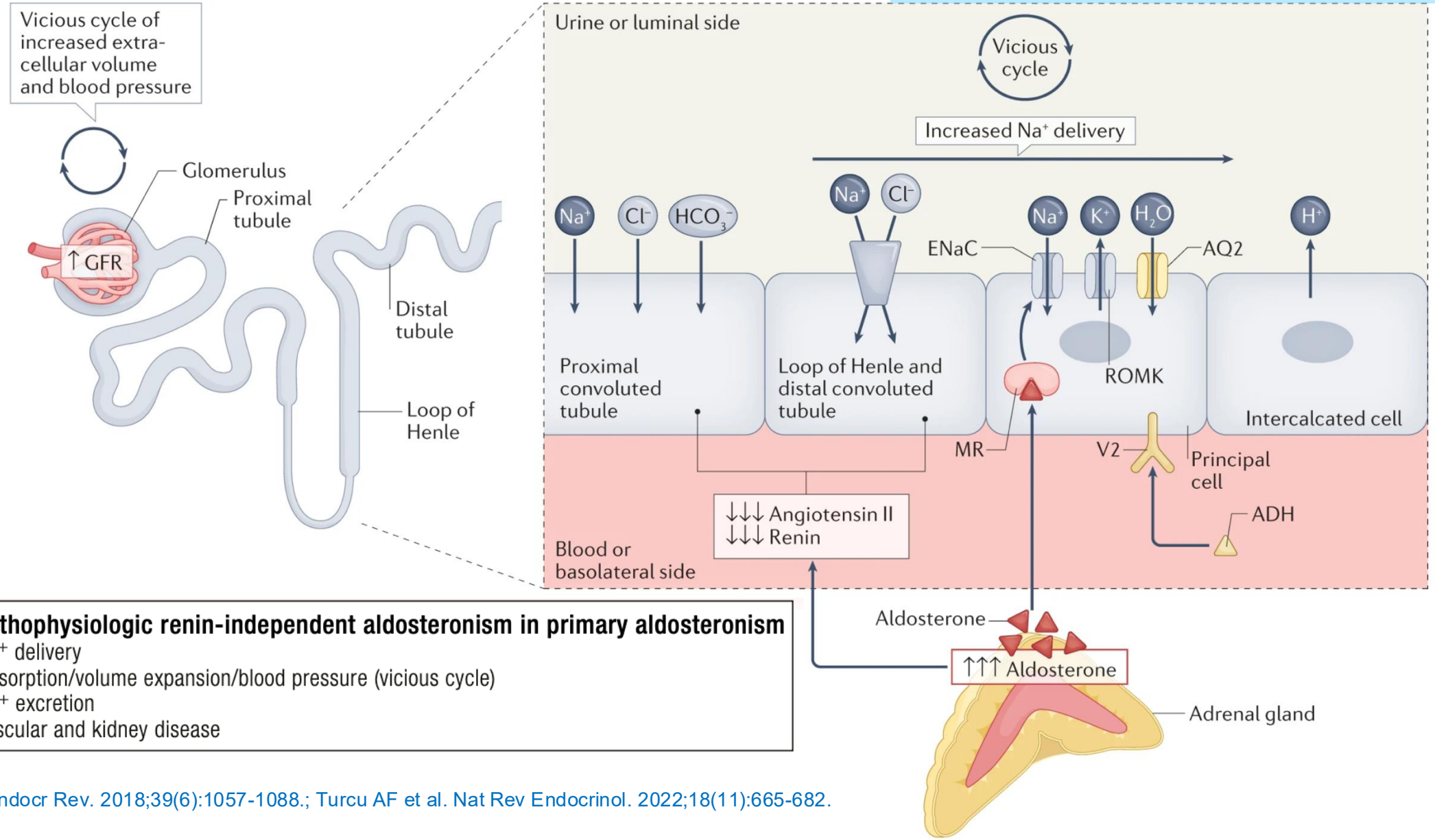
Answer:
A. Adrenal tumor

ACTH-independent tumor

UFC = urine free cortisol; LNSC = late-night salivary cortisol

Primary Aldosteronism (PA)

1. **Suppression of renin**
2. **Inappropriate/dysregulated production of aldosterone**



Summary: pathophysiologic renin-independent aldosteronism in primary aldosteronism

- ↑↑↑ Distal Na^+ delivery
- ↑↑↑ Na^+ reabsorption/volume expansion/blood pressure (vicious cycle)
- ↑↑↑ K^+ and H^+ excretion
- ↑↑↑ Cardiovascular and kidney disease

Vaidya A et al. Endocr Rev. 2018;39(6):1057-1088.; Turcu AF et al. Nat Rev Endocrinol. 2022;18(11):665-682.

The Journal of Clinical Endocrinology & Metabolism, 2025, **110**, 2453–2495
https://doi.org/10.1210/clinem/dgaf284
Advance access publication 14 July 2025
Clinical Practice Guideline

Primary Aldosteronism: An Endocrine Society Clinical Practice Guideline

Gail K. Adler,[1] Michael Stowasser,[2] Ricardo R. Correa,[3] Nadia Khan,[4] Gregory Kline,[5] Michael J. McGowan,[6] Paolo Mulatero,[7] M. Hassan Murad,[8] Rhian M. Touyz,[9] Anand Vaidya,[1] Tracy A. Williams,[10] Jun Yang,[11,12] William F. Young,[8] Maria-Christina Zennaro,[13,14] and Juan P. Brito[8,15]

High-risk populations for PA

High-risk populations	Prevalence
Severe or resistant hypertension	11.3-29.1%
Unexplained or diuretic-induced hypokalemia	28.1%
Hypertension with adrenal mass	4.4%
Hypertension with sleep apnea	
Hypertension with atrial fibrillation	42.5%
Strong personal or family history	
Debated expansion of eligible populations	
New-onset hypertension	
Stage 2 hypertension	
All hypertension	

Vaidya A, et al. Am J Hypertens. 2022;35(12):967–988.

2025 ES Guidelines

Suggest PA screening for

all individuals with HT.

Adler GK, et al. J Clin Endocrinol Metab. 2025;110(9):2453-2495.

THAILAND: Limited resource
May not be applicable
for universal screening.

PA Screening

Individuals with Hypertension

↓

Measure Aldosterone, Renin, and Potassium*

↓

Meets Criteria for Primary Aldosteronism**

Renin concentration or activity is low or suppressed, while aldosterone concentration is inappropriately high relative to renin

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

↓

- Aldosterone (immunoassay) ≥ 10 ng/dL (≥ 277 pmol/L)
- Aldosterone (LC-MS/MS) ≥ 7.5 ng/dL (≥ 208 pmol/L)

AND

Aldosterone to renin ratio (ARR) is increased

- Aldosterone (immunoassay, ng/dL) / PRA (ng/mL/h) > 20
- Aldosterone (immunoassay, pmol/L) / DRC (mU/L) > 70
- Aldosterone (LC-MS/MS, ng/dL) / PRA (ng/mL/h) > 15
- Aldosterone (LC-MS/MS, pmol/L) / DRC (mU/L) > 52

*Seated position in the morning
*Ideally without venous stasis (release tourniquet after venipuncture and wait at least 5 sec before withdrawing blood) to avoid factitious rises in K+.
*Avoiding dietary sodium restriction during the few days prior to screening
*Low potassium may lead to a falsely low aldosterone

Medications that interfere with PA screening

Effects	Medications
↓ Renin	β-blocker, central acting α-2 agonists (clonidine, α-methyldopa), NSAIDs, OCP (E+P), HRT: ↓ DRC
↑ Renin	MRA, diuretics, ACEI, ARB, SGLT2i OCP (E+P), HRT: ↑ PRA
↓ Aldosterone	ACEI, ARB, β-blocker, central acting α-2 agonists (clonidine, α-methyldopa)
↑ Aldosterone	MRA, diuretic Combined OCP (E+P), HRT

Adler GK, et al. J Clin Endocrinol Metab. 2025;110(9):2453-2495.

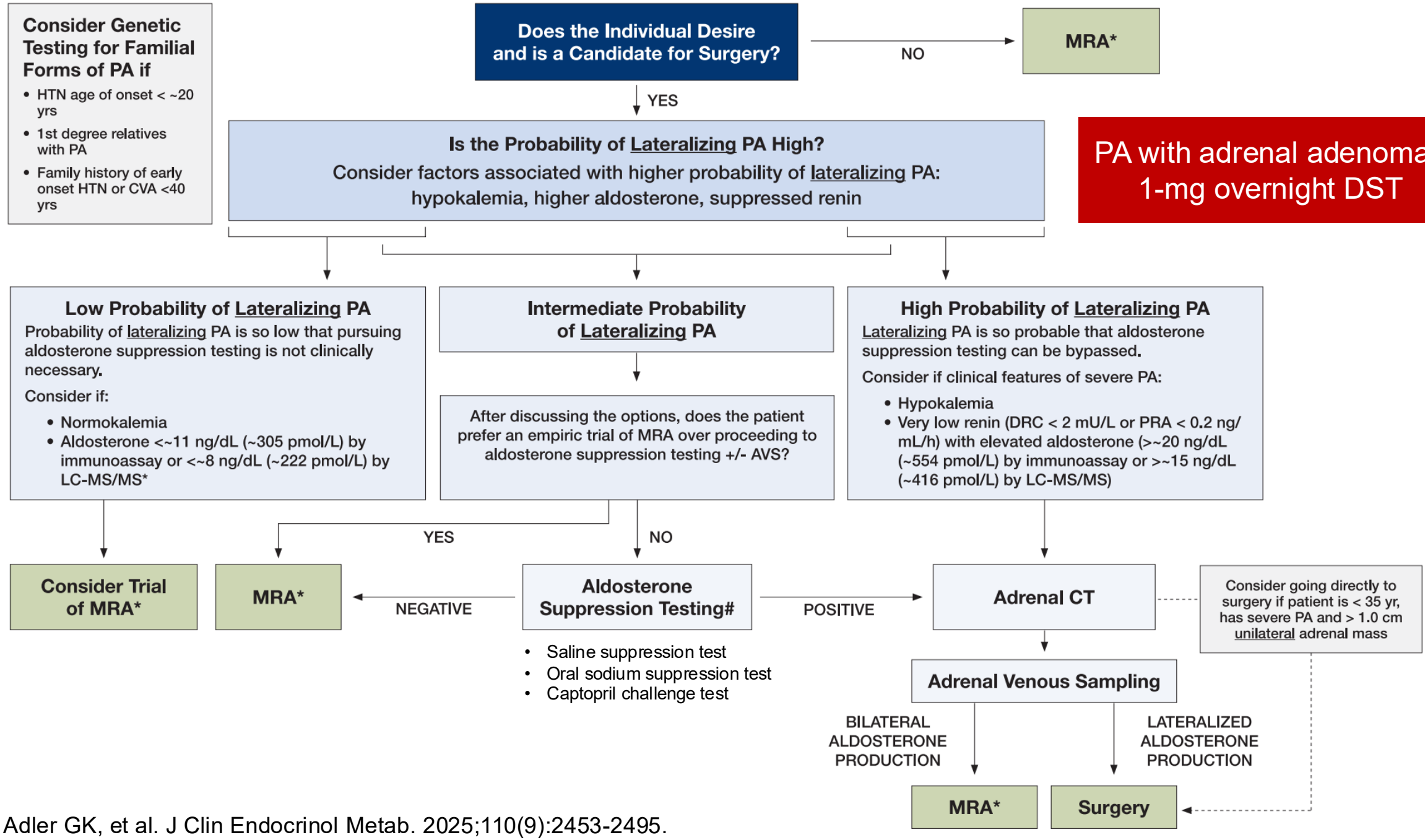
Anti-HT med withdrawal strategy

1. **No medication withdrawal**
   - Possible false positive (↓ renin if on β-blocker, clonidine, α-methyldopa)

2. **Minimal medication withdrawal**
   - Stop 4 wks: MRA, ENaC inhibitor (amiloride, triamterene)
   - Stop 2 wks: β-blocker, clonidine, α-methyldopa
   - Replace with: hydralazine, α-blocker, non-dihydropyridine CCB

3. **Ideal full medication withdrawal**
   - Stop 4 wks: MRA, ENaC inhibitor (amiloride, triamterene), other diuretics
   - Stop 2 wks: β-blocker, clonidine, α-methyldopa,
     ACEI, ARB, dihydropyridine CCB, SGLT2i
   - Replace with: hydralazine, α-blocker, non-dihydropyridine CCB

Adler GK, et al. J Clin Endocrinol Metab. 2025;110(9):2453-2495.

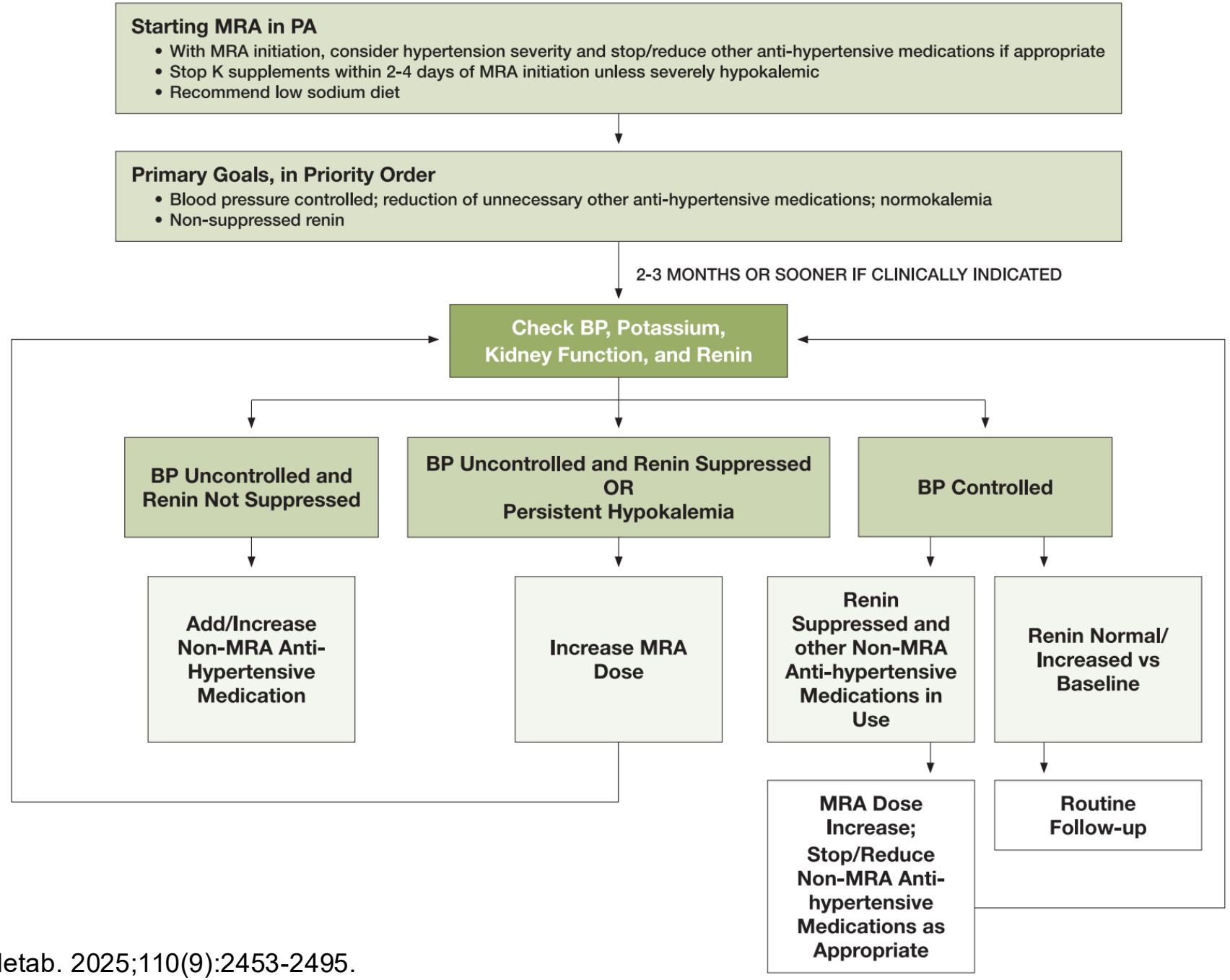


Adler GK, et al. J Clin Endocrinol Metab. 2025;110(9):2453-2495.

MRA therapy

Spironolactone

- Starting dose: 12.5-25 mg/d
- Possible max dose in PA: 200 mg/d
- Side effects: gynecomastia, sexual dysfunction (men), menstrual irregularities (women)



Adler GK, et al. J Clin Endocrinol Metab. 2025;110(9):2453-2495.

AVS

Adrenal Venous Sampling

Successful catheterization?

Selectivity index

$$\frac{\text{Cortisol adrenal vein}}{\text{Cortisol inferior vena cava}}$$

- > 1.4-3 without cosyntropin stimulation
- > 5 after cosyntropin stimulation

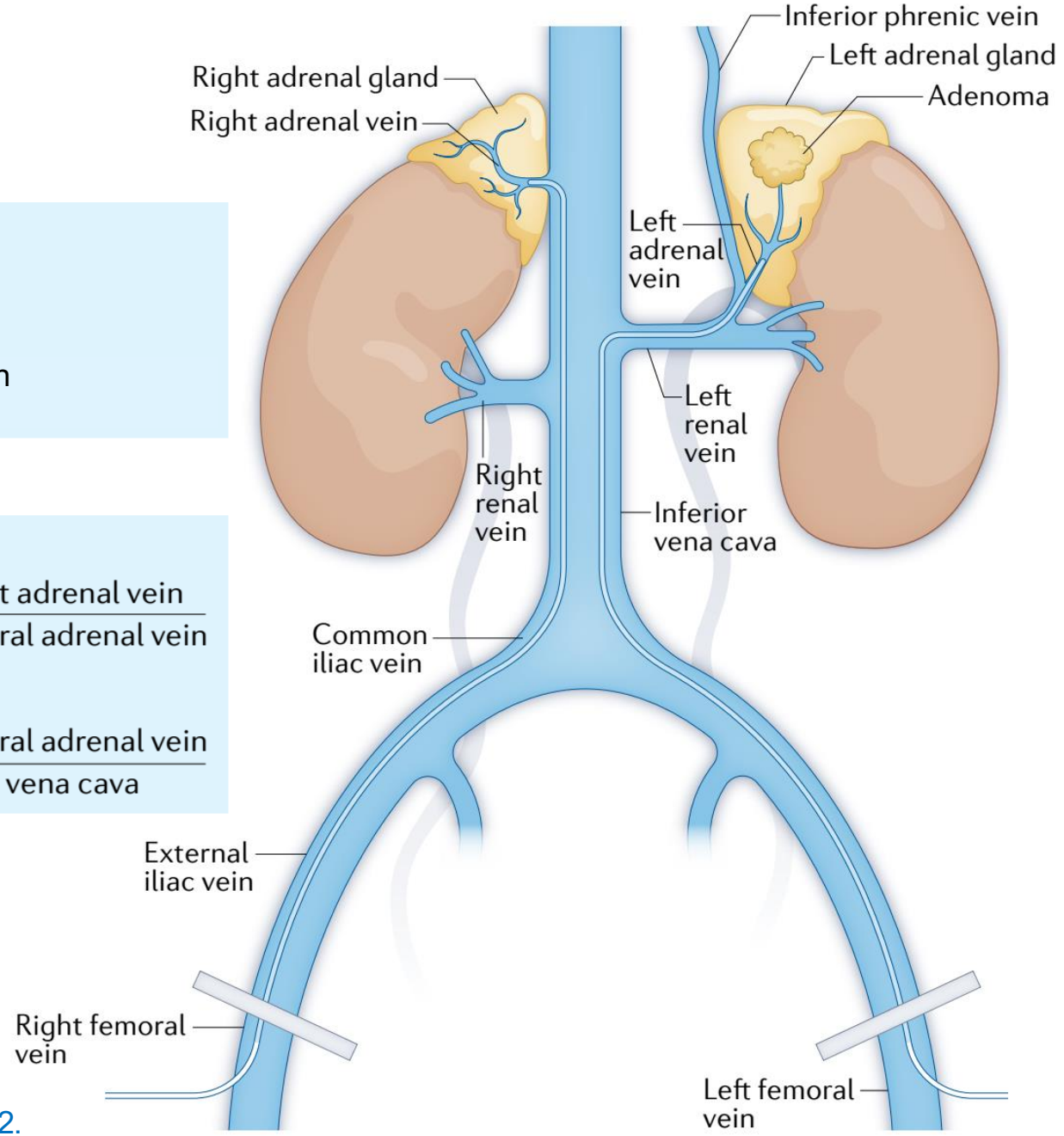
Lateralization?

Lateralization index ≥4

$$\frac{\text{Aldosterone:cortisol ratio of the dominant adrenal vein}}{\text{Aldosterone:cortisol ratio of the contralateral adrenal vein}}$$

Contralateral suppression index <1

$$\frac{\text{Aldosterone:cortisol ratio of the contralateral adrenal vein}}{\text{Aldosterone:cortisol ratio of the inferior vena cava}}$$



Turcu AF et al. Nat Rev Endocrinol. 2022;18(11):665-682.

Q18

A 55-yr-old man: resistant HT Rx with HCTZ, amlodipine, losartan

- BP 152/98, P 72
- Serum electrolytes: normal

Which of the following is the most appropriate test?

A. Adrenal CT

B. Aldosterone measurement after oral sodium loading

C. 24-h urine K measurement

D. Plasma renin activity measurement

Answer: D. renin

In patients with suspected PA taking an ACEI/ARB, an elevated serum renin level excludes PA

Q19 A 52-yr-old man: difficult-to-control hypertension, biochem confirmed PA

- BP 149/98, P 75
- CT: 0.8-cm right adrenal mass, 13 HU

Which of the following is the most appropriate management?

A. Adrenal vein sampling

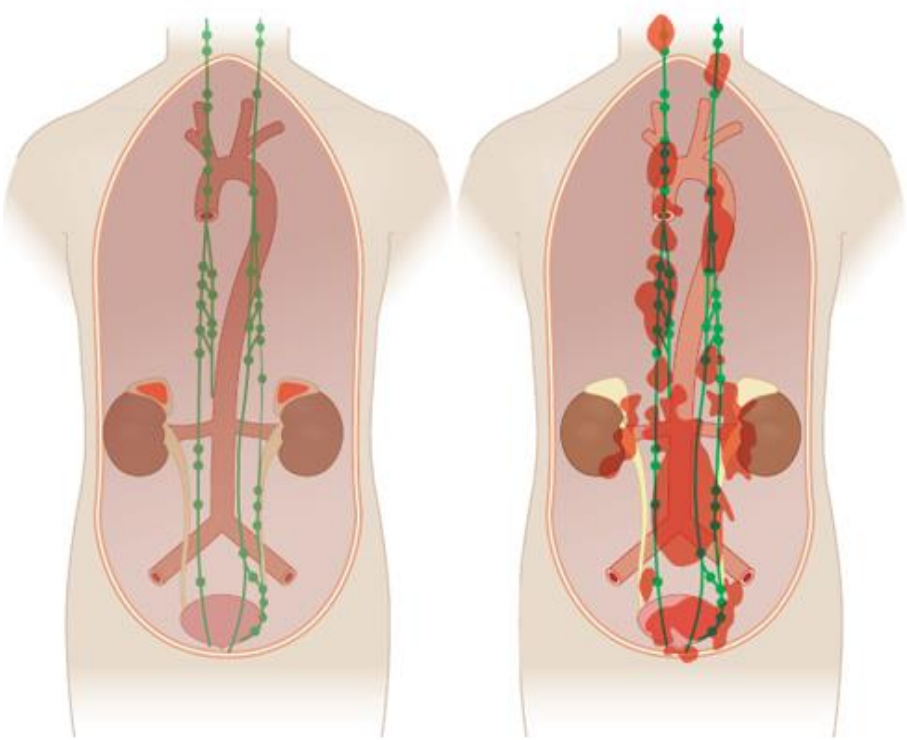
B. Increase metoprolol

C. Increase losartan

D. Right adrenalectomy

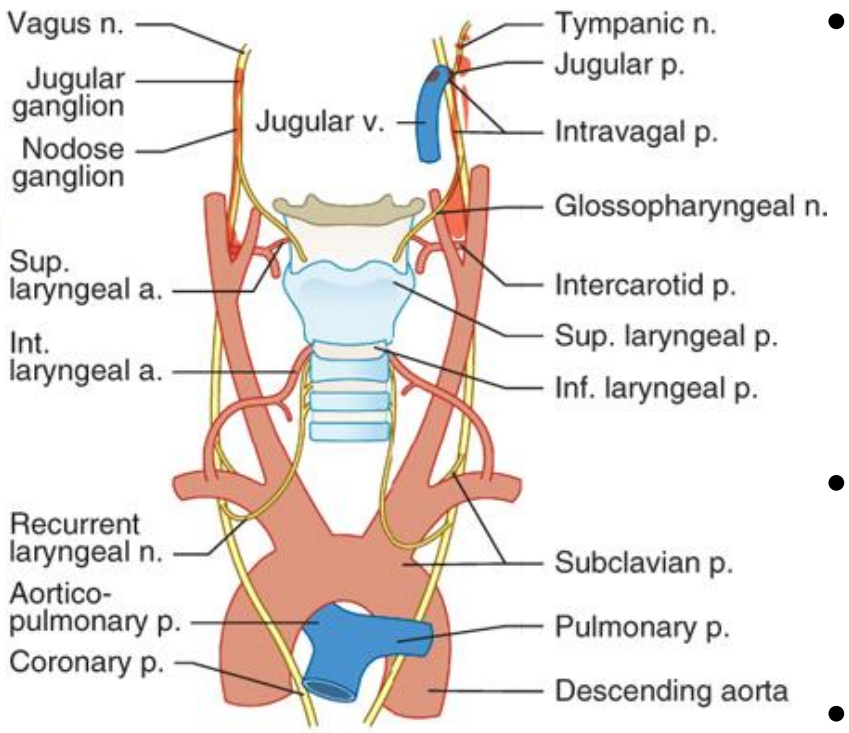
Answer: A. AVS

Pheochromocytoma/Paraganglioma (PPGL)



A Adrenal pheochromocytoma

B Extra-adrenal pheochromocytoma



C Head and neck paraganglioma

- "Classic triad"
  - ✓ episodic headache
  - ✓ diaphoresis
  - ✓ palpitation
- Also occur in normotensive patients
- Newly Dx Takotsubo syndrome or unexplained DCM need to evaluation of PPGLs

Genetic PPGL

~40% germline mutation

Cluster I Hypoxic pathway

SDHA, *SDHB*, *SDHC*,

SDHD, *SDHAF2*, *FH*,

VHL, *IDH1/2*, *MHD2*,

EGLN1/2, HIF2/EPAS, KIF1B

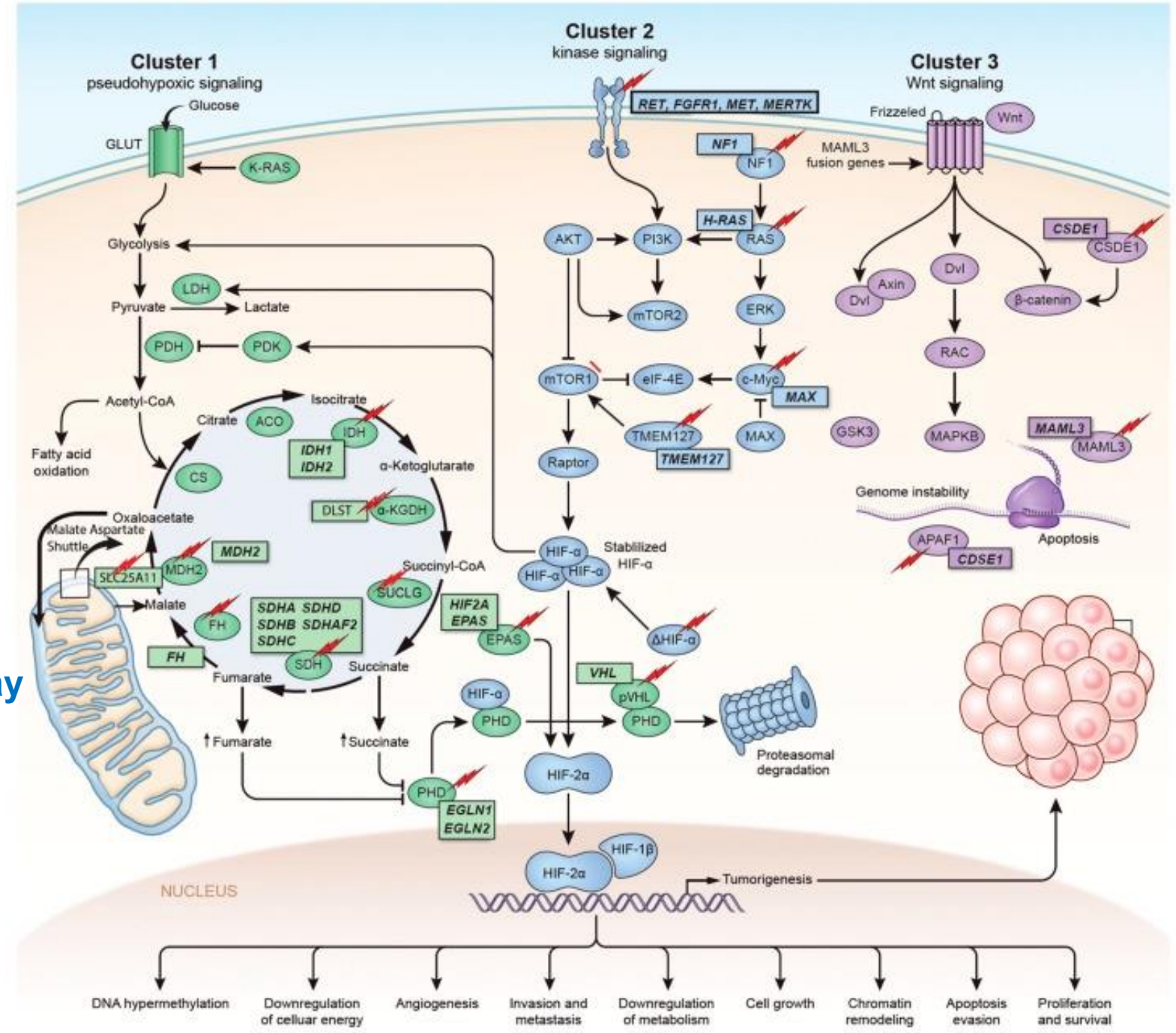
Cluster II Kinase signaling pathway

RET, *NF1*, *TMEM127*,

MAX and *HRAS*

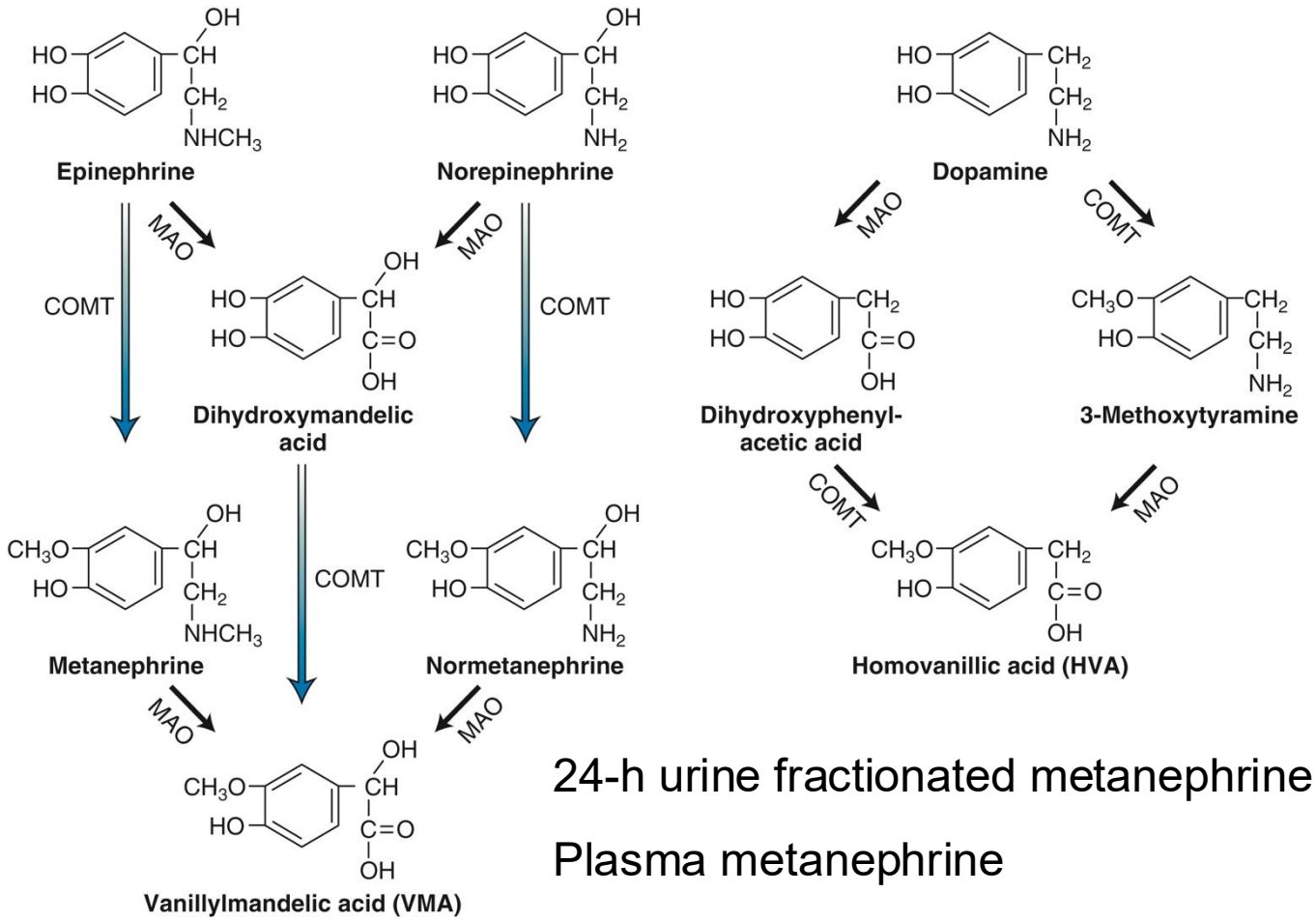
Cluster III Wnt signaling

CSDE1 and *MAML3*



Cancers (Basel). 2022; 14(3): 594.

PPGL



24-h urine fractionated metanephrine

Plasma metanephrine

Diagnostic: > 2xULN

Williams Textbook of Endocrinology, 15th Edition

Suspected pheochromocytoma

- Hyperadrenergic spells
- Resistant hypertension
- MEN2, NF1, VHL
- Adrenal incidentaloma
- Pressor response during anesthesia, surgery, or angiography
- Onset of hypertension at a young age < 20 yrs
- Idiopathic dilated cardiomyopathy
- Cyanotic congenital heart disease

Medications that May Increase Measured Levels of Fractionated Catecholamines and Metanephrines

Tricyclic antidepressants (including cyclobenzaprine)
Levodopa
Alpha-methyldopa
Drugs containing adrenergic receptor agonists (e.g., decongestants)
Amphetamines
Buspirone and antipsychotic agents
Prochlorperazine
Reserpine
Withdrawal from clonidine and other drugs
Illicit drugs (e.g., cocaine, heroin)
Ethanol

acetaminophen, mesalamine, sulfasalazine interfere with LC-ECD methods

Evaluation of PPGL indicated (Table 2)

- Exclude drugs which could cause false positives
- Avoid exercise on day of testing
- Patient supine for 30 minutes

Biochemical testing

- Plasma free metanephrines or
- 24 hour urine fractioned metanephrines

Normal

High metanephrines
<3-4 times normal value

High metanephrines
>3-4 times normal value

Repeat plasma free metanephrines

Confirm reference values are for supine position and according to age

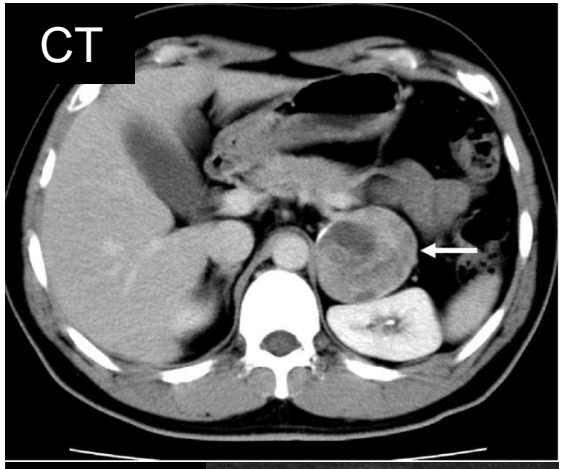
Imaging
MRI abdomen and pelvis
If negative consider CT/MRI head, neck and chest versus functional imaging

< 2 times normal value
PPGL unlikely
Follow patient and repeat biochemical testing

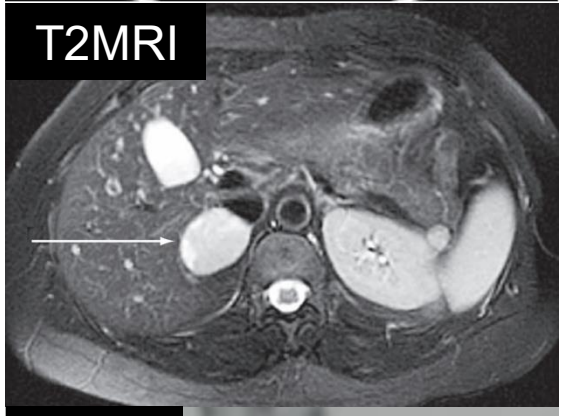
> 2 times normal value

Imaging with MRI versus functional imaging

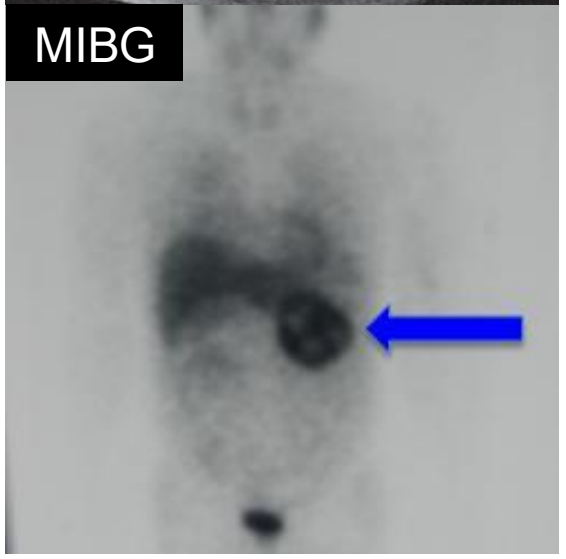
Functional imaging
To detect metastasis or multifocal disease, or localize tumor when CT/MRI are negative



- CT abdomen & pelvis: 1st choice
- Noncontrast CT < 10 HU exclude pheo



T2 hyperintense
"Light bulb sign"



Functioning imaging for searching metastasis or multiple lesion

Perioperative management of pheochromocytoma

Initiate α-blocker and high-sodium diet (to prevent postural hypotension): Titulate until BP goals

BP uncontrolled or α-blocker side effects

↓

Add calcium channel blocker

↓

Persistent postural hypotension

↓

Increase high-sodium diet or saline infusion

Heart rate above target

↓

Add β-blocker

Preoperative goals:
1. BP < 130/80 mmHg with upright systolic blood pressure >90 mmHg
2. HR 60 –70 bpm seated/ 70 – 80 bpm standing

Postop complications:
hypotension, hypoglycemia

Drugs known to provoke pheochromocytoma paroxysms

Drug class	Relevant clinical use
β-adrenergic blockers	Used to treat symptoms from catecholamine excess, such as hypertension, cardiomyopathy, and migraine
Opiate analgesics	Induction of surgical anesthesia
Sympathomimetics	Decongestants, anti-obesity agents, control of low blood pressure during surgical anesthesia
Dopamine D2 receptor antagonists	Control of psychosis, hot flushes, nausea, vomiting, and tranquilizing effect
Tricyclic antidepressants	Insomnia, nocturnal enuresis, headaches, neuropathic pain, and depression
Serotonin and norepinephrine reuptake inhibitors	Depression, anxiety, panic attacks, and anti-obesity agents
Monoamine oxidase inhibitors	Not usually used as antidepressants
Chemotherapeutic agents	Treatment of malignant paraganglioma
Neuromuscular agents	Induction of surgical anesthesia
Peptide and steroid hormones	Diagnostic testing

Adequacy of preoperative α blockade

No in-hospital BP > 160/90 for 24 h prior to Sx

No orthostatic hypotension with BP< 80/45

No ST or T wave changes for 1 wk prior to Sx

No > 5 PVCs/min

Fagundes GFC et al. J Endocr Soc. 2022;6(2):bvac004.

Q20 W/U pheochromocytoma

Answer: A. Amitriptyline

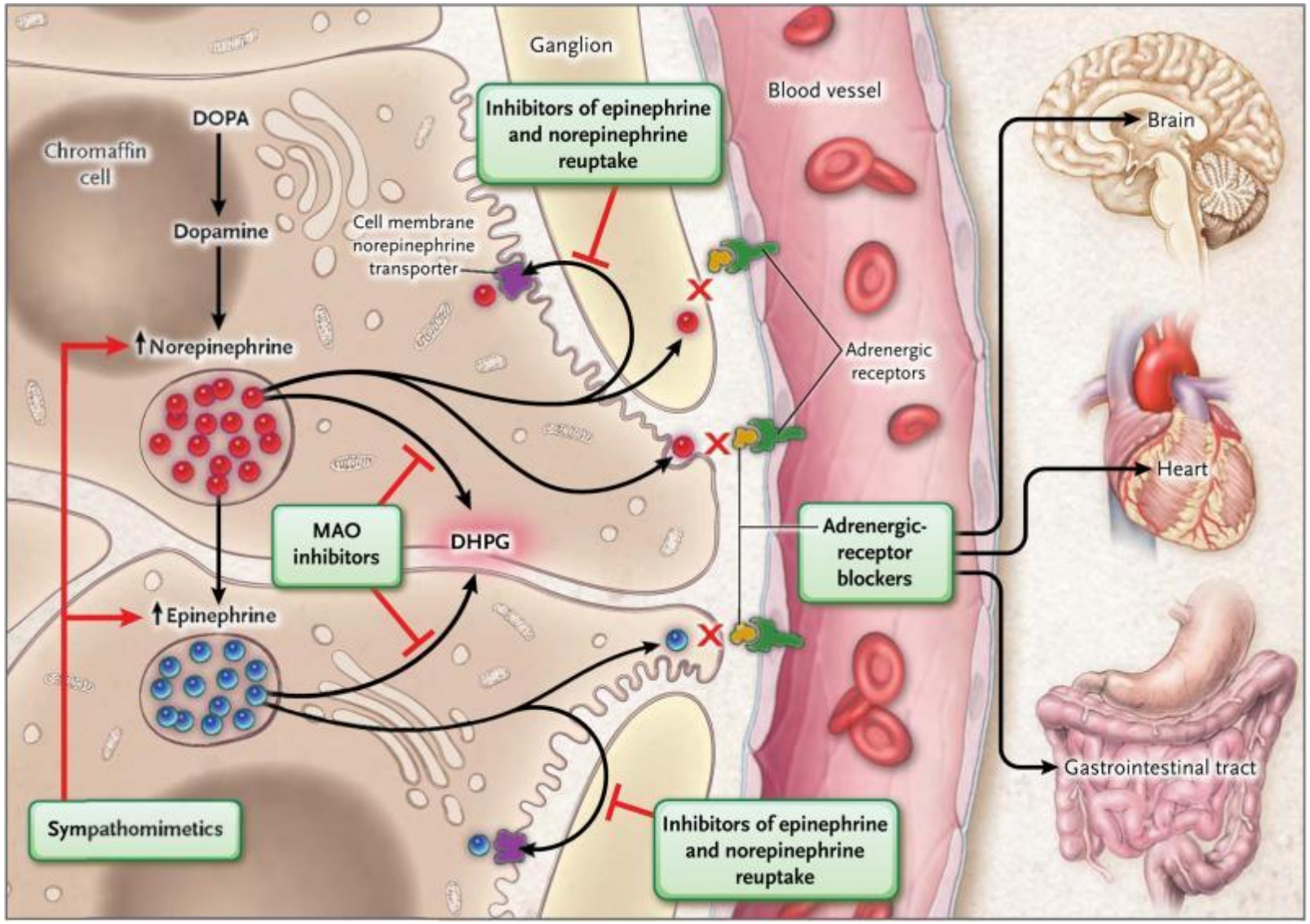
Which of the following medications should be discontinued prior to screening for pheochromocytoma?

A. Amitriptyline

B. Chlorthalidone

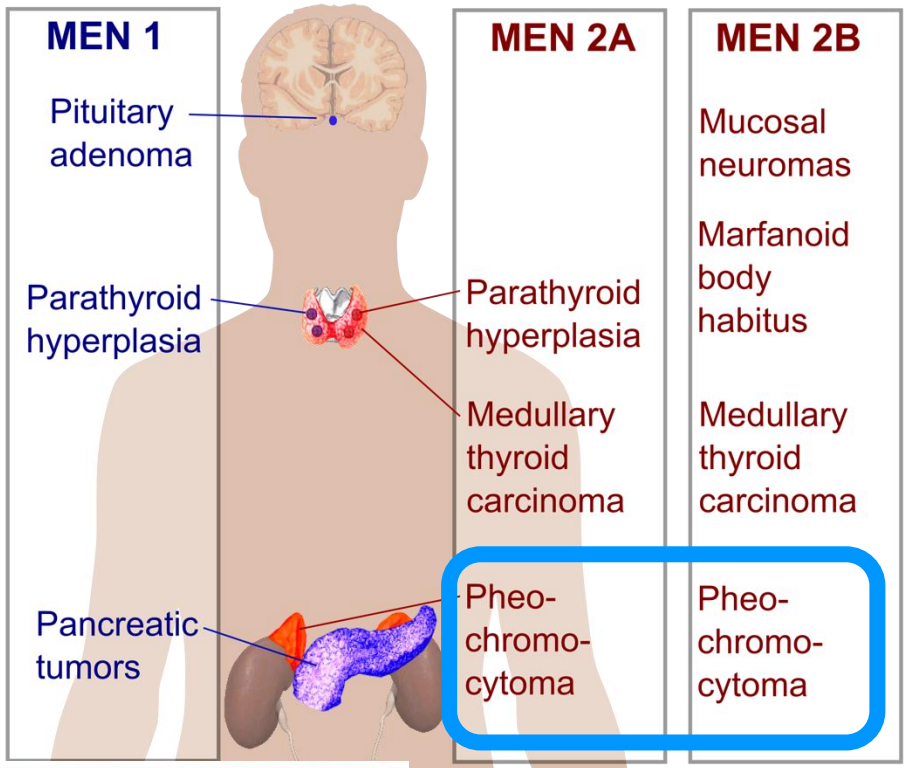
C. Metoprolol

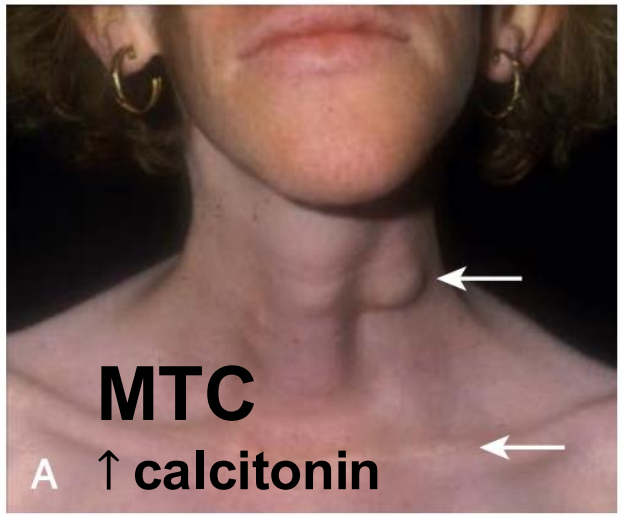
D. Omeprazole

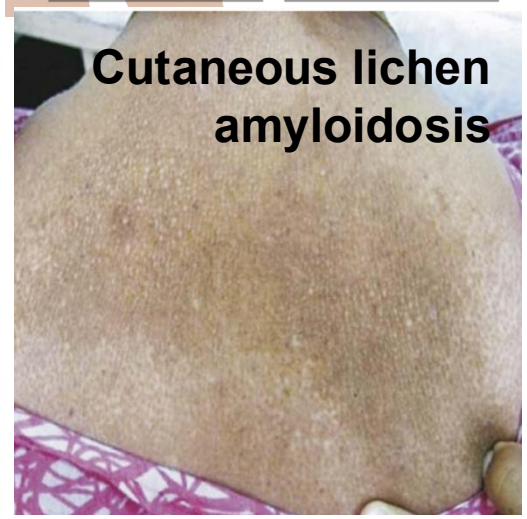


Neary NM, King KS, Pacak K. N Engl J Med. 2011; 364(23): 2268–2270.

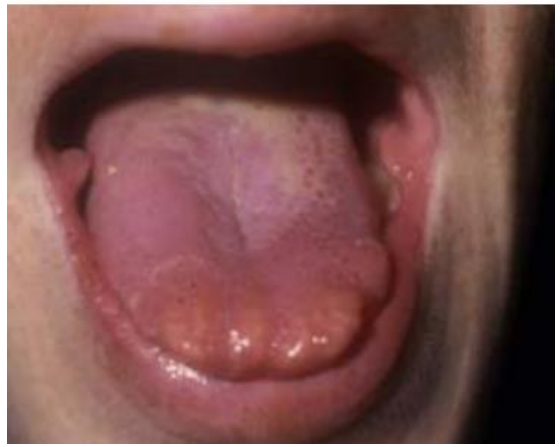
Multiple endocrine neoplasia type 2

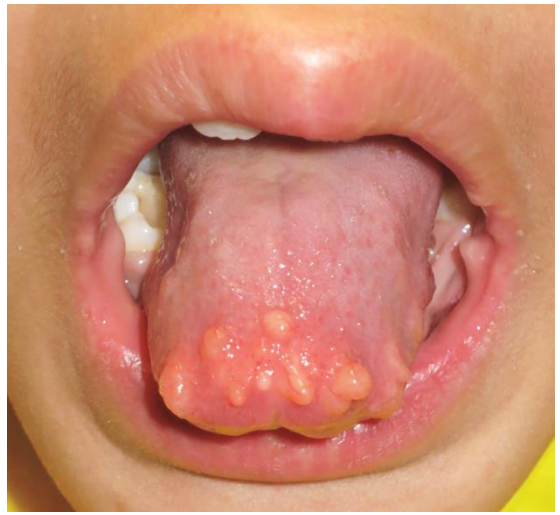


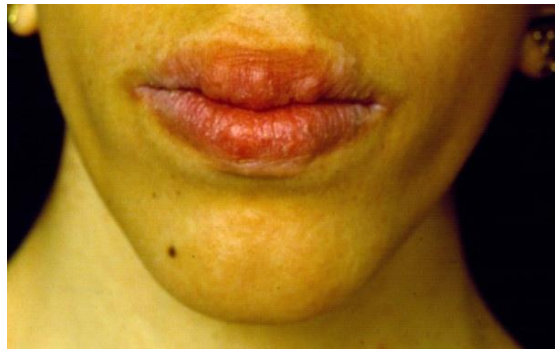




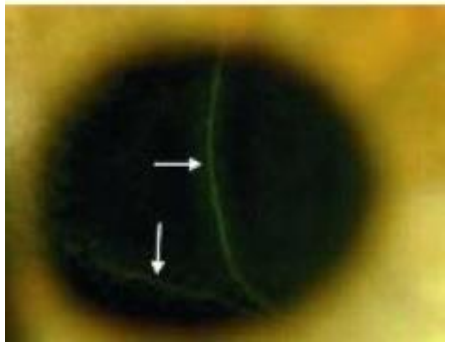
Mucosal neuroma





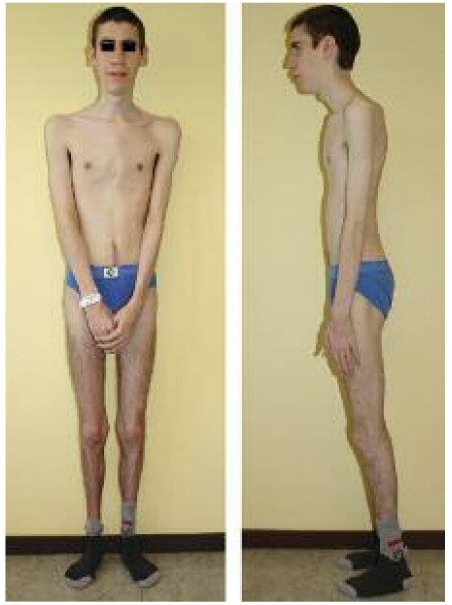


Mucosal neuroma

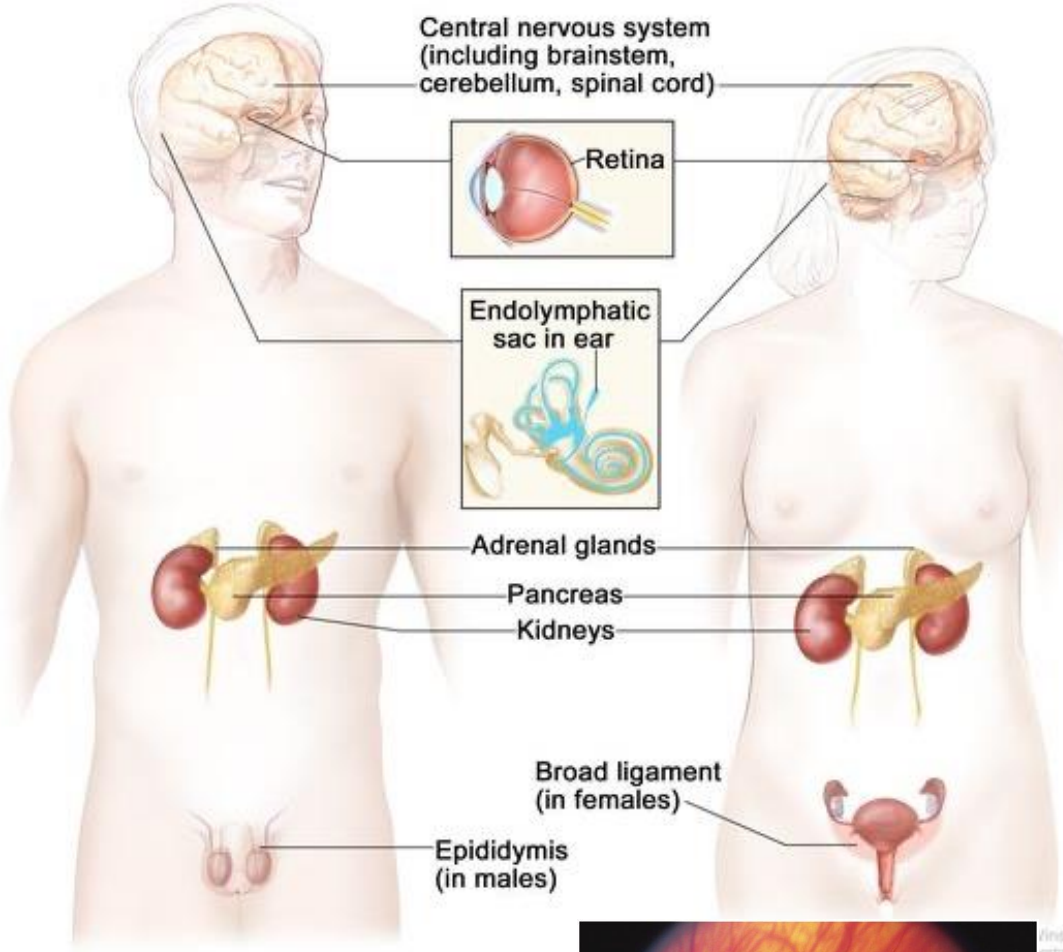


Corneal nerve hypertrophy

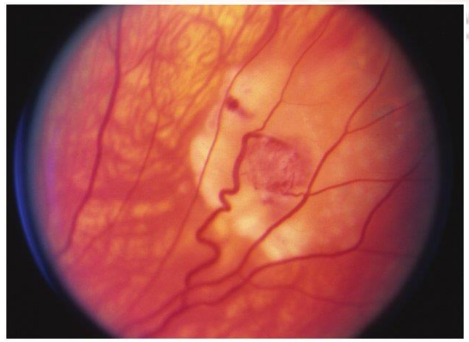
Marfanoid body habitus



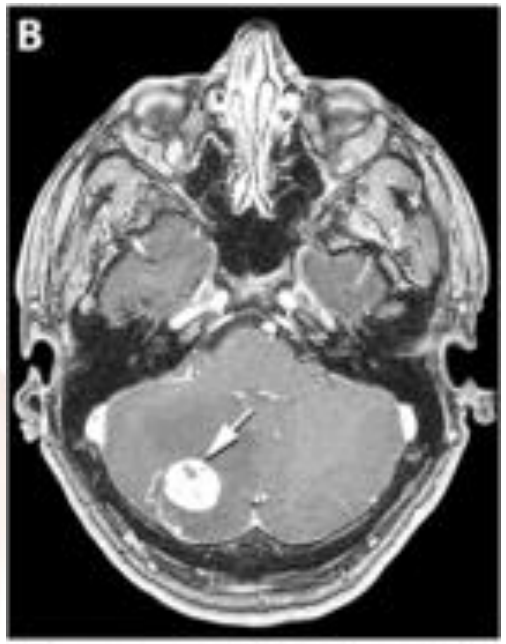
Von Hippel-Lindau

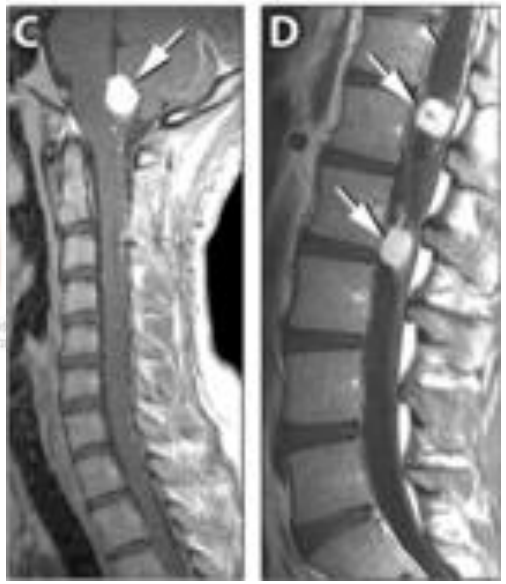


Retinal hemangioblastomas



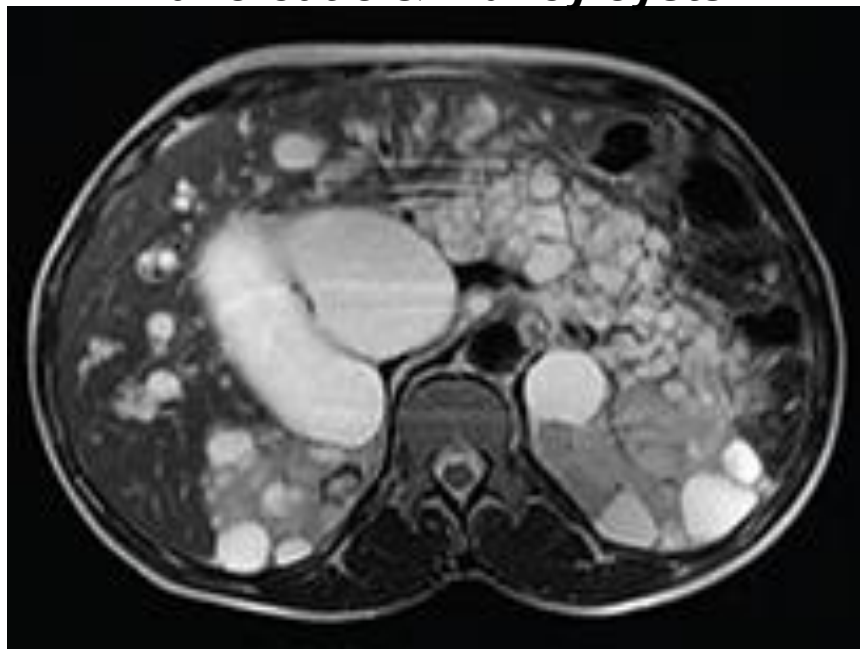
CNS hemangioblastomas

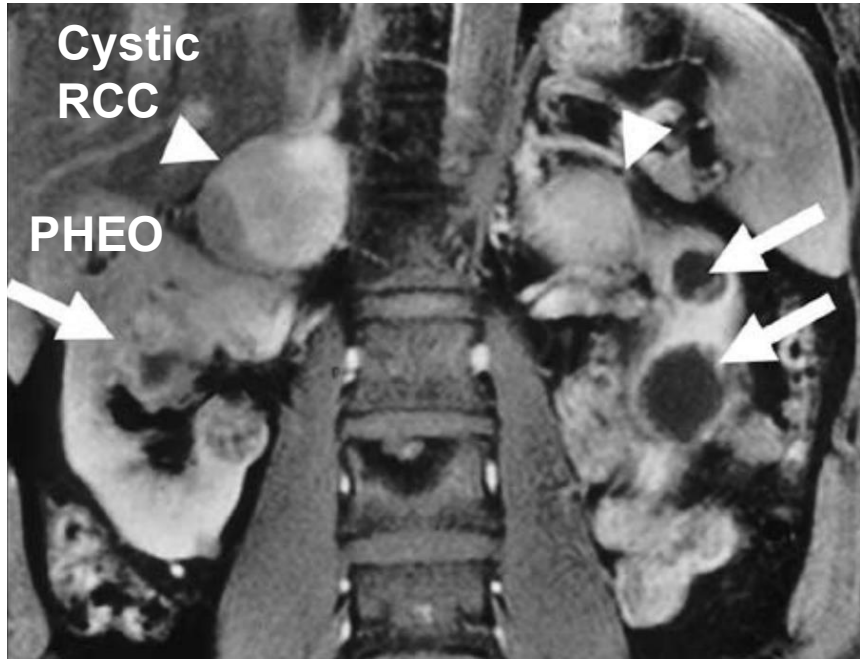




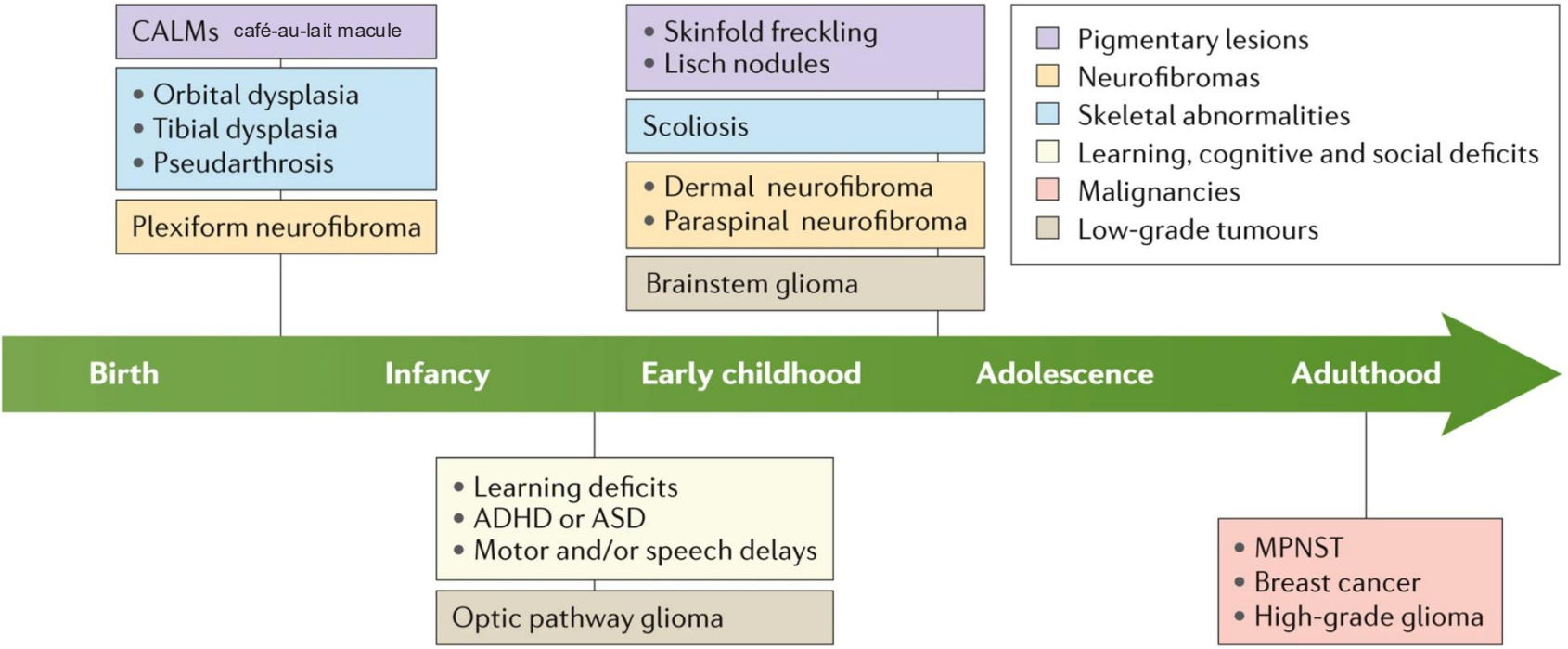
Cerebellar & spinal

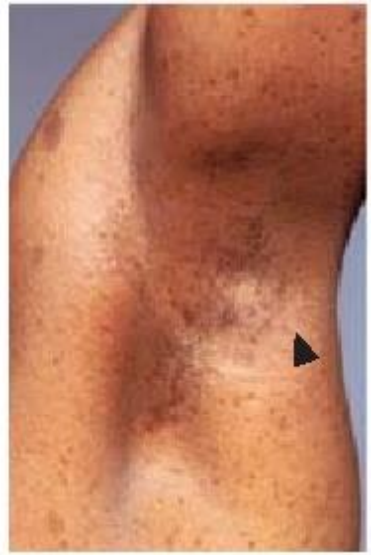
Pancreatic & kidney cysts



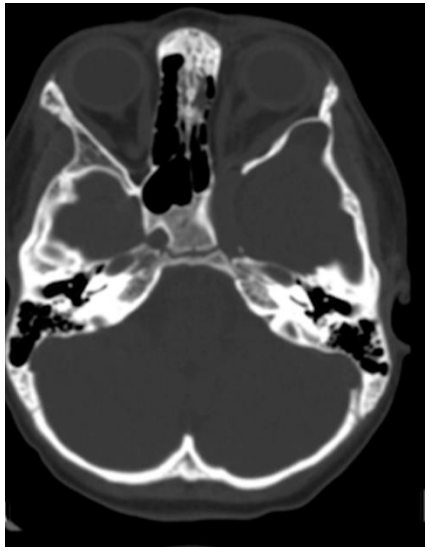


Neurofibromatosis type 1





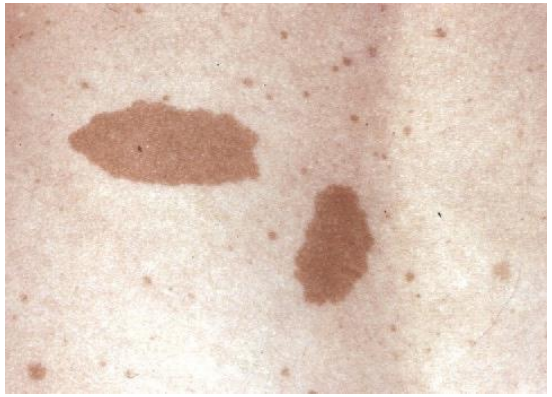
Skinfold freckling



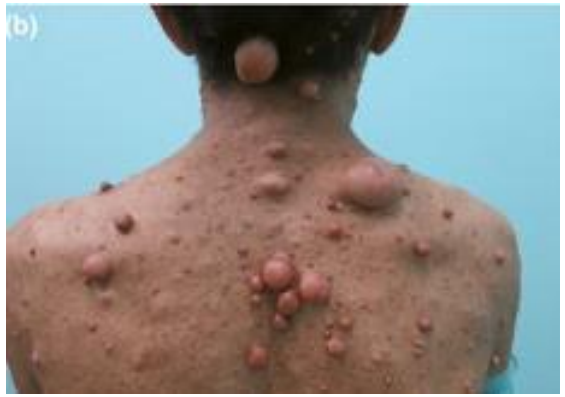
Sphenoid wing dysplasia/ pseudoarthrosis

NF1 patients have higher predilection to develop tumors like pheochromocytoma, GIST, and pancreatic NET

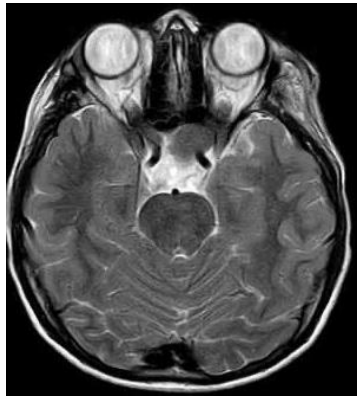
Nature Reviews | Disease Primers



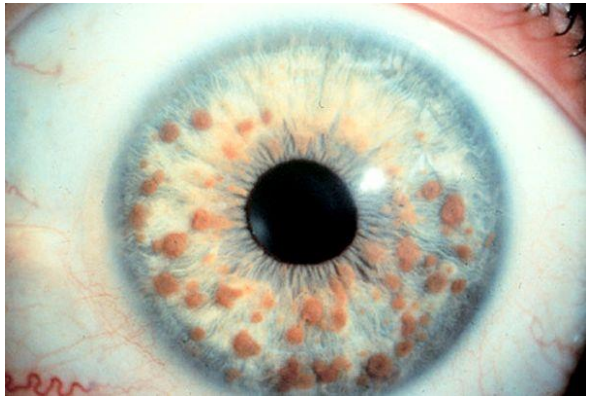
Café-au-lait macule



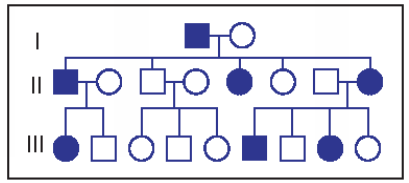
Neurofibromas



Optic glioma



Lisch nodules



1st-degree relative

Adrenal Insufficiency (AI)

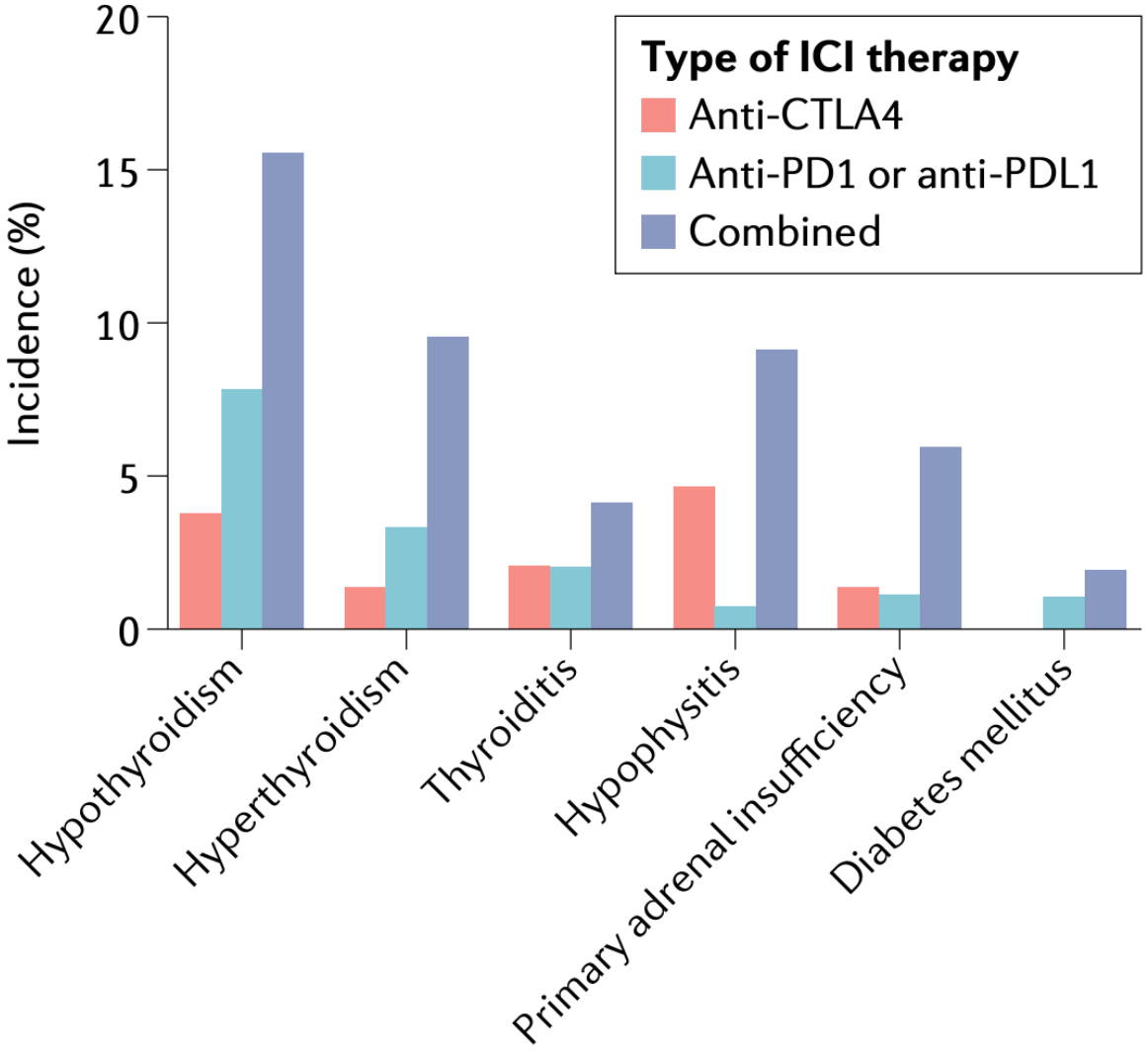
- **Bilateral adrenal incidentalomas:** AI and CAH should be excluded.
- **Iatrogenic AI:** inhaled corticosteroid (CS, fluticasone) & CYP3A4 inhibitor (protease inhibitor); megestrol acetate
- **Concurrent hypothyroidism & AI:** LT4 should be started only after CS replacement
- TSH < 10 in patients with newly Dx AI might not indicate hypothyroidism;

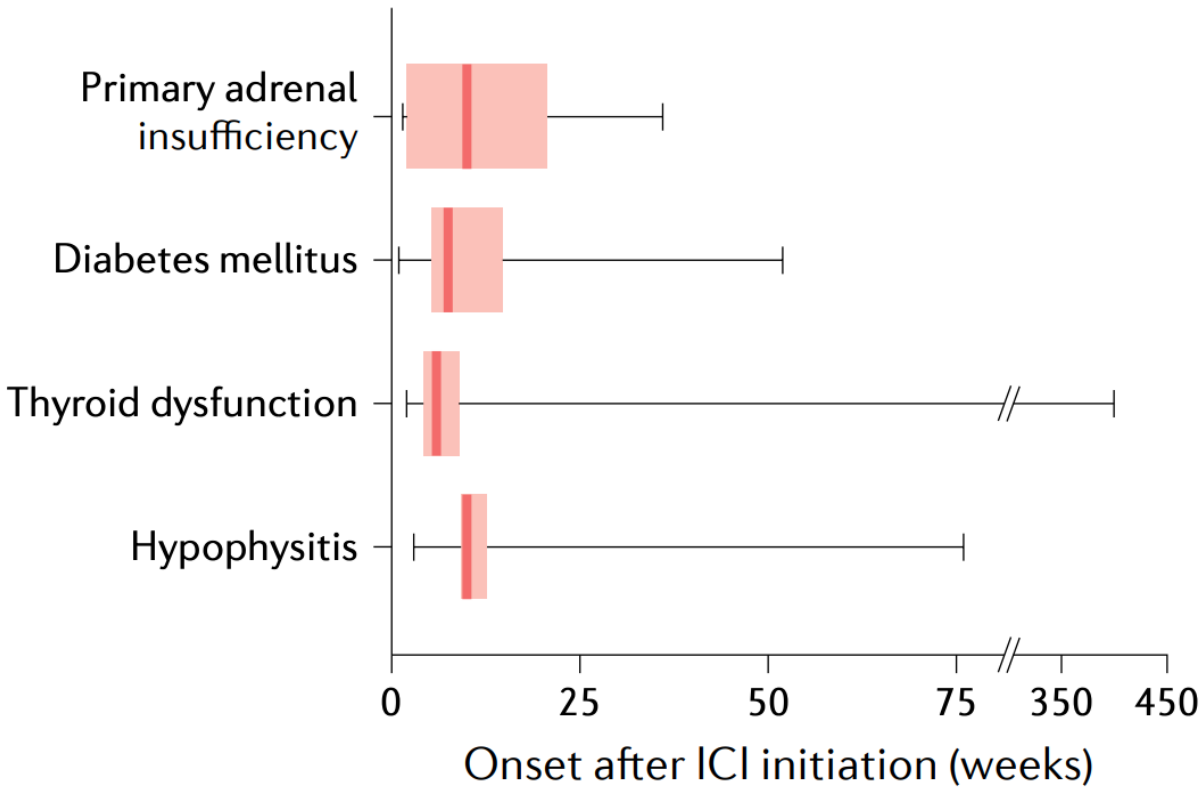
  TSH often normalize with CS replacement alone
- **Special situations**
  - Shift workers: changing timing according to the individual schedule
  - Hemodialysis patients: no longer need for fludrocortisone; CS plan (CS might be lost through HD)
  - Essential HT in 1°AI patients: check fludrocortisone dose, preferred CCB, α-blocker

ACEI/ARB not effective

CS = corticosteroid

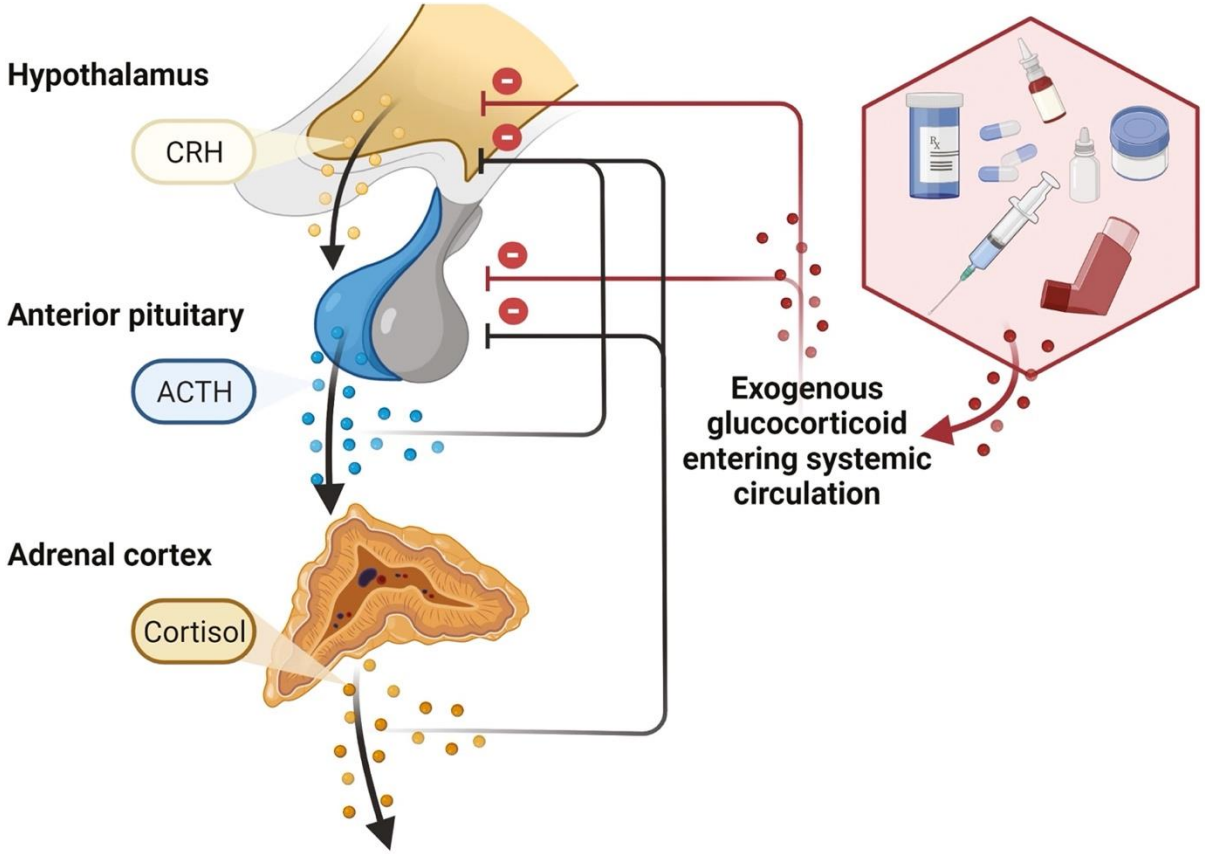
Endocrine toxicities of immune checkpoint inhibitors





Wright JJ et al. Nat Rev Endocrinol. 2021;17(7):389-399.

Glucocorticoid-induced Adrenal Insufficiency



Hypothalamic-Pituitary-Adrenal (HPA) Axis

Borresen SW et al. J Clin Endocrinol Metab. 2022;107(7):2065-2076.

NOT considered to have HPA suppression

- Any patient who has been taking any dose of GC for < 3-4 weeks
- Patients who have received **morning** doses of < 5 mg/day of prednisone or its equivalent for any length of time

Concomitant medications affecting the HPA axis

- CYP3A4 inhibitors: amiodarone, cyclosporine, verapamil, itraconazole, several antiviral meds (protease inhibitors), grapefruit juice
- HPA axis suppressors: opioids

GC = glucocorticoid

F Beuschlein et al. J Clin Endocrinol Metab. 2024;109(7):1657-1683.

Grade	General Characteristics	Characteristic Operations
Grade I (Minor)	Minimal to mild risk independent of anesthesia Minimal to moderately invasive procedure Potential blood loss of < 500 mL	Minor general surgical procedures (skin/ subcutaneous tissue procedures, inguinal hernia repair, breast biopsy) Endoscopy (including cystoscopy, hysteroscopy, bronchoscopy, minor laparoscopy, arthroscopy) Minor gynecologic procedures (tubal ligation, dilation, and curettage) Minor otolaryngology procedures (myringotomy tubes, tonsillectomy/ rhinoplasty)
Grade II (Moderate)	Moderate risk independent of anesthesia Moderately to significantly invasive procedures Potential blood loss of 500-1500 mL	Open or laparoscopic resection/reconstruction of the digestive tract; cholecystectomy Thyroidectomy Cystectomy, nephrectomy Hysterectomy or myomectomy Laminectomy Joint replacement
Grade III (Major)	Major to critical risk independent of anesthesia Highly invasive procedure Potential blood loss >1500 mL Usual postoperative intensive care unit stay with invasive monitoring	Any major orthopedic-spinal, oropharyngeal, or genitourinary repair or reconstruction Any intracranial, major vascular, or cardiothoracic procedure

PERIOPERATIVE MANAGEMENT OF PATIENTS ON GCs

Regimen	Degree of Sx Stress	GC regimen
Patients currently on GCs	Grade I Minor	• Continue daily dose of GC • 25 mg of IV HC at induction if not able to tolerate PO • Resume oral daily preop. GC regimen
	Grade II Moderate	• Continue daily dose of GC • 25-50 mg of HC IV at induction • 15-25 mg HC q 6 hours. until PO is tolerated and hemodynamically stable • Resume oral daily preop. GC regimen
	Grade III Major	• Continue daily dose of GC • 50 mg of HC IV at induction • 25 mg of HC IV q 6 hours on day 1 and until hemodynamically stable, then 15 mg IV q 6 hours until PO is tolerated • Resume oral daily preop. GC regimen

GC = glucocorticoid; HC = hydrocortisone

Cardenas SMC et al. J Endocr Soc. 2022;7(2):bvac185.

PERIOPERATIVE MANAGEMENT OF PATIENTS ON GCs

Regimen	GC regimen
Patients who stopped or plan to stop GCs before surgery	• Assess HPA axis in patients with intermediate to high risk • The closer the date of discontinuing GCs before surgery, the higher the risk of AI • Rx based on the degree of surgical stress in those who have abnormal HPA axis
Adrenal crisis	• 100 mg of HC IV (IM if no IV access) • 50 mg q 6 hours until hemodynamically stable and then taper* • Taper depending on clinical response-IV fluids (normal saline), dextrose 5% if hypoglycemia

*Some experts favor continuous glucocorticoid infusion
GC = glucocorticoid; HC = hydrocortisone

Cardenas SMC et al. J Endocr Soc. 2022;7(2):bvac185.


GOOD
LUCK!