ENDOCRINE REVIEW

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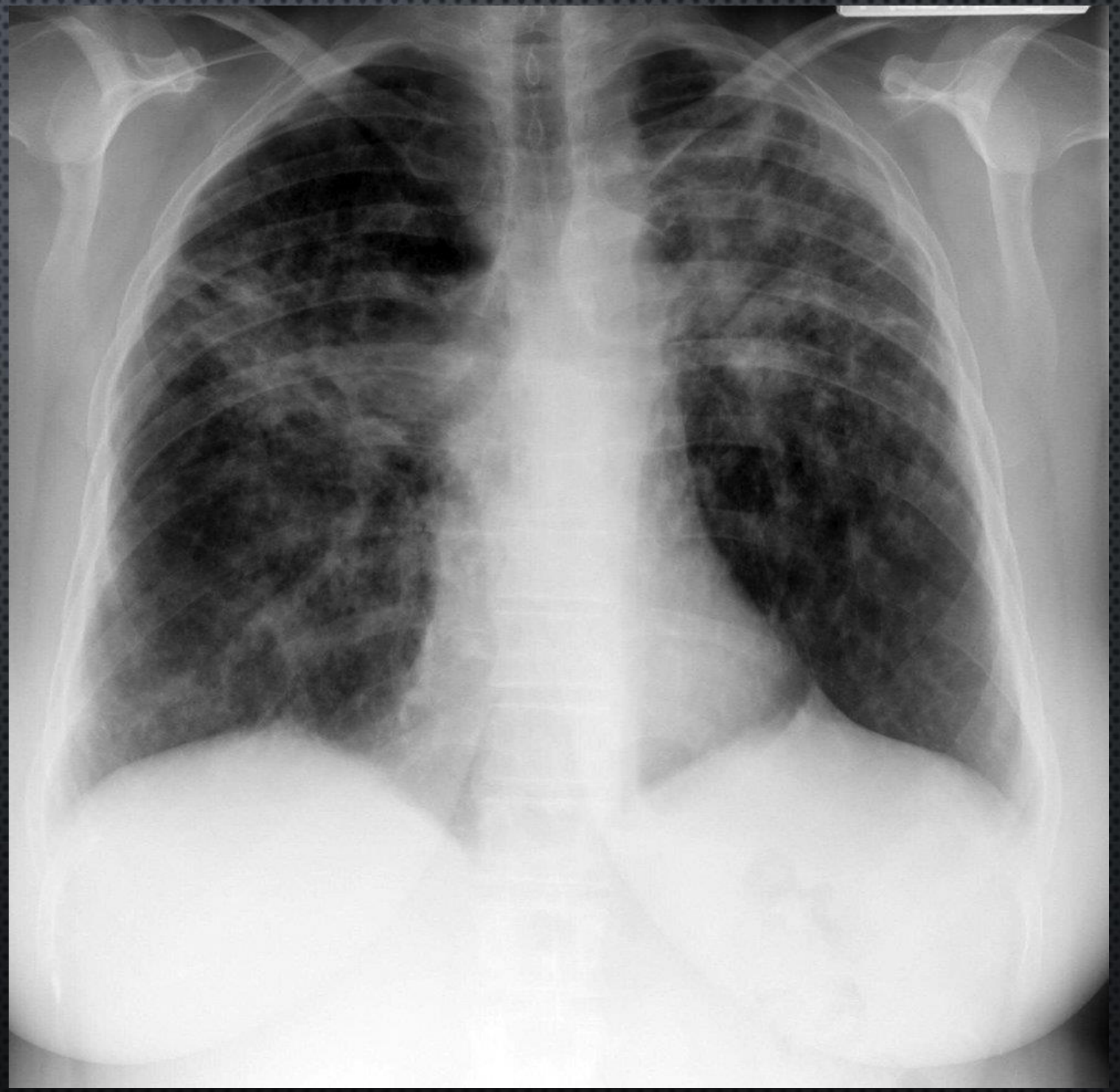
APRIL 30, 2019



Question 19 →

#1 – (MKSAP 7)

- A 25-year-old woman is evaluated for anterior neck pain, fatigue, exercise intolerance, excessive sweating, and tremors that began 6 weeks ago. Other than an upper respiratory infection 2 months ago, she has been healthy. Medical history is otherwise unremarkable, and she takes no medications.
- On physical examination, pulse rate is 105/min. Other vital signs are normal. The patient's thyroid gland is tender to palpation and is without discrete nodules. No thyroid bruit is auscultated. Bilateral lid lag is noted, but there is no proptosis, conjunctival injection, or chemosis. There is a fine tremor of her outstretched hands. Deep tendon reflexes are brisk.
- Laboratory studies show a serum thyroid-stimulating hormone (TSH) level less than 0.01 mU/mL (0.01 mU/L), a serum free thyroxine (T_4) level of 2.8 ng/dL (36.1 pmol/L), and a serum total triiodothyronine (T_3) level of 190 ng/dL (2.9 nmol/L). Urine pregnancy test is negative.
- What is the most likely diagnosis?

C – SUBACUTE THYROIDITIS

#1 – Subacute thyroiditis

- DDX hyperthyroidism:
- Graves
- Toxic multinodular goiter
- Toxic adenoma
- Thyroiditis
- Medication-induced
- Thyrotoxicosis factitial
- Hcg-mediated
- Struma ovarii (ovarian tumor w/ 50% thyroid tissue)
- Follicular thyroid cancer mets
- Thyrotrope adenoma

#1 – SUBACUTE THYROIDITIS

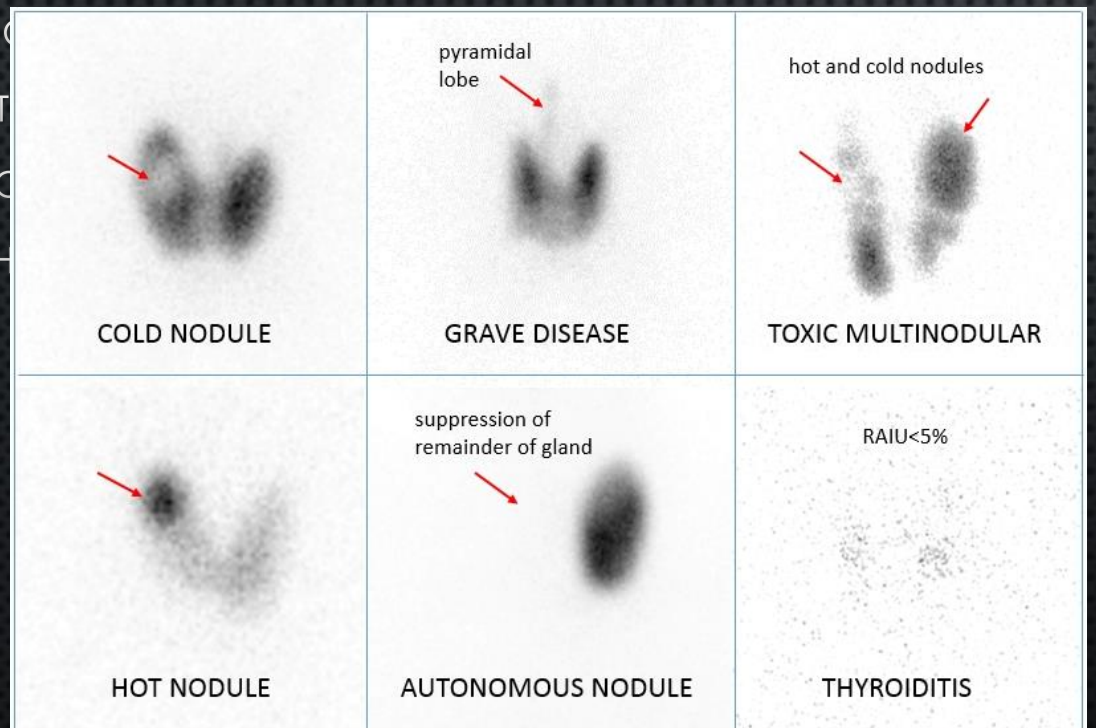
- presents following a VIRAL upper respiratory tract infection
- Classically TENDER or painful thyroid
- Destructive aka causes leakage of stored thyroid hormone from damaged thyroid follicles
- can be confirmed by determining radioactive iodine uptake, which would be low (<10%).

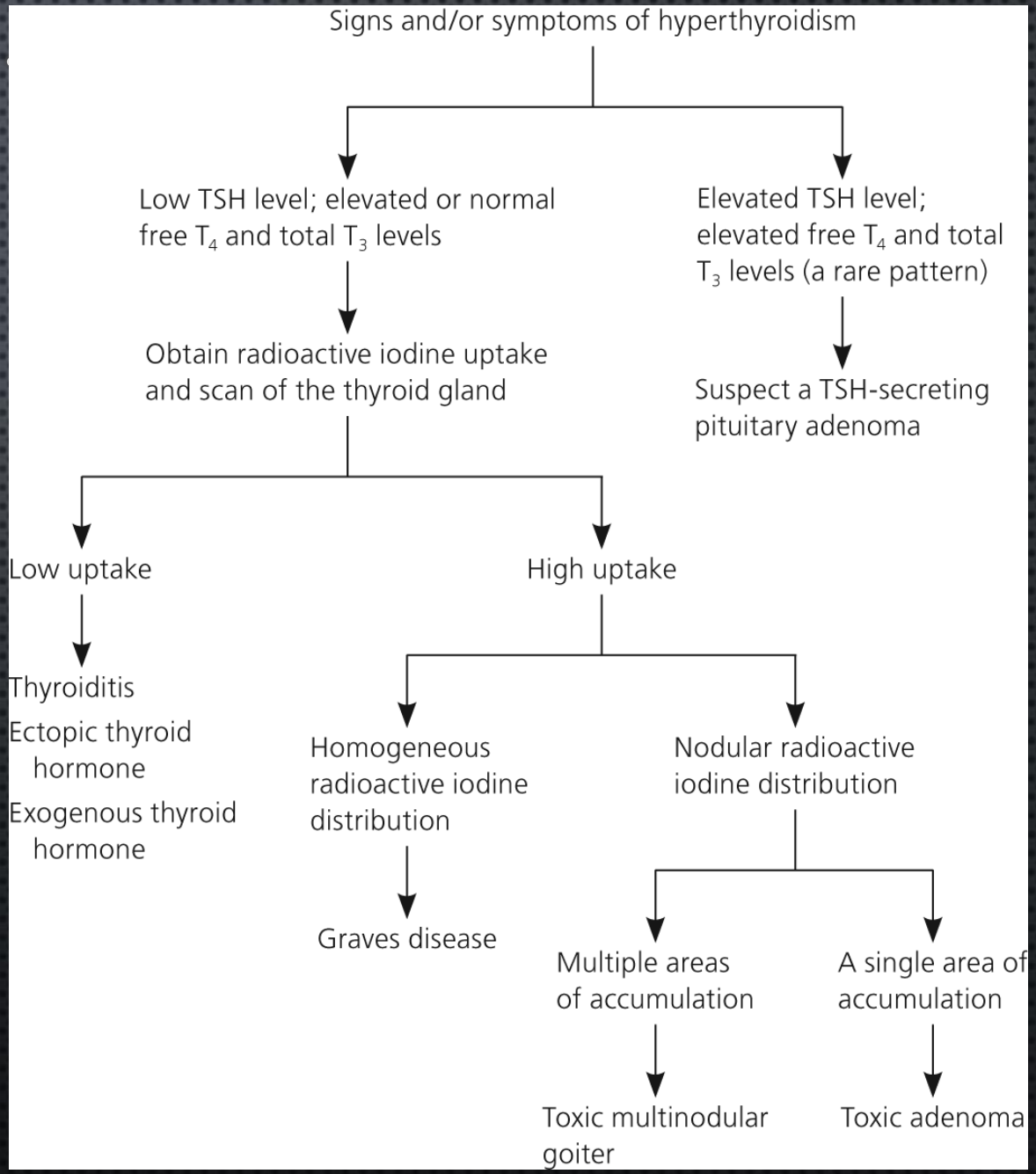
- Management = symptom control
- b-blockers and NSAIDs (rarely steroids)

- thyrotoxicosis typically lasts 2 to 6 weeks
- FOLLOWED BY A HYPOTHYROID PHASE after stored thyroid hormone is depleted, typically lasting 6 to 12 weeks – may need levothyroxine therapy!
- Most eventually recover to a euthyroid state

#1 – COMPARE UPTAKE SCANS…

- DDX HYPERTHYROIDISM:
- GRAVES
- TOXIC MULTINODULAR GOITER
- TOXIC ADENOMA
- THYROIDITIS
- MEDICATION-INDUCED (AMIO, LITHIUM)
- THYROTOXICOSIS FACTITIAL
- H
- S
- F
- T



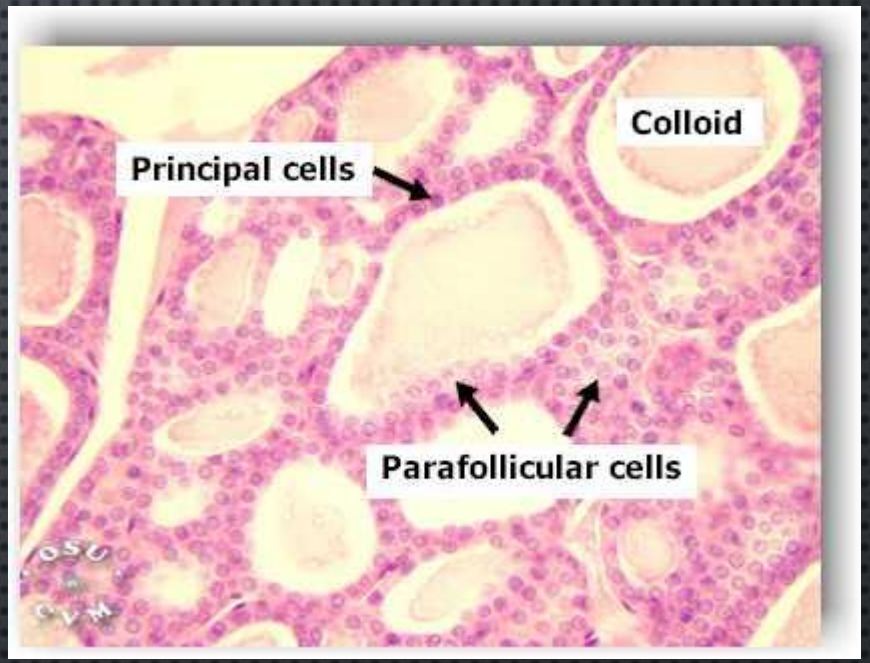


#2 – (MKSAP 76)

- A 69-year-old woman is seen in the office following a left thyroid lobectomy and isthmusectomy 1 week ago for management of compressive symptoms related to a large left thyroid nodule. The preoperative thyroid/neck ultrasound showed the nodule without suspicious features and no abnormal cervical lymph nodes. The pathology report describes a 4.5-cm left adenomatous nodule in a background of multinodular hyperplasia. There is a single focus of papillary thyroid carcinoma measuring 0.5 cm in the greatest dimension. No lymphovascular or extrathyroidal invasion is noted. Surgical margins are negative.
- The patient is currently feeling well and reports complete resolution of her prior symptoms. Her medical history is otherwise unremarkable, and she takes no medications.
- On physical examination, vital signs are normal. There is a well-healed anterior neck scar. Laboratory studies show a serum thyroid-stimulating hormone (TSH) level of 1.8 mU/mL (1.8 mU/L).
- What is the most appropriate treatment?

D – NO ADDITIONAL TREATMENT

#2 – THYROID CANCERS



- Follicular Epithelial Derived – Differentiated:
  - Papillary: (85%) often to LN, rarely distant mets
  - Follicular: (15%) Lung and bone mets, rarely LN
- Follicular Epithelial Derived – Undifferentiated:
  - Anaplastic (3%) – rare, aggressive, usually large, mean survival 5 months
- Other thyroid cancers:
  - Medullary – from parafollicular cells that make calcitonin – MEN 2A and 2B
  - ~primary thyroid lymphoma – rapidly growing mass

#2 – MANAGEMENT … D CANCERS

- **STEP 1 = SURGERY**
- **TUMOR <1 CM WITHOUT EXTRATHYR… MY**
- ALL OTHERS = TOTAL THYROIDECTO…
- STEP 2 = RADIOIODINE THERAPY

ATA risk stratification system to estimate risk of persistent/recurrent disease

Low risk	Intermediate risk	High risk
Papillary thyroid cancer with all of the following present:	**Any of the following present:**	**Any of the following present:**
▪ No local or distant metastases	Microscopic invasion into the perithyroidal soft tissues	Macroscopic tumor invasion
▪ All macroscopic tumor has been resected	Cervical lymph node metastases or ^{131}I avid metastatic foci in the neck on the post-treatment scan done after thyroid remnant ablation	Incomplete tumor resection with gross residual disease
▪ No invasion of locoregional tissues	Tumor with aggressive histology or vascular invasion (aggressive histologies include tall cell, insular, columnar cell carcinoma, Hürthle cell carcinoma, follicular thyroid cancer, hobnail variant)	Distant metastases
▪ Tumor does not have aggressive histology (aggressive histologies include tall cell, insular, columnar cell carcinoma, Hürthle cell carcinoma, follicular thyroid cancer, hobnail variant)	Clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension*	Postoperative serum thyroglobulin suggestive of distant metastases
▪ No vascular invasion	Multifocal papillary thyroid microcarcinoma with extrathyroidal extension and *BRAF* V600E mutated (if known)*	Pathologic N1 with any metastatic lymph node ≥3 cm in largest dimension*
▪ No ^{131}I uptake outside the thyroid bed on the post-treatment scan, if done		Follicular thyroid cancer with extensive vascular invasion (>4 foci of vascular invasion) *
▪ Clinical N0 or ≤5 pathologic N1 micrometastases (<0.2 cm in largest dimension)*		
Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer*		
Intrathyroidal, well-differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion*		
Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including *BRAF* V600E mutated (if known)*		

#2 – Management of Differentiated Thyroid Cancers

- Step 1 = surgery
- Tumor <1 cm without extrathyroidal extension and no lymph nodes = lobectomy
- All others = total thyroidectomy

- Step 2 = radioiodine therapy for high and maybe intermediate risk

- Step 3 = External beam radiotherapy (EBRT) can be used as adjuvant therapy for: older patients with gross extrathyroid extension at the time of surgery or selected younger patients with extensive disease and poor histologic features (poorly differentiated histology) whose disease is resected but in whom there is a high likelihood of residual microscopic disease.

#2 – MANAGEMENT OF DIFFERENTIATED THYROID CANCERS

- **AMERICAN THYROID ASSOCIATION (ATA) LOW RISK –**
  - THYROIDECTOMY + DETECTABLE SERUM THYROGLOBULIN (TG) LEVELS:

    TSH = 0.1 TO 0.5 MU/L.
  - LOBECTOMY OR UNDETECTABLE SERUM TG LEVELS: TSH = MID TO LOWER HALF OF THE REFERENCE RANGE (0.5 TO 2.0 MU/L)
- **●ATA INTERMEDIATE RISK –**0.1 TO 0.5 MU/L
- **●ATA INTERMEDIATE OR HIGH RISK –** <0.1 MU/L.

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Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including *BRAF* V600E mutated (if known)*		

WEIRD.

#3 – (MKSAP 65)

- A 45-year-old man is seen for follow-up evaluation for depression and to review the results of laboratory testing. He was seen 1 month ago for a 6-month history of depressed mood, difficulty sleeping, decreased appetite, 2.3-kg (5-lb) weight loss, and fatigue. Major depressive disorder was diagnosed, and escitalopram was prescribed. Today the patient reports a significant improvement in his mood, appetite, and the quality of his sleep since starting treatment.
- On physical examination, vital signs and physical examination are normal. Screening laboratory studies from 1 month ago show a thyroid-stimulating hormone (TSH) level of 7 mU/mL (7 mU/L) and a free thyroxine (T_4) level of 1.0 ng/dL (12.9 pmol/L).
- What is the most appropriate management?

E – REPEAT TSH IN 2 MONTH

#3 – SUBCLINICAL HYPOTHYROIDISM

- Step 1 = rule out transient elevation in TSH! (or normal elevation… 10=normal for 80yo!)
- Step 2 = repeat TSH, T4, (and TPO antibodies if undecided about tx) in 2-3 months
- Definition: An early form of primary hypothyroidism affecting up to 10% of the population. 2-4% progress to overt hypothyroidism.

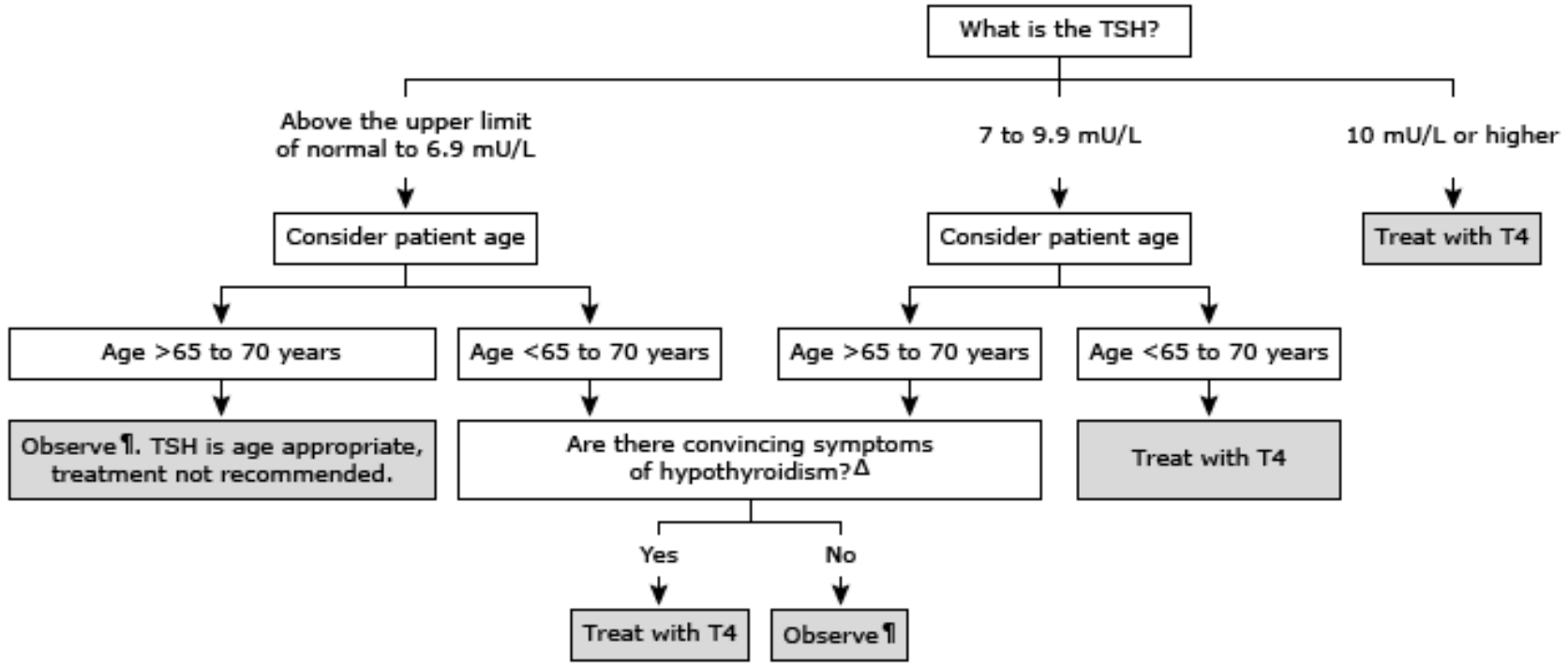
Ddx transient elevation TSH:

Acute illness – after ~24 hours

Indications to treat:

TSH>10
Trying to get pregnant
Symptomatic
Anti-TPO positive
~lipids abnl
~ ovulation dysfunction
~ osteoporosis

Indications for thyroid hormone replacement in nonpregnant adults with subclinical hypothyroidism*



What's New

Treatment of subclinical hy

The treatment of subclinical hypothyroidism is controversial. In a meta-analysis of 21 randomized trials (over 2000 nonpregnant adults with baseline thyroid-stimulating hormone [TSH] values ranging from 4.4 to 12.8 mIU/L), there were no differences in hypothyroid signs or symptoms or general quality of life between the levothyroxine (T4)-treated and placebo groups after a mean follow-up of eight months [1]. However, observational data show a benefit of T4 treatment in reducing ischemic heart disease events and overall mortality in younger individuals with subclinical hypothyroidism, and we suggest T4 treatment in most patients <65 years of age with a TSH ≥7.0 mIU/L (algorithm 1). (See "Subclinical hypothyroidism in nonpregnant adults", section on 'Hypothyroid signs and symptoms'.)

Still a moving target!

#4 – (MKSAP 11)

- A 70-year-old man was admitted to the hospital 3 days ago with an ST-elevation myocardial infarction complicated by pulmonary edema and atrial fibrillation. He underwent emergency cardiac catheterization and left anterior descending (LAD) artery stent placement. Today the patient is feeling much better with complete resolution of his initial presenting symptoms.
- Medications are aspirin, atorvastatin, clopidogrel, lisinopril, metoprolol, and low-molecular-weight heparin.
- On physical examination, pulse rate is 92/min. Other vital signs are normal.
- Cardiac examination reveals new findings of an irregularly irregular rhythm and an S_4. His physical examination is otherwise normal.

Thyroid studies are shown.

What is the most likely diagnosis?

Laboratory studies obtained at the time of cardiac catheterization:	
Thyroid-stimulating hormone (TSH)	0.2 µU/mL (0.2 mU/L)
Thyroxine (T_4), total	6.5 µg/dL (83.8 nmol/L)
Thyroxine (T_4), free	1.0 ng/dL (12.9 pmol/L)
Triiodothyronine (T_3), total	60 ng/dL (0.9 nmol/L)

C – NONTHYROIDAL ILLNESS SYNDROME

#4 – NONTHYROIDAL ILLNESS SYNDROME

- **Definition:** nonthyroidal illness syndrome (euthyroid sick syndrome) is most often seen in critically ill hospitalized patients and is characterized by a **reduced** serum triiodothyronine (T_3) level, low or **low-normal** serum thyroxine (T_4) level, and **normal or low** (but detectable) serum thyroid-stimulating hormone (TSH) level.

- Mechanisms:
  - 1) changes in the peripheral uptake of thyroid hormones
  - 2) reduced levels of thyroid hormone–binding proteins
  - 3) alterations in the expression and activity of deiodinases

Very low serum T_4 levels are associated with poor overall outcome, but treatment with levothyroxine has unfortunately not shown improvement in mortality.

#5 – (MKSAP 50)

A 45-year-old woman comes to the office to review her thyroid function test results. Thyroid function testing was ordered in response to a recent diagnosis of hypercholesterolemia. The patient is otherwise well, and she takes no medications.

On physical examination, vital signs are normal. Her physical examination is normal with the exception of slowed relaxation phase of deep tendon reflexes.

Laboratory studies show a serum thyroid-stimulating hormone (TSH) level of 24 mU/mL (24 mU/L) and a free thyroxine (T_4) level of 0.65 ng/dL (8.4 pmol/L).

Which of the following is the most appropriate treatment?

C – WEIGHT-BASED REPLACEMENT DOSE OF LEVOTHYROXINE

#5 – LEVOTHYROXINE DOSING

Table 3. Levothyroxine Dosing Guidelines for Hypothyroidism in Adults

Population	*Dosing*
Nonpregnant patients	1.6 mcg per kg per day initial dosage[26]
Older patients; patients with known or suspected cardiac disease	25 or 50 mcg daily starting dosage; increase by 25 mcg every three to four weeks until full replacement dosage reached[19,20]
Pregnant patients	Increase to nine doses weekly (one extra dose on two days of the week) at earliest knowledge of pregnancy; refer to endocrinologist[21]
Patient with subclinical hypothyroidism	TSH < 10 mIU per L: 50 mcg daily, increase by 25 mcg daily every six weeks until TSH = 0.35 to 5.5 mIU per L TSH ≥ 10 mIU per L: 1.6 mcg per kg per day[26]

TSH = thyroid-stimulating hormone.

Major symptoms and signs of hypothyroidism

Mechanism	Symptoms	Signs
Slowing of metabolic processes	Fatigue and weakness Cold intolerance Dyspnea on exertion Weight gain Cognitive dysfunction Mental retardation (infantile onset) Constipation Growth failure	Slow movement and slow speech Delayed relaxation of tendon reflexes Bradycardia Carotenemia
Accumulation of matrix substances	Dry skin Hoarseness Edema	Coarse skin Puffy facies and loss of eyebrows Periorbital edema Enlargement of the tongue
Other	Decreased hearing Myalgia and paresthesia Depression Menorrhagia Arthralgia Pubertal delay	Diastolic hypertension Pleural and pericardial effusions Ascites Galactorrhea

#6 – (MKSAP 26)

- A 24-year-old woman is evaluated for a 6-month history of amenorrhea. Previously, menstrual cycles were regular. She also notes vaginal dryness. She reports no acne, stretch marks, breast discharge, or changes in weight. Medical history is otherwise unremarkable, and she takes no medications.
- On physical examination vital signs are normal. BMI is 26. Vulvovaginal atrophy is noted on pelvic examination. The remainder of the examination is unremarkable.
- Laboratory studies show undetectable beta-human chorionic gonadotropin. Prolactin and thyroid-stimulating hormone levels are within normal limits.
- Which of the following is the most appropriate next diagnostic test?

B – FOLLICLE STIMULATING HORMONE MEASUREMENT

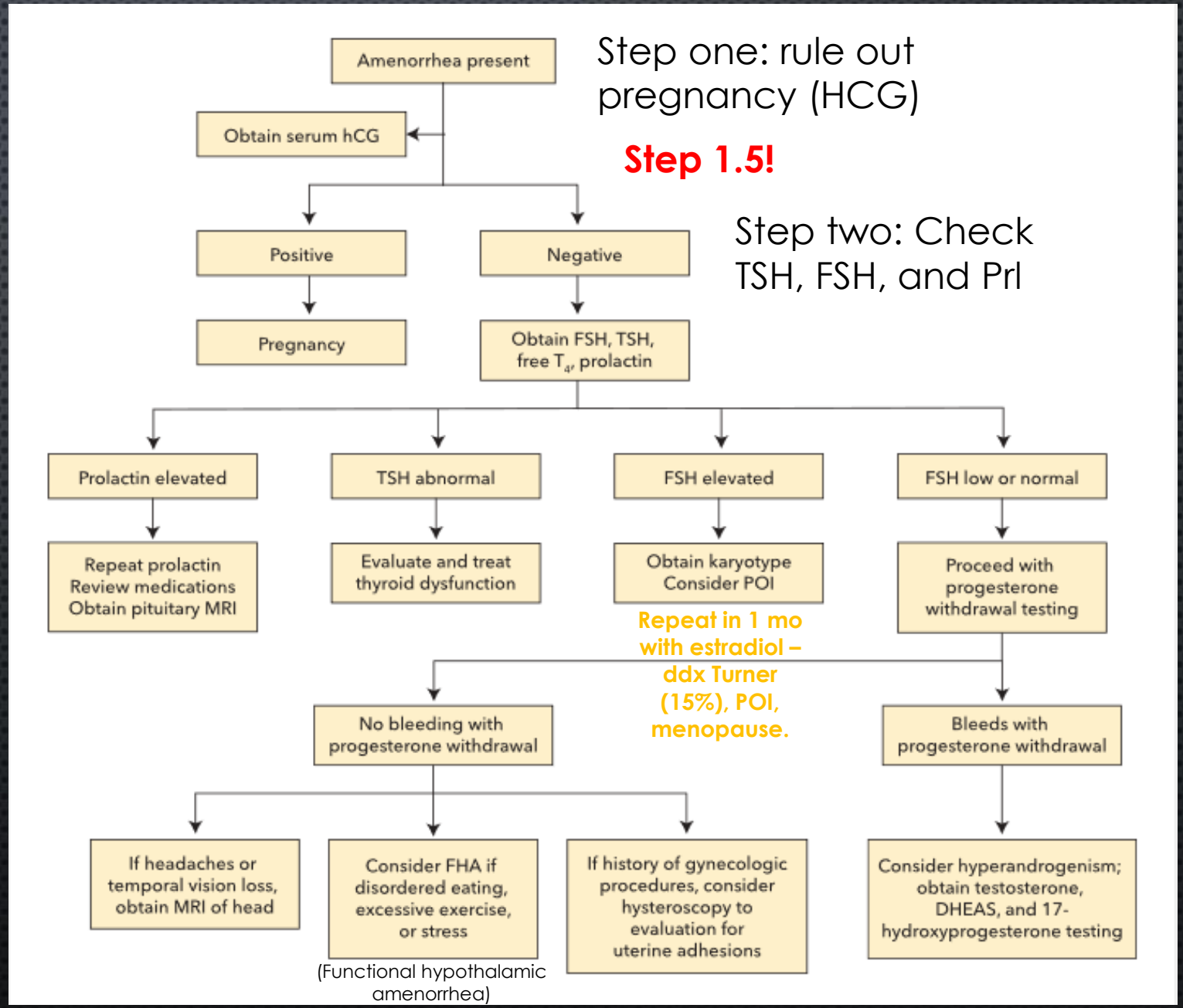
(TO WORK HER UP FOR…)

SECONDARY AMENORRHEA

#6 – SECONDARY AMENORRHEA

- DEFINITION: HAD NORMAL PERIODS BEFORE – NOT A PRIMARY UTERUS/ENDOCRINE PROBLEM, AND HAVE NOW BEEN AMENORRHOEIC FOR >3 MONTHS

- STEP 1.5 = H&P! MEDS, DRUG EXPOSURE, CHANGES IN WEIGHT (EATING DISORDER, PCOS), EXERCISE HISTORY, PSYCHOSOCIAL STRESSORS, AUTOIMMUNE SX (VITILIGO) AND FAMILY HISTORY RELATED TO MENARCHE. SYMPTOMS CAN INCLUDE HEADACHES OR VISUAL CHANGES SUGGESTING PITUITARY PATHOLOGY, SYMPTOMS OF THYROID EXCESS OR DEFICIENCY, GALACTORRHEA SUGGESTING HYPERPROLACTINEMIA, OR VASOMOTOR SYMPTOMS/VAGINAL ATROPHY ASSOCIATED WITH ESTROGEN DEFICIENCY.
- PHYSICAL EXAMINATION SHOULD ALSO INCLUDE EVALUATION FOR FEATURES OF TURNER SYNDROME, SUCH AS A LOW HAIRLINE, WEBBED NECK, SHIELD CHEST, AND WIDELY SPACED NIPPLES.



POI = primary ovarian insufficiency

#7 – (MKSAP 18)

- A 34-year-old transgender woman is evaluated during a routine examination. She desires gender-affirming hormone therapy. Her gender incongruence diagnosis has been made and confirmed by qualified medical providers. She smokes one pack of cigarettes per day, with a 15-pack-year history. Medical history is otherwise unremarkable. She takes no medications.
- On physical examination, vital signs are normal. She has male hair distribution. Normal male genitalia are present. There are no evident inguinal hernias.
- In addition to advising smoking cessation, which of the following is the most appropriate next step in management?

D – REFER FOR FERTILITY PRESERVATION COUNSELING

#7 – Transgender Medicine

- Transgender medicine is the care of persons whose gender identity differs from the sex that was assigned at birth.
- Gender incongruence is persistent incongruence between gender identity and external sexual anatomy at birth absent of a confounding mental disorder.
- A transgender man is someone with a male gender identity and a female birth assigned sex.
- a transgender woman (as in this patient) is someone with a female gender identity and a male birth assigned sex.
- "Many Transgender people avoid health care because of discriminatory or disrespectful interactions in prior health care encounters. Providing a safe environment is critical to ensure that transgender people establish and continue primary and gendering-affirming care. "

#7 – TRANSGENDER MEDICINE

- GENDER-AFFIRMING HORMONE THERAPY (GAHT):
  - MUST BE PATIENT-CENTERED AND INDIVIDUALIZED TO THE PATIENT'S GOALS
  - DISCUSSION OF THE RISKS/BENEFITS ASSOCIATED WITH TREATMENT AND INFORMED CONSENT ARE ESSENTIAL BEFORE BEGINNING TREATMENT

  CRITERIA TO CONSIDER:

  - PERSISTENT, WELL-DOCUMENTED GENDER DYSPHORIA
  - CAPACITY TO MAKE A FULLY INFORMED DECISION
  - AGE OF MAJORITY IN A GIVEN COUNTRY
  - CONTROL OF SIGNIFICANT MEDICAL OR PSYCHOLOGICAL CONDITIONS

  GAHT LIMITS FERTILITY, THUS REPRODUCTIVE OPTIONS SHOULD BE DISCUSSED WITH PATIENTS PRIOR TO INITIATION OF GAHT.

  MOST PHYSICAL CHANGES OCCUR OVER THE COURSE OF 2 YEARS, BUT THE EXACT TIMELINE OF CHANGE IS HIGHLY VARIABLE.

#7 – TRANSGENDER MEDICINE - FEMINIZING

TYPICALLY ESTRADIOL IN COMBINATION WITH AN ANDROGEN BLOCKER

GOALS: BREAST DEVELOPMENT; FAT REDISTRIBUTION; AND REDUCTIONS IN MUSCLE MASS, BODY HAIR, ERECTILE FUNCTION, SPERM COUNT, AND TESTICULAR SIZE.

ESTROGEN = INCREASES RISK: DEEP VENOUS THROMBOSIS (DVT) AND (LESSER) ISCHEMIC STROKE AND MYOCARDIAL INFARCTION

CONTRAINDICATIONS TO E = A HISTORY OF DVT, ESTROGEN-SENSITIVE NEOPLASM, AND END-STAGE LIVER DISEASE AND SMOKING!

ANTI-ANDROGEN THERAPY, SUCH AS SPIRONOLACTONE GOALS = DIMINISHES SECONDARY MALE SEX CHARACTERISTICS AND MINIMIZES THE ESTROGEN DOSE NEEDED, THUS REDUCING RISKS ASSOCIATED WITH HIGH-DOSE EXOGENOUS ESTROGEN THERAPY.

MONITORING TESTOSTERONE AND ESTRADIOL LEVELS FOR ADEQUATE RESPONSE TO THERAPY IS NECESSARY FOR THE FIRST YEAR.

#7 – TRANSGENDER MEDICINE - MASCULINIZING

ACHIEVED USING TOPICAL OR INJECTED TESTOSTERONE WITH A GOAL OF CESSATION OF MENSES, FACIAL HAIR GROWTH, VOICE DEEPENING, FAT REDISTRIBUTION, INCREASED MUSCLE MASS AND BODY HAIR, AND CLITORAL GROWTH.

CONTRAINDICATIONS TO TESTOSTERONE THERAPY INCLUDE PREGNANCY, UNSTABLE CORONARY ARTERY DISEASE, AND POLYCYTHEMIA.

MONITORING TESTOSTERONE AND ESTRADIOL LEVELS FOR ADEQUATE RESPONSE TO THERAPY SHOULD OCCUR FOR THE FIRST YEAR. HEMOGLOBIN ALSO SHOULD BE MONITORED.

#8 – (MKSAP 46)

- A 55-year-old man is referred for evaluation of fatigue, weight gain, decreased libido, and difficulty maintaining an erection. Sexual functioning was normal until 6 months ago, and he has fathered two children. Medical history is significant for polysubstance abuse that is being managed with daily methadone. His medical history is otherwise unremarkable, and his only medication is methadone.
- On physical examination, vital signs are normal.
- Neurological, genitalia, and the remainder of the physical examination are normal.

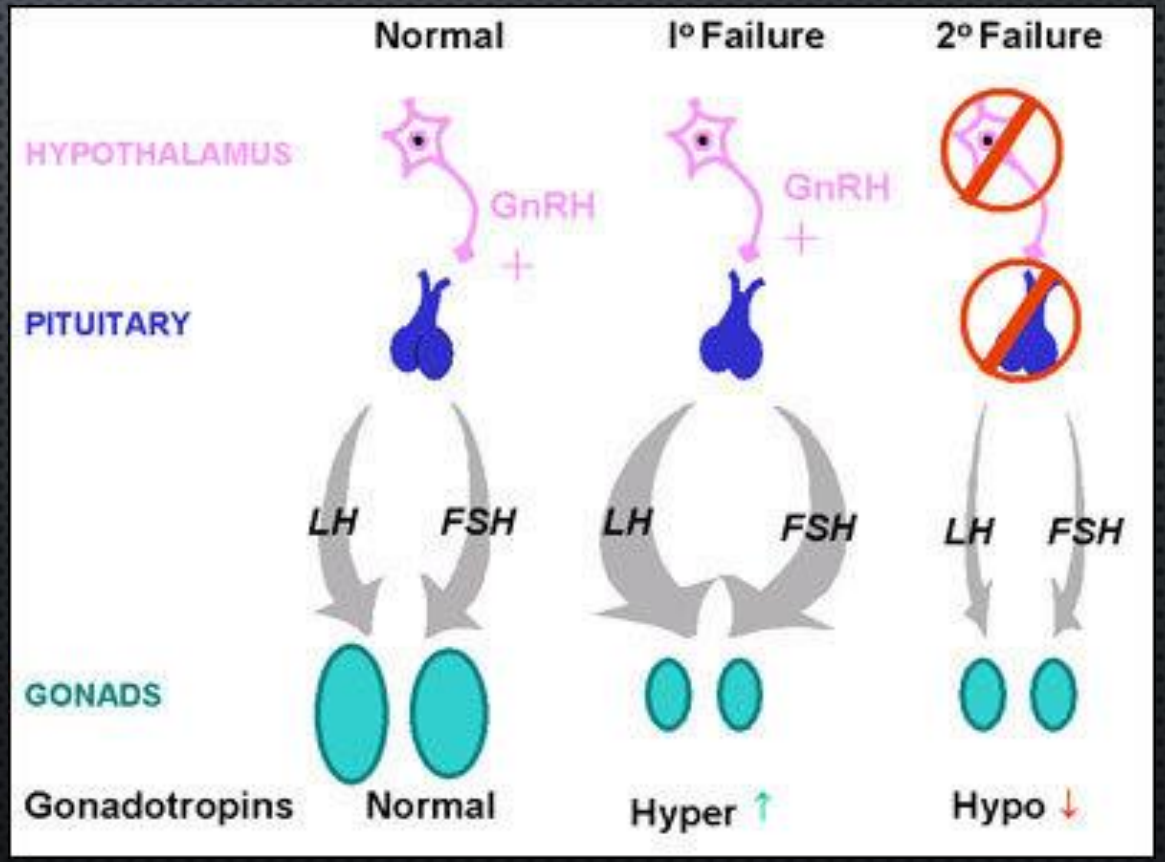
What is the most likely etiology of the hypogonadism?

Laboratory studies:	
Follicle-stimulating hormone	5 mU/mL (5 U/L)
Luteinizing hormone	4 mU/ml (4 U/L)
Prolactin	12 ng/mL (12 µg/L)
Testosterone	185 ng/dL (6.4 nmol/L)
Thyroid-stimulating hormone	2.4 µU/mL (2.4 mU/L)
Thyroxine (T_4), free	1.3 ng/dL (16.8 pmol/L)

B – CHRONIC OPIOID THERAPY

#8 – SECONDARY HYPOGONADISM

- SECONDARY HYPOGONADISM = LOW GNRH (GONADOTROPIN-RELEASING HORMONE) FROM THE HYPOTHALAMUS OR LOW FSH AND LH FROM THE ANTERIOR PITUITARY. [THIS PT HAS LOW/LOW NORMAL FSH AND LH AND LOW TESTOSTERONE]
- CAUSES:
- UNTREATED SLEEP APNEA
- EXOGENOUS TESTOSTERONE ADMINISTRATION
- OBESITY
- HYPERPROLACTINEMIA
- CHRONIC OPIOID USE
- GLUCOCORTICOID USE
- INFILTRATIVE DISEASE (LYMPHOMA OR HEMOCHROMATOSIS)



#9 – (MKSAP 68)

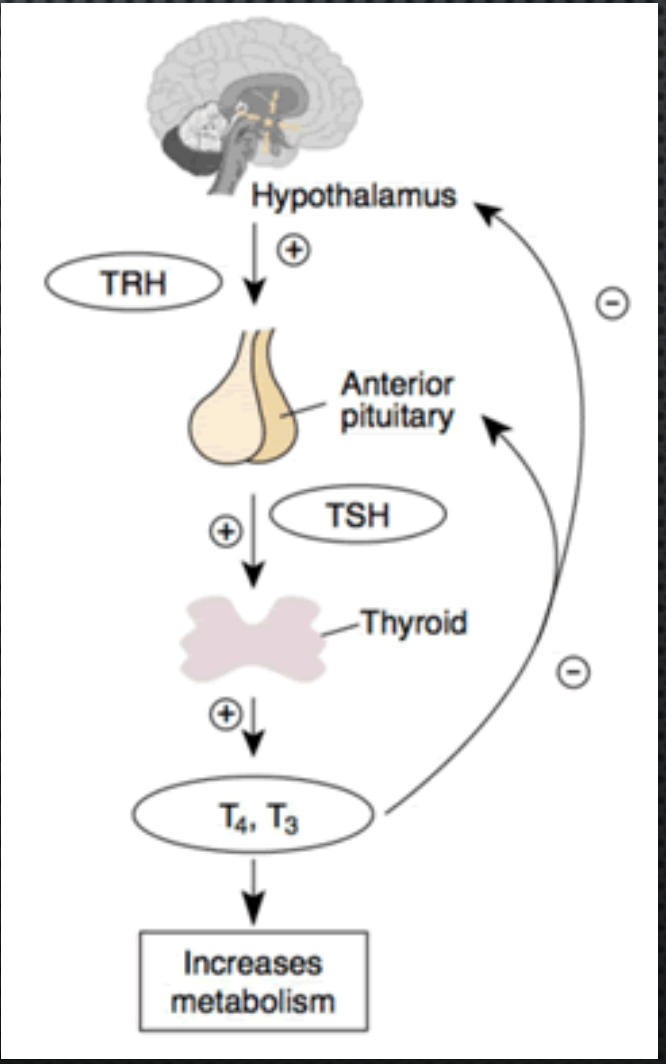
- A 59-year-old woman is evaluated for fatigue and weight gain over the past 2 months. Her medical history is significant for a pituitary tumor, treated with surgery followed by radiation therapy, at age 54. She has recently self-initiated calcium and vitamin D and a multivitamin. Her only other medication is levothyroxine.
- On physical examination, vital signs are normal. BMI is 31.The remainder of the physical examination is normal.
- Which of the following is the most appropriate next step in management?

B – MEASURE FREE THYROXINE (T4) LEVEL

#9 – SECONDARY HYPOTHYROIDISM

TSH CANNOT BE USED TO MONITOR AND ASSESS FOR ADEQUACY OF THYROID HORMONE REPLACEMENT DOSING. INSTEAD, THE LEVOTHYROXINE DOSE IS ADJUSTED BASED ON FREE T_4 LEVELS WITH THE GOAL OF OBTAINING A VALUE WITHIN THE NORMAL REFERENCE RANGE (USUALLY UPPER HALF)

LEVOTHYROXINE SHOULD BE TAKEN ON AN EMPTY STOMACH, 1 HOUR BEFORE OR 3 HOURS AFTER INGESTION OF FOOD. MEDICATIONS THAT WOULD INTERFERE WITH ABSORPTION, SUCH AS CALCIUM- OR IRON-CONTAINING SUPPLEMENTS SHOULD BE SEPARATED BY 4 HOURS.



#10 – (MKSAP 4)

- A 23-year-old woman is seen in follow-up for evaluation of amenorrhea of 4 months' duration. Her only other medical problem is schizophrenia treated with risperidone.
- On physical examination, vital signs and physical examination are normal.

Laboratory studies:	
Prolactin	220 ng/mL (220 µg/L)
Thyroid-stimulating hormone	2.2 µU/mL (2.2 mU/L)
Thyroxine (T_4), free	1.2 ng/dL (15.5 pmol/L)
Urine human chorionic gonadotropin	Negative

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

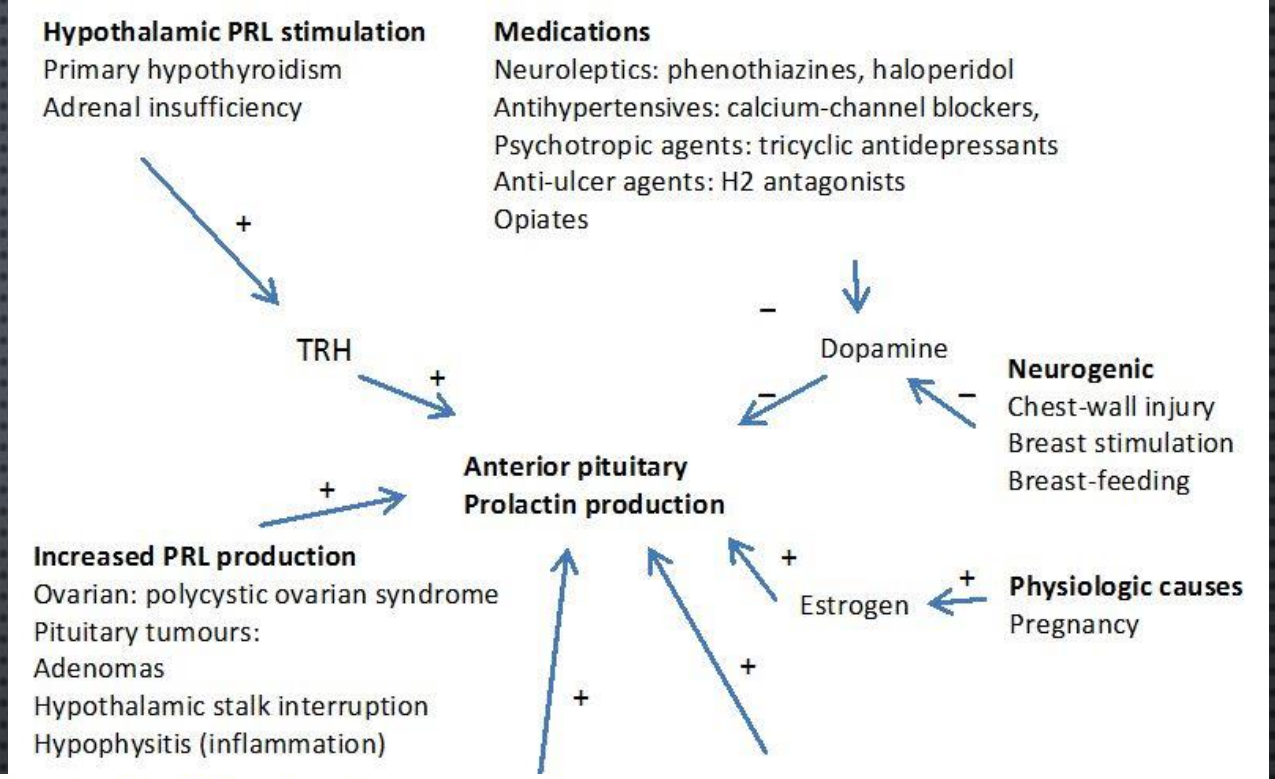
A – OBTAIN A PITUITARY MRI

#10 – HYPERPROLACTINEMIA

PRL >200 CONCERNING FOR TUMOR

HIGH PRL DIFFERENTIAL:

- PREGNANCY
- PRIMARY HYPOTHYROIDISM – WHICH CAN CAUSE DIFFUSE HYPERTROPHY OF THE PITUITARY GLAND
- NONFUNCTIONING PITUITARY ADENOMAS CAN ALSO CAUSE HYPERPROLACTINEMIA BY COMPRESSING THE PITUITARY STALK AND DECREASING DOPAMINE INHIBITION OF PROLACTIN SECRETION
- MEDS - ANTIPSYCHOTIC CAUSE ANTIDOPAMINERGIC EFFECT THAT INTERRUPTS THE INHIBITION OF PROLACTIN BY DOPAMINE



Control of Prolactin secretion

Pituitary disconnection increases Prl

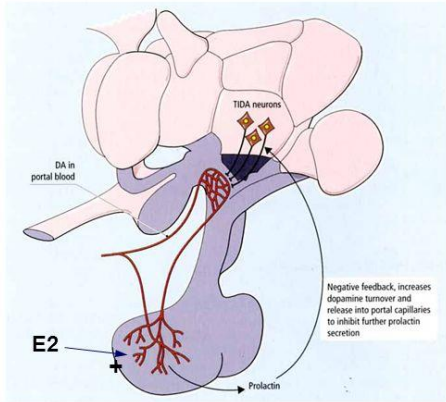
- prolactin inhibitory factor (PIF)
  - Dopamine (DA)
  - GABA
  - GnRH-associated peptide (GAP)
- prolactin releasing factors
  - vasoactive intestinal polypeptide (VIP)
  - thyrotrophin releasing hormone (TRH)
  - oestrogen

Prl short loop feedback

- Prl-R on tuberoinfundibular dopamine associated neurons (TIDA)
- Prl inhibits its own release

Oestrogen

- stimulates Prl synthesis and release by lactotrophs



Short-loop feedback

EssRep7 Fig 1.12

#11 – (MKSAP 51)

- A 24-year-old woman is evaluated for 6 months of amenorrhea, weight gain, and depressed mood. Medical history is otherwise unremarkable, and she takes no medications.
- On physical examination, blood pressure is 134/86 mm Hg and pulse rate is 82/min. BMI is 31. Other vital signs are normal. The patient has facial plethora. Skin examination reveals multiple ecchymoses. There are wide pigmented striae on the abdomen as well as a dorsocervical fat pad.

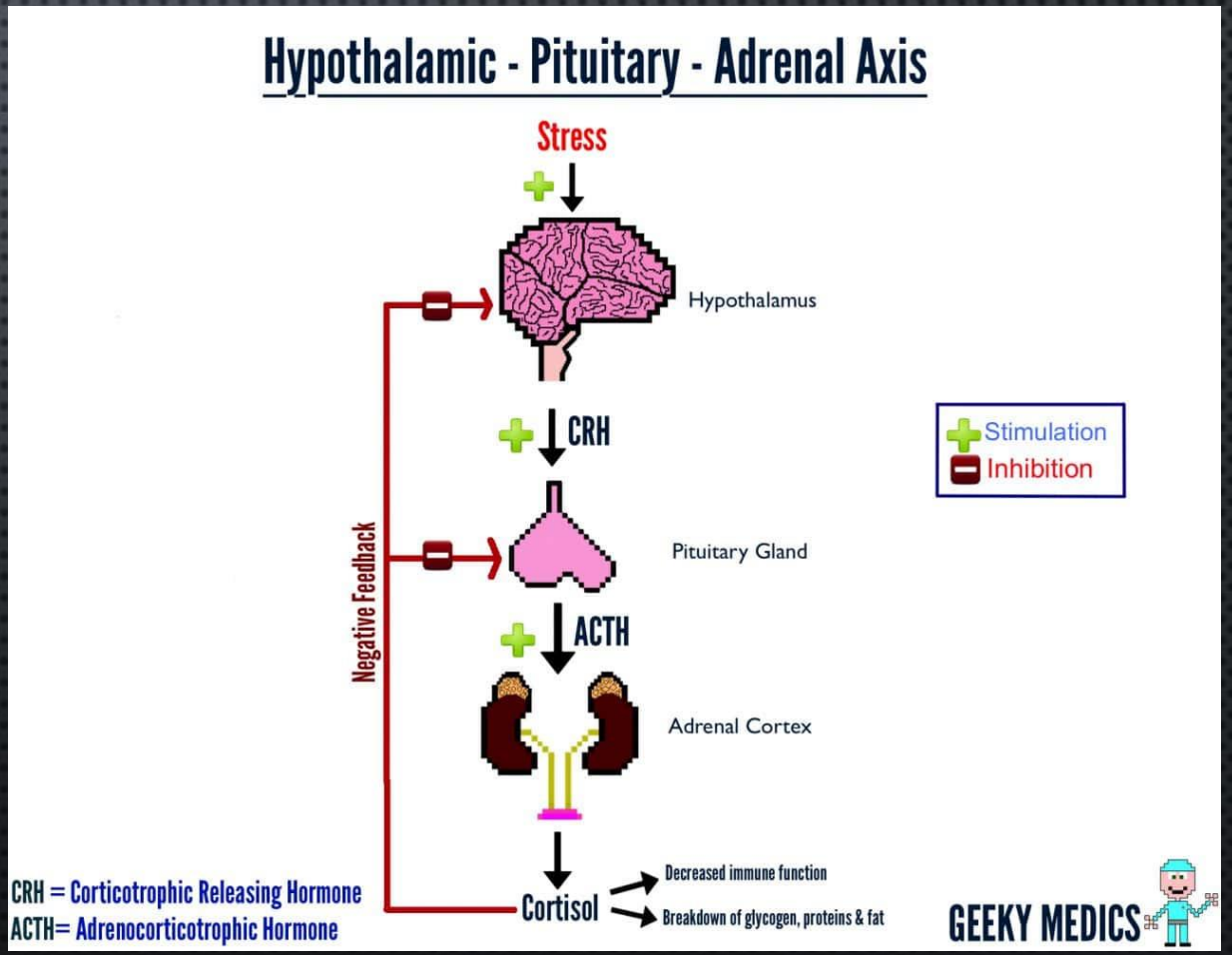
Laboratory studies:	
Cortisol, free, urine	
Initial measurement	120 µg/24 h (330.7 nmol/24 h)
Repeat measurement	240 µg/24 h (661.3 nmol/24 h)
Cortisol after 1 mg dexamethasone test	6.0 µg/dL (165.6 nmol/L)

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

A – ADRENOCORTICOTROPIN HORMONE (ACTH) LEVEL

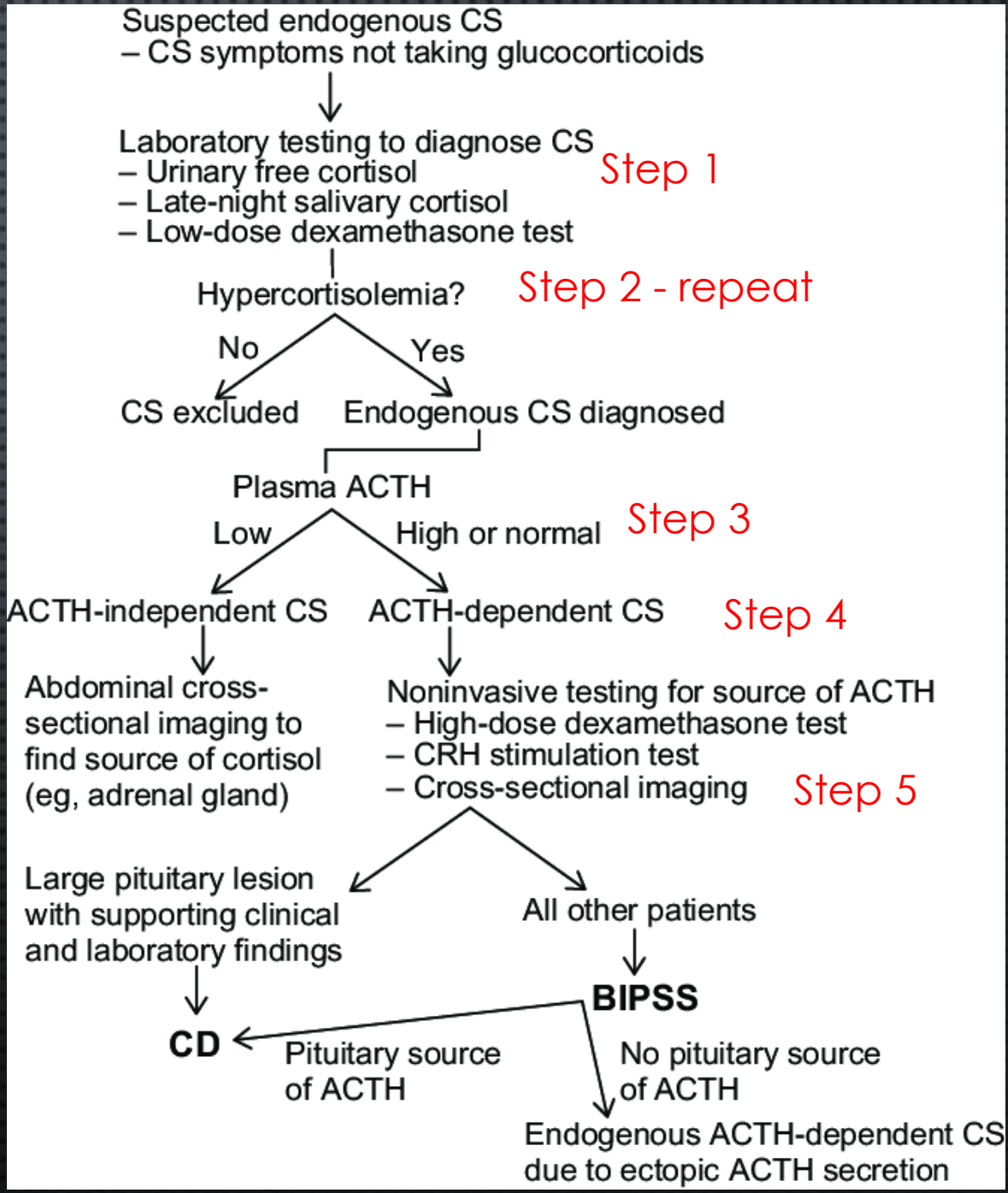
#11 – CUSHING

- CUSHING SYNDROME = HYPERCORTISOLISM FROM ANY CAUSE, EXOGENOUS OR ENDOGENOUS, ACTH-DEPENDENT OR NOT
- CUSHING DISEASE IS THE TERM USED TO INDICATE EXCESS CORTISOL PRODUCTION DUE TO AN ACTH-SECRETING PITUITARY ADENOMA
- THE MOST COMMON CAUSE OF SYNDROME = DISEASE



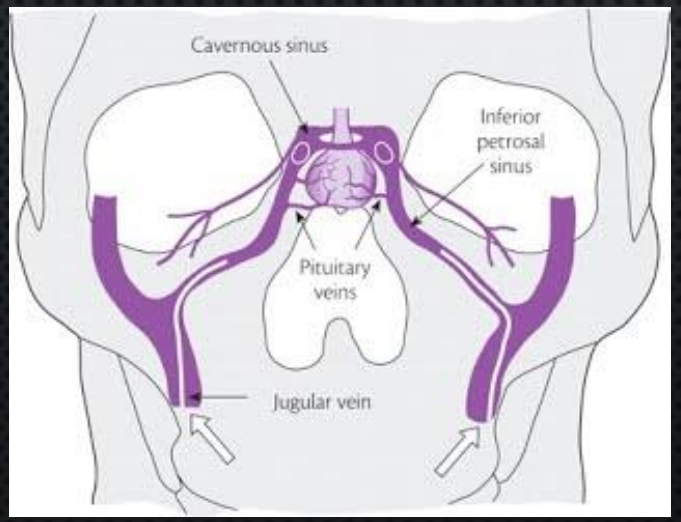
#11 – CUSHING

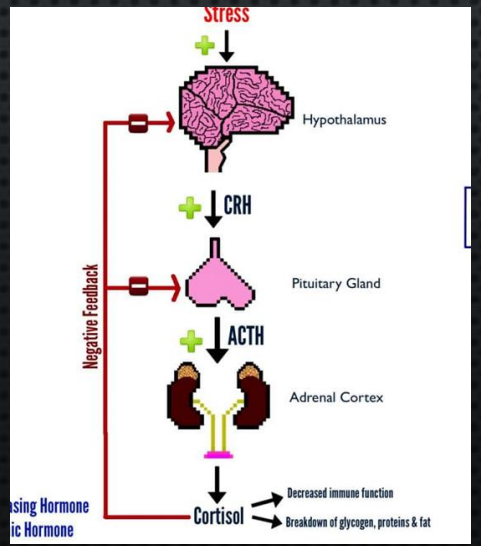
- STEP 1 – THINK IT'S HIGH? PROVE IT! (TRY TO SUPPRESS IT!)
- STEP 2 – CONFIRM IT A SECOND TIME
- STEP 3 – SEE IF IT'S ACTH-DEPENDENT
  - -IF NOT, SOURCE IS LIKELY ADRENAL ADENOMA
- STEP 4 – IF ACTH-DEPENDENT, GET AN MRI OF BRAIN TO PROVE CUSHING DISEASE
- STEP 5 - IF NO PITUITARY TUMOR (OR A TUMOR LESS THAN 6 MM), 8MG DEX SUPPRESSION TEST. A PITUITARY SOURCE OF ACTH WILL RESPOND TO NEGATIVE FEEDBACK FROM HIGH DOSES OF DEX, SUPPRESSING AM CORTISOL BY >50% (ECTOPIC SOURCE OF ACTH WILL NOT)
- BUT…

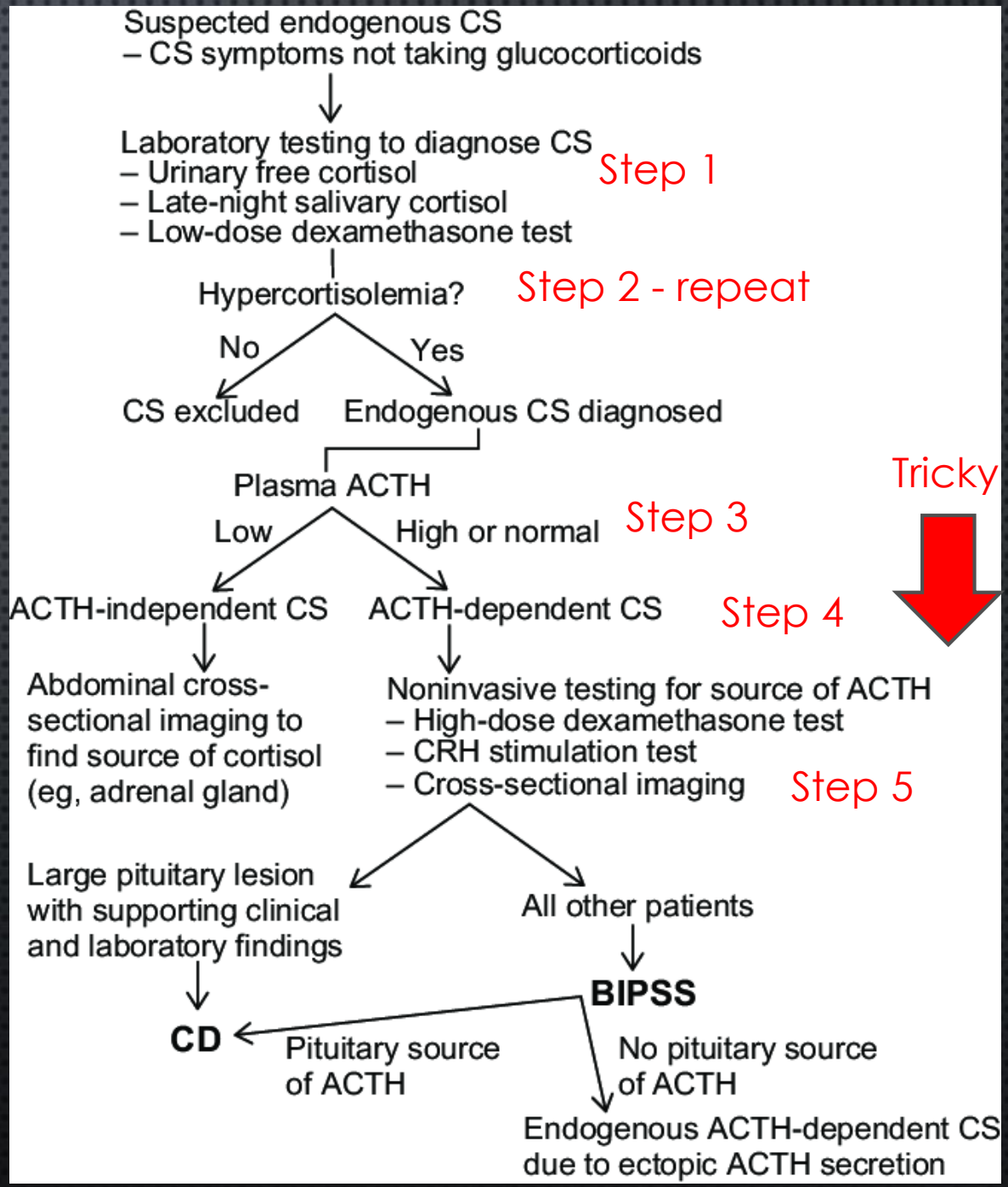


#11 – CUSHING

- BUT 8MG SUPPRESSION TEST IS ONLY 88%/57% SENSITIVITY/SPECIFICITY FOR CUSHING DISEASE, SO INFERIOR PETROSAL SINUS SAMPLING (IPSS) IS OFTEN RECOMMENDED BEFORE PITUITARY SURGERY
- IN IPSS, ACTH LEVELS IN THE PETROSAL SINUS ARE COMPARED WITH THOSE IN THE PERIPHERY AFTER THE ADMINISTRATION OF CORTICOTROPIN-RELEASING HORMONE (CRH). A CENTRAL TO PERIPHERAL GRADIENT GREATER THAN 2.0 BEFORE CRH OR GREATER THAN 3.0 AFTER CRH IS DIAGNOSTIC OF CUSHING DISEASE.







#12 – (MKSAP 66)

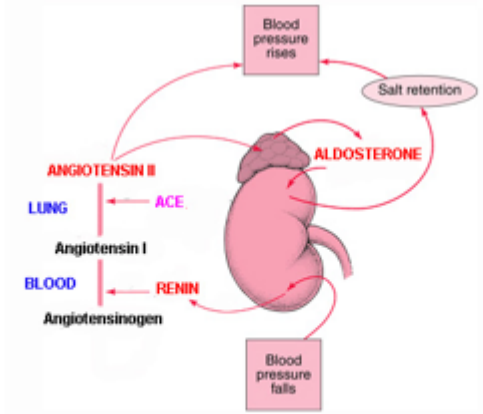
- A 52-year-old man is evaluated for difficult-to-control hypertension. Biochemical evaluation confirms a diagnosis of primary aldosteronism. Medications are amlodipine, losartan, and metoprolol.
- On physical examination, blood pressure is 149/98 mm Hg and pulse rate is 75/min. The remainder of the vital signs and physical examination are unremarkable.
- CT scan shows a 0.8-cm right adrenal mass with a density of 13 Hounsfield units.
- Which of the following is the most appropriate management?

A – ADRENAL VEIN SAMPLING

#12 – PRIMARY HYPERALDOSTERONISM

- STEP 1 = BIOCHEMICALLY CONFIRM HYPERALDO
- STEP 2 = CT (NOT MRI) TO LOOK FOR ADRENAL HYPERPLASIA AND NODULES
- STEP 3 = CONFIRM THE MASS IS SECRETING (DETERMINE THE SOURCE OF ALDOSTERONE SECRETION WHEN IMAGING IS UNREVEALING AND TO CONFIRM LATERALIZATION WHEN IMAGING DEMONSTRATES AN ADRENAL ADENOMA, SUCH AS IN THIS CASE)

	Renin	Aldo	Ddx
Primary	↓	↑	adrenal adenoma/carcinoma, adrenal hyperplasia syndromes
Secondary	↑	↑	RAS, low effective circulating volume
Mimics	↓	↓	AME, licorice ingestion, Liddle's syndrome



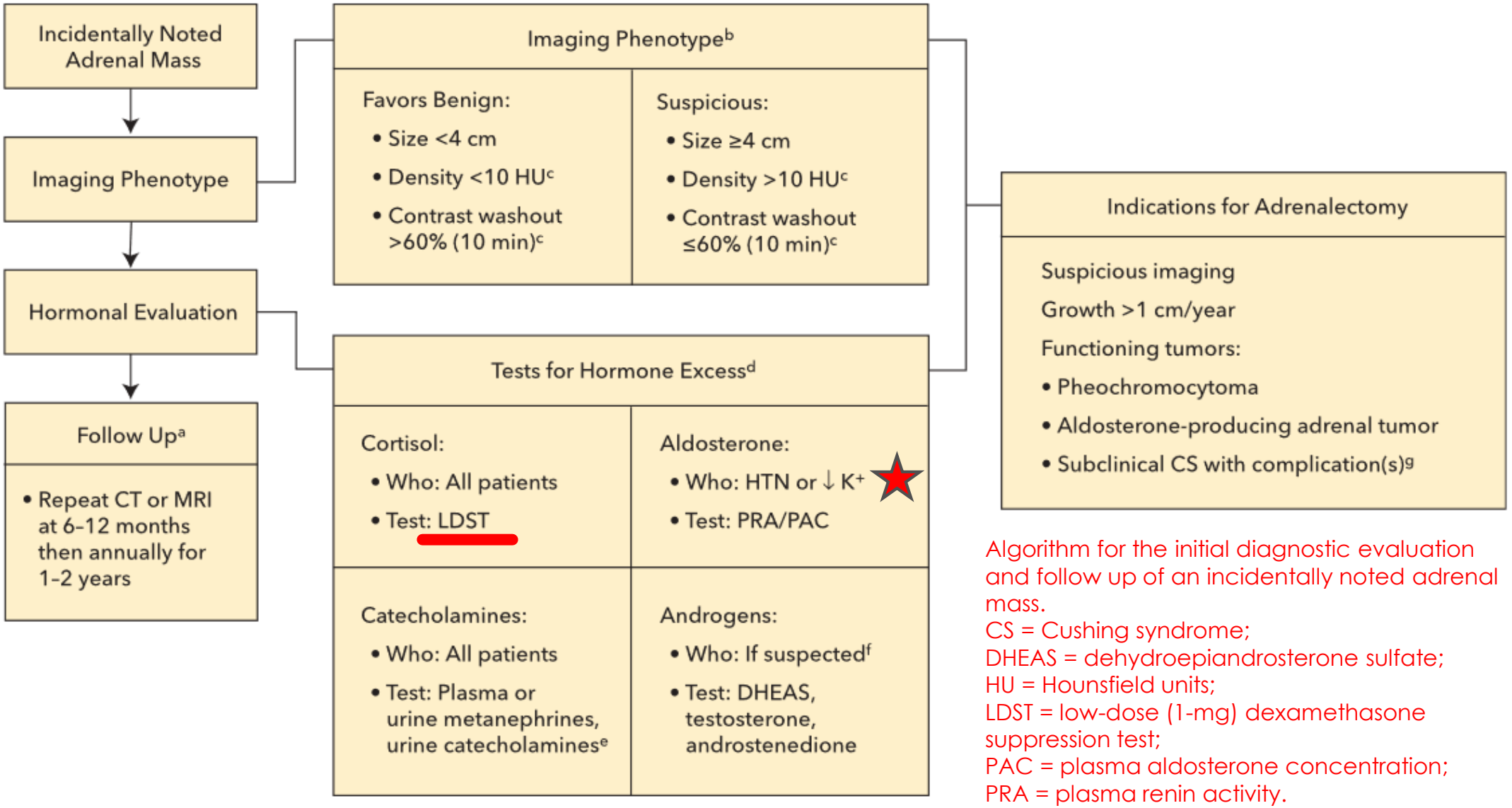
Adrenal vein sampling is especially important in older patients because of a higher frequency of nonfunctioning adrenal incidentalomas. Patients with an aldosterone-secreting adenoma are usually offered adrenalectomy, whereas those with primary aldosteronism due to bilateral adrenal hyperplasia are treated medically. Omission of adrenal vein sampling can lead to misdiagnosis in approximately 25% of cases!

#13 – (MKSAP 39)

- A 38-year-old woman is seen in follow-up to discuss the findings of an abdominal and pelvic CT scan done to evaluate renal colic, which has since resolved. The abdominal CT scan showed two small nonobstructing renal calculi in the right kidney and a 1.6-cm left adrenal mass with a density of 21 Hounsfield units (indeterminate for adrenal adenoma). Other than nephrolithiasis, the remainder of the medical history is unremarkable, and she takes no medications.
- On physical examination, vital signs and the remainder of the examination are unremarkable.
- Laboratory studies show normal serum electrolytes.
- Which of the following is the most appropriate test to perform next?

B – 24-HOUR URINE TOTAL METANEPHRINE MEASUREMENT

#13 – ADRENAL INCIDENTALOMA



Algorithm for the initial diagnostic evaluation and follow up of an incidentally noted adrenal mass.
CS = Cushing syndrome;
DHEAS = dehydroepiandrosterone sulfate;
HU = Hounsfield units;
LDST = low-dose (1-mg) dexamethasone suppression test;
PAC = plasma aldosterone concentration;
PRA = plasma renin activity.

#14 – (MKSAP 24)

- A 42-year-old woman is evaluated prior to surgery following a diagnosis of pheochromocytoma. Her symptoms are palpitations, hypertension, and sweating for 8 months' duration. Medications are lisinopril and hydralazine.
- On physical examination, blood pressure is 155/98 mm Hg. Other vital signs and the remainder of the examination are normal.
- Which of the following is the most appropriate next step in management?

E – START PHENOXYBENZAMINE

Pheochromocytoma

- TRIAD: Palpitation, headache, diaphoresis
- only in <50%
- Syndromes:
  - MEN 1
  - Von Hippel-Lindau
  - Neurofibromatosis type II
- Diagnosis: CT scan w/ contrast
- Who to test:
  - Typical triad
  - All adrenal masses
  - Hypertension on 3+ drugs
  - Idiopathic cardiomyopathy
  - Hypertension during anesthesia
  - Paragangliomas
  - Syndromes (listed)
  - Family history
- Treat - Surgical resection

#14: PHEO-CHROMO-CYTOMA

	α_1 receptor	α_2 receptor	β_1 receptor	β_2 receptor
Norepinephrine	Smooth muscle, hypothalamus	Nerve endings, stomach, hypothalamus	Heart, fat cells, kidneys, brain (posterior lobe of pituitary gland)	No interaction
Epinephrine	Smooth muscle	No interaction	Heart, fat cells, kidneys	Lungs, arterioles, stomach, liver or pancreas, uterus, skeletal muscle
End effect	Vasoconstriction, elevated blood pressure, mydriasis, decreased ability to defecate and/or urinate	Vasodilatation, lowers blood pressure, constipation	Increases heart rate, increases cardiac output and force of contraction, increased conduction, lipolysis, release of renin, release of antidiuretic hormone	Relaxation of smooth muscle (vasodilatation, bronchodilatation, constipation), increased glucose production and insulin release, contraction of skeletal muscle

- Phenoxybenzamine
  - Irreversible, nonspecific alpha blocker (mostly1)
  - Start 10-14 days prior
  - Titrate to goal BP 130/80 (seating) and SBP >90 when standing
  - Side effect: postural hypotension (Rx: HIGH SODIUM DIET)
  - Start beta-blocker second, treats reflex tachycardia (NEVER START BETA-BLOCKER FIRST – we need Beta2 to oppose alpha1!)
- Metyrosine
  - Catecholamine synthesis inhibitor
  - Given if tumor is very large or metanephrines are significantly high
  - Significant side effects
- Alpha-1 blockers (selective)
  - Prazosin, terazosin, doxazosin
  - Cheaper and fewer side effects than phenoxybenzamine

#15 – (MKSAP 25)

- A 60-year-old man is evaluated during a routine office visit. He was diagnosed with type 2 diabetes mellitus 6 years ago. Medical history is significant for coronary artery disease, hypertension, hyperlipidemia, and biliary pancreatitis. Medications are lisinopril, metoprolol, metformin, aspirin, and atorvastatin.
- On physical examination, other than a blood pressure of 152/91 mm Hg, the vital signs are normal. BMI is 27. The remainder of the examination is normal.
- Laboratory studies show a hemoglobin A_{1C} level of 8.2%.
- Which of the following is the most appropriate treatment for this patient?

A – EMPAGLIFLOZIN

#15 – SGLT2 INHIBITORS

THE Hospitalist

ALL CONTENT

SGLT2 inhibitors morph into HF drugs

Publish date: February 7, 2019

Author(s): Bruce Jancin; MDedge News

EXPERT ANALYSIS FROM ACC SNOWMASS 2019

SNOWMASS, COLO. – The oral sodium-glucose cotransporter-2 (SGLT2) inhibitors are the focus of a slew of ongoing phase 3 clinical trials in patients with symptomatic heart failure but no diabetes.

"We have a wide array of exciting opportunities to modify cardiovascular risk with agents that were initially developed for the therapy of diabetes. I think we're increasingly moving to an age where these agents are actually cardiovascular drugs that happen to lower blood glucose, rather than the other way around, which is how they were initially conceived," Akshay S. Desai, MD <https://physiciandirectory.brighamandwomens.org/details/40/akshay-desai-cardiovascular_medicine-heart_transplant-boston> , observed at the Annual Cardi

Empagliflozin received approval from the FDA for patients with type 2 diabetes and established cardiovascular disease based upon the results of the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME). This study demonstrated a reduction in the primary composite outcome (cardiovascular-related death, nonfatal myocardial infarction, nonfatal stroke) and all-cause mortality when empagliflozin was added to standard care versus placebo. Empagliflozin has the additional potential benefit of inducing weight loss and blood pressure lowering in this patient with overweight and uncontrolled hypertension.

Metformin	1.0 to 2.0	Weight neutral
Additional therapy[¶]		
Insulin (usually with a single daily injection of intermediate- or long-acting insulin initially)	1.5 to 3.5	No dose limit, rapidly effective, improved lipid profile
Sulfonylurea (shorter-acting agents preferred)	1.0 to 2.0	Rapidly effective
GLP-1 receptor agonist (daily to weekly injections)	0.5 to 1.0	Weight loss, reduced cardiovascular mortality (liraglutide, semaglutide) in patients with established CVD
Thiazolidinedione	0.5 to 1.4	Improved lipid profile (pioglitazone), potential decrease in MI (pioglitazone)
Glinide	0.5 to 1.5[Δ]	Rapidly effective
SGLT2 inhibitor	0.5 to 0.7	Weight loss, reduction in systolic blood pressure, reduced cardiovascular mortality in patients with established CVD
DPP-4 inhibitor	0.5 to 0.8	Weight neutral
Alpha-glucosidase inhibitor	0.5 to 0.8	Weight neutral
Pramlintide	0.5 to 1.0	Weight loss

Decrease hepatic gluconeogesnsis, decrease insulin resistance, decrease weight, TGAs/chol

Increase release insulin from beta cells (glipizide)

Decrease hepatic gluconeogenesis, slow gastric emptying, early satiety [incretin mimetic] (exenatide Trulicity)

Bind PPAR gamma receptors = increase glucose transport, decrease insulin resistance, lipids (pioglitazone)

Increases release from beta cells (repaglinide = Prandin)

Blocks resorption of glucose by the kidney thereby increasing excretion of glucose in the urine (canagliflozin Invokana, empagliflozin Jardiance)

Mimetic = decrease gastric emptying, weight loss, early satiety, decreased hepatic gluconeogenesis (sitagliptin Januvia)

Inhibits breakdown of carbs and decreases absorption of glucose (acarbose)

Complements insulin, no hypoglycemia, slows gastric emptying (amylin analogue)

#16 – (MKSAP 72)

- A 66-year-old man recently diagnosed with type 2 diabetes mellitus is evaluated in the emergency department for nausea, vomiting, and fatigue. He was diagnosed with type 2 diabetes 18 months ago. In the past month metformin was discontinued due to severe diarrhea, and glipizide and empagliflozin were initiated. In addition to type 2 diabetes, medical history is significant for coronary artery disease, hypertension, and dyslipidemia. Medications are aspirin, lisinopril, metoprolol, atorvastatin, glipizide, and empagliflozin.
- On physical examination, temperature is normal, blood pressure is 90/60 mm Hg, pulse rate is 120/min, and respiration rate is 22/min. Dry mucous membranes are noted. There is diffuse abdominal tenderness to palpation without guarding. Other than tachycardia, the remainder of the examination is normal.

Laboratory studies:	
Sodium	133 mEq/L (133 mmol/L)
Bicarbonate	10 mEq/L (10 mmol/L)
Glucose	150 mg/dL (8.3 mmol/L)
Anion gap	17 mEq/L (17 mmol/L)
β-hydroxybutyrate	Elevated

- Which of the following is most likely responsible for the patient's findings?

C – EMPAGLIFLOZIN

Sulfonylurea (shorter-acting agents preferred)	1.0 to 2.0	Rapidly effective	Weight gain, hypoglycemia (especially with glibenclamide or chlorpropamide)
GLP-1 receptor agonist (daily to weekly injections)	0.5 to 1.0	Weight loss, reduced cardiovascular mortality (liraglutide, semaglutide) in patients with established CVD	Requires injection, frequent GI side effects, long-term safety not established, expensive
Thiazolidinedione	0.5 to 1.4	Improved lipid profile (pioglitazone), potential decrease in MI (pioglitazone)	Fluid retention, HF, weight gain, bone fractures, potential increase in MI (rosiglitazone) and bladder cancer (pioglitazone)
Glinide	0.5 to 1.5$^{\Delta}$	Rapidly effective	Weight gain, 3 times/day dosing, hypoglycemia
SGLT2 inhibitor	0.5 to 0.7	Weight loss, reduction in systolic blood pressure, reduced cardiovascular mortality in patients with established CVD	Vulvovaginal candidiasis, urinary tract infections, bone fractures, lower limb amputations, acute kidney injury, DKA, long-term safety not established
DPP-4 inhibitor	0.5 to 0.8	Weight neutral	Long-term safety not established, expensive, possible increased risk of HF with saxagliptin
Alpha-glucosidase inhibitor	0.5 to 0.8	Weight neutral	Frequent GI side effects, 3 times/day dosing
Pramlintide	0.5 to 1.0	Weight loss	3 injections daily, frequent GI side effects, long-term safety not established, expensive

Sodium-glucose cotransporter 2 (SGLT2) inhibitors (canagliflozin, dapagliflozin, and empagliflozin) improve glycemia by increasing excretion of glucose by the kidney. SGLT2 is expressed in the proximal tubule and mediates reabsorption of approximately 90% of the filtered glucose load. SGLT2 inhibitors promote excretion of glucose by the kidneys and thereby modestly lower elevated blood glucose levels in patients with type 2 diabetes. Euglycemic diabetic ketoacidosis has been reported in patients with type 2 diabetes taking SGLT2 inhibitors. Because of this, the FDA issued a Drug Safety Communication that warns of an increased risk of

diabetic ketoacidosis with uncharacteristically mild to moderate glucose elevations (euglycemic diabetic ketoacidosis) associated with the use of all the approved SGLT2 inhibitors. SGLT2 inhibitors should be discontinued in patients who develop acidosis on these agents.

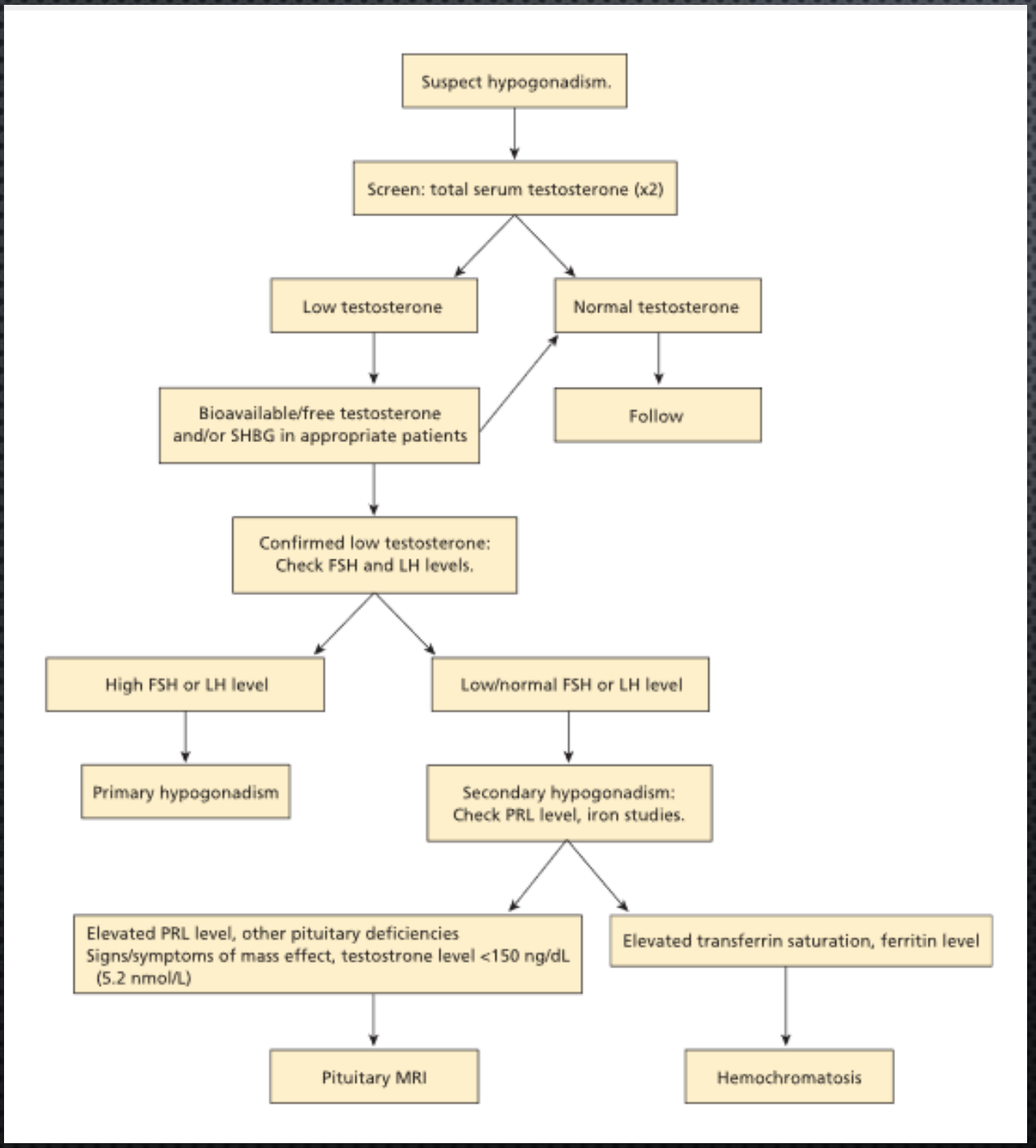
#17 – (MKSAP 13)

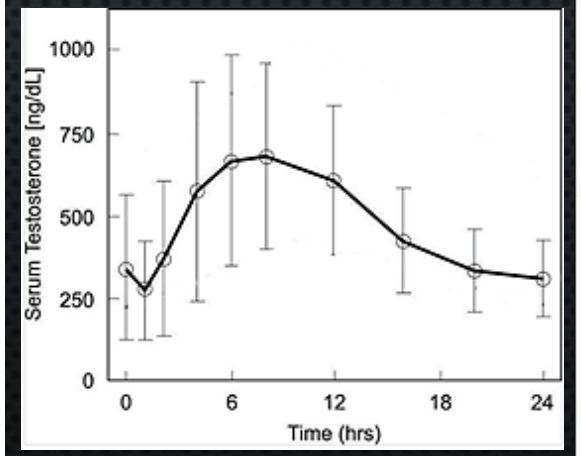
- A 47-year-old man is evaluated during a follow-up visit to manage fatigue and decreased libido. Medical history is significant for hypertension and dyslipidemia. Medications are hydrochlorothiazide and atorvastatin.
- On physical examination, vital signs are normal. He has normal hair distribution, no gynecomastia, and normal testicular examination.
- Laboratory studies obtained at 3 PM revealed a total testosterone level of 275 ng/dL (9.5 nmol/L) and a luteinizing hormone level of 5 mU/mL (5 U/L).
- Which of the following is the most appropriate management?

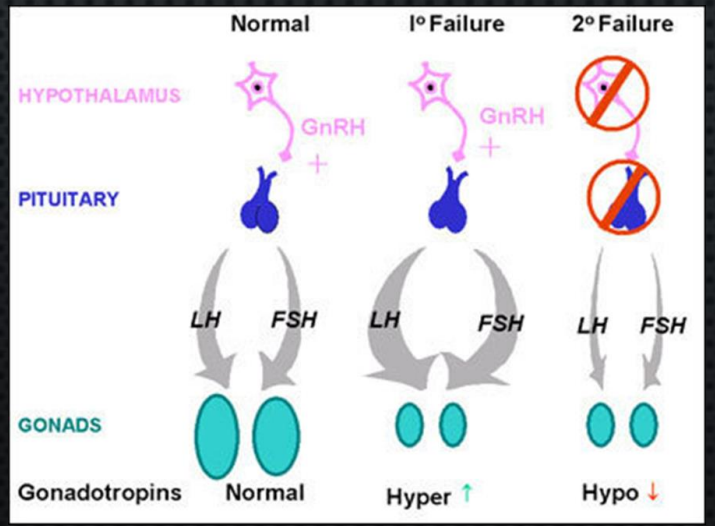
C – MEASURE 8AM TESTOSTERONE

#17 – MALE HYPOGONADISM

- DIAGNOSIS = SIGNS AND SYMPTOMS CONSISTENT WITH ANDROGEN DEFICIENCY + LOW MORNING TESTOSTERONE ON AT LEAST TWO OCCASIONS
- (T IS DIURNAL, AND CAN'T BE DONE DURING ACUTE ILLNESS)
- AFTER CONFIRMATION, DETERMINE PRIMARY OR SECONDARY HYPOGONADISM BY MEASUREMENT OF LUTEINIZING HORMONE (LH) AND FOLLICLE-STIMULATING HORMONE (FSH) LEVELS. ELEVATED GONADOTROPIN LEVELS ARE SEEN IN PRIMARY HYPOGONADISM WITH LH AND FSH LEVELS LOW OR INAPPROPRIATELY NORMAL IN SECONDARY HYPOGONADISM.







#18 – (MKSAP 40)

- A 57-year-old woman is evaluated during hospitalization following surgical fixation of a right femur neck pathologic fracture. Pathology of the femur shows a neoplasm containing numerous giant cells consistent with brown tumor.
- On physical examination, vital signs are normal. There is a palpable mass on the lower left side of the right neck. There is an incision with surgical staples on the right hip. The remainder of the examination is unremarkable.
- Neck ultrasound shows a solid hypervascular mass (6 × 2.9 × 3 cm) posterior to the left lobe of the thyroid, with compression and displacement of the trachea. A parathyroidectomy is planned.
- Which of the following is the most appropriate test to perform next?

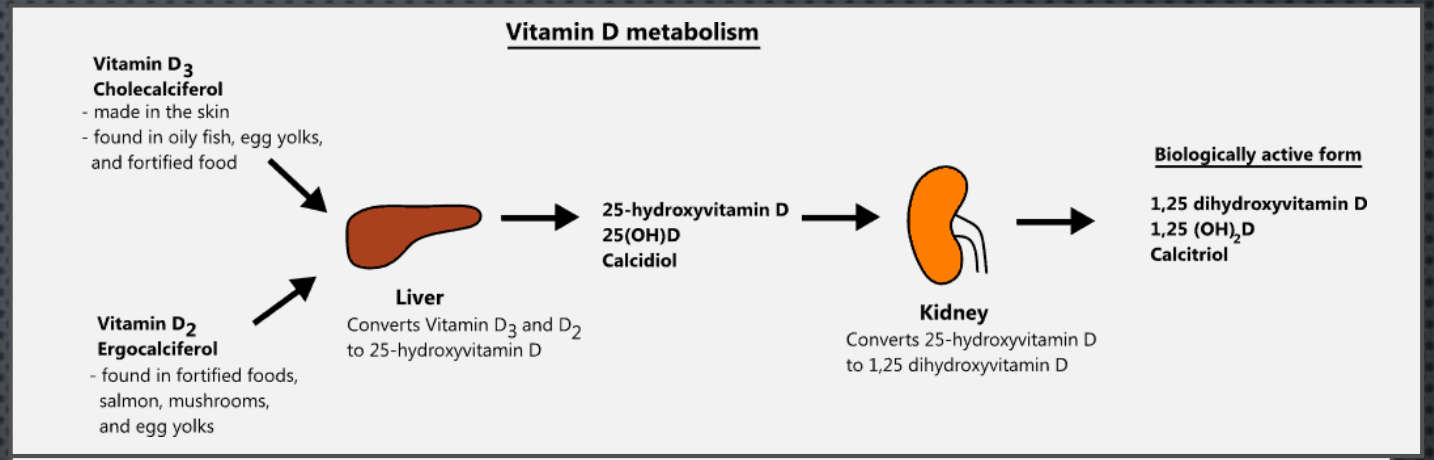
Laboratory studies:	
Alkaline phosphatase	260 U/L
Calcium	13.2 mg/dL (3.3 mmol/L)
Creatinine	1.6 mg/dL (141.4 µmol/L)
Phosphorus	1.9 mg/dL (0.6 mmol/L)
Parathyroid hormone	1142 pg/mL (1142 ng/L)

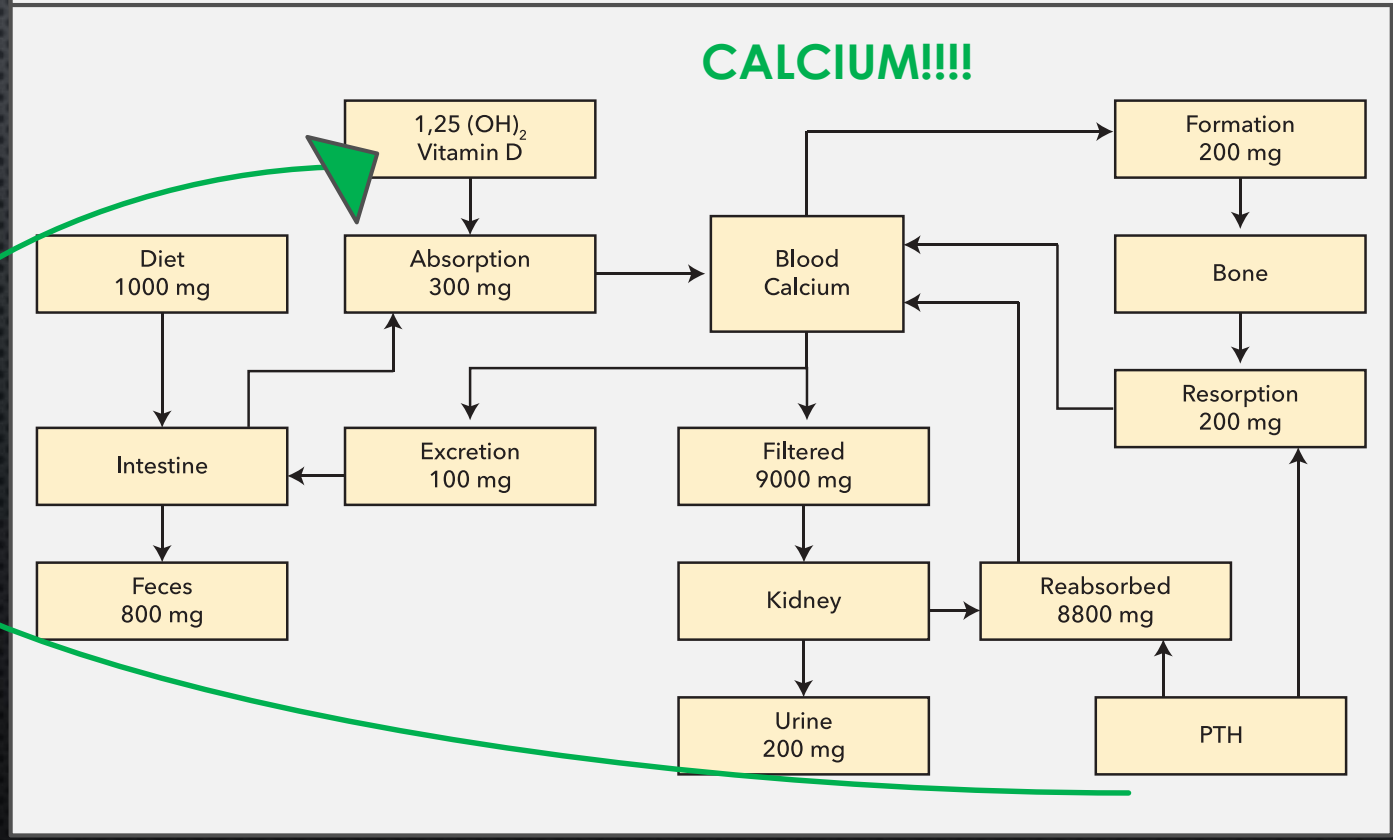
C – 25-HYDROXYVITAMIN D LEVEL

#18 – CALCIUM AND VITAMIN D

- PTH = DECREASES RENAL EXCRETION OF CALCIUM
- INCREASES CONVERSION OF 25-HYDROXYVITAMIN D TO THE ACTIVE METABOLITE 1,25-DIHYDROXYVITAMIN D
- 1,25-DIHYDROXYVITAMIN D = INCREASES THE EFFICIENCY OF INTESTINAL CALCIUM ABSORPTION
- 25-HYDROXYVITAMIN D = STORAGE FORM, BEST TO MEASURE

- Primary HPT increases conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, causing frequent deficiency
- Supplementation of vitamin D in them reduces PTH, decrease bone turnover, and improves bone mineral density
- Treating deficiency perioperatively helps manage transient hypocalcemia, which routinely occurs after parathyroidectomy and especially in severe HPT where high bone turnover (as evidence by an elevated alkaline phosphatase) portends hungry bone syndrome (other glands shut down)

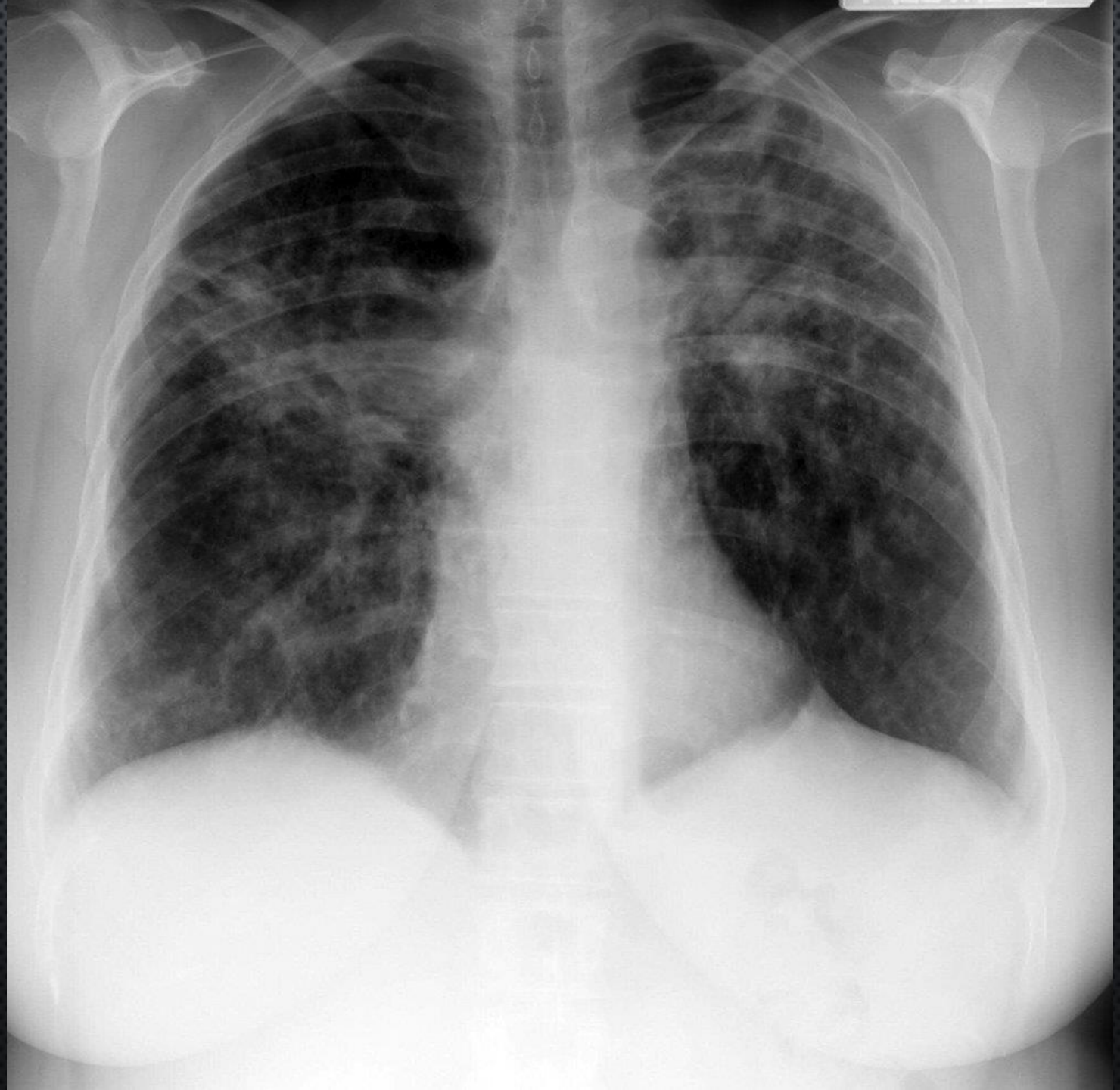




#19 – (MKSAP 31)

- A 57-year-old woman is evaluated for cough, exertional dyspnea, and fatigue for 12 months' duration. Medical history is otherwise unremarkable, and she takes no medications.
- On physical examination, temperature is 38.1 °C (100.6 °F), blood pressure is 132/78 mm Hg, pulse rate is 84/min, respiratory rate is 18/min; oxygen saturation is 95% breathing ambient air. The cardiac examination is normal. There are no wheezes or crackles on pulmonary examination. The remainder of the examination is unremarkable.
- CXR is shown.
- A tuberculin skin test is normal.
- Which of the following is the most appropriate laboratory test to perform next?

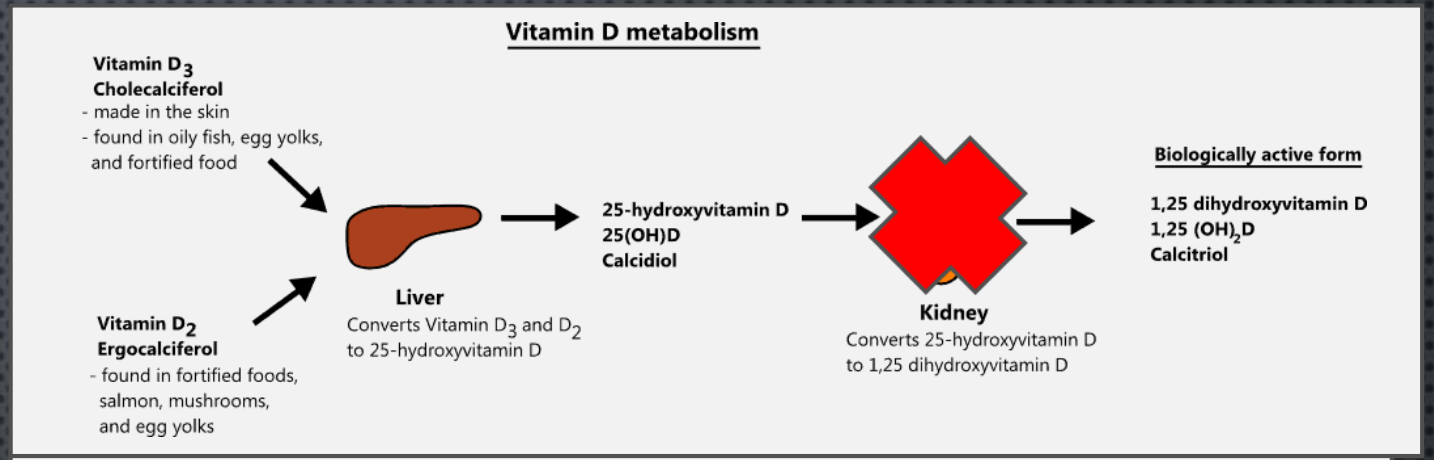
Laboratory studies:	
Calcium	11.1 mg/dL (2.8 mmol/L)
Creatinine	1.2 mg/dL (106.1 µmol/L)
Phosphorus	4.7 mg/dL (1.5 mmol/L)
Parathyroid hormone	<10 pg/mL (10 ng/L)

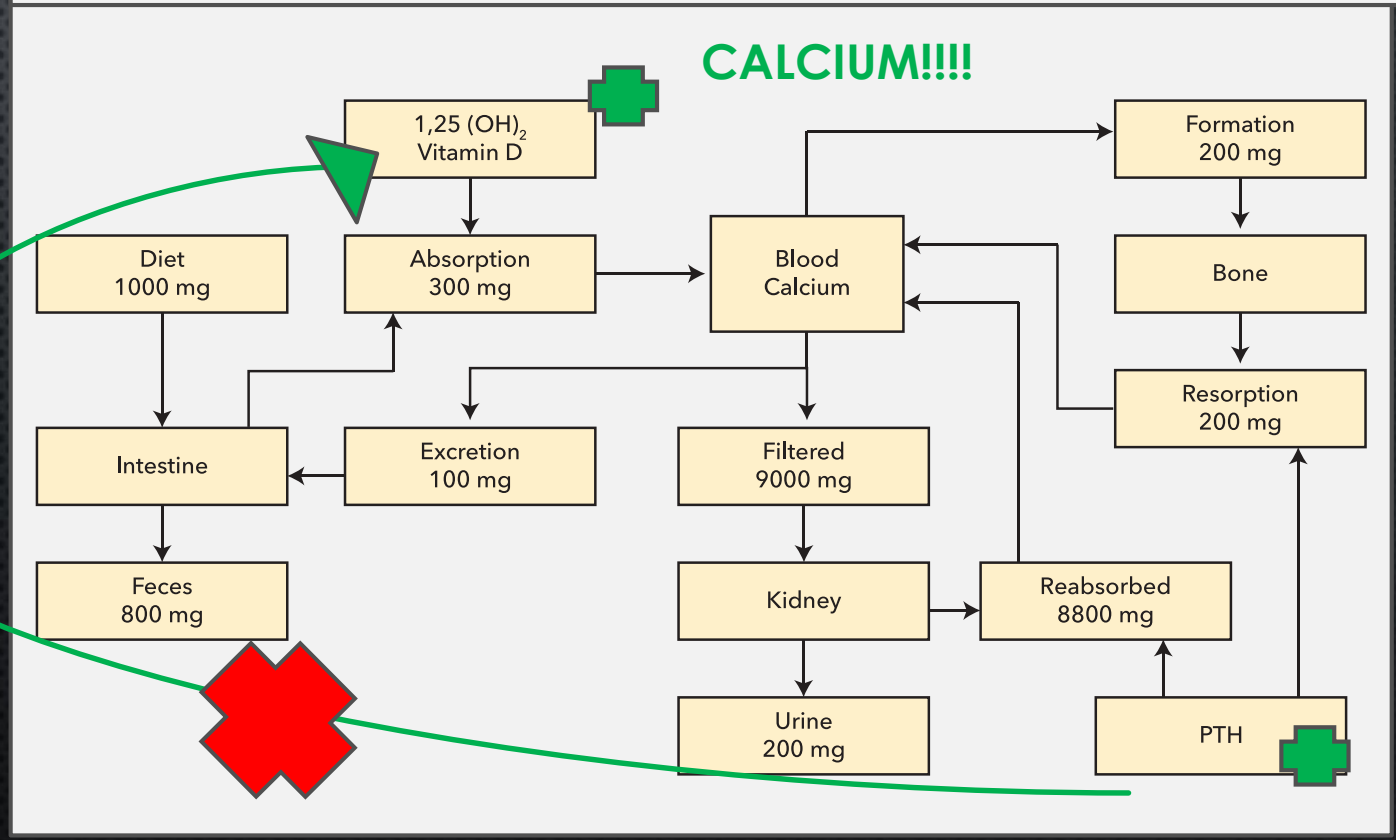


C – 1,25-DIHYDROXYVITAMIN D LEVEL

#19 – VITAMIN D-MEDIATED HYPERCALCEMIA

- CXR = "EXTENSIVE INFILTRATES THAT ARE MOST PROMINENT IN THE UPPER LUNG ZONES AND ARE ASSOCIATED WITH HILAR ENLARGEMENT, HIGHLY SUGGESTIVE OF PULMONARY SARCOIDOSIS"
- MACROPHAGES WITHIN GRANULOMAS CONVERT 25-HYDROXYVITAMIN D TO 1,25-DIHYDROXYVITAMIN D WITHOUT REGULATION BY PARATHYROID HORMONE IN CONTRAST TO RENAL CONVERSION OF VITAMIN D.
- AN ELEVATED 1,25-DIHYDROXYVITAMIN D LEVEL AND SUPPRESSED PARATHYROID HORMONE IS DIAGNOSTIC OF VITAMIN D-DEPENDENT HYPERCALCEMIA
- AS VITAMIN D ENHANCES ABSORPTION OF BOTH CALCIUM AND PHOSPHORUS, CONCURRENT ELEVATION OF SERUM CALCIUM AND PHOSPHORUS IS ALSO SUGGESTIVE OF VITAMIN D-DEPENDENT HYPERCALCEMIA.





#20 – (MKSAP 30)

- A 21-year-old woman is seen in the office following parathyroidectomy for hyperparathyroidism. The pathology of three resected enlarged parathyroid glands showed hyperplasia. Her medical history is significant for oligomenorrhea. Family history is notable for hypercalcemia and kidney stones in her father, who died at age 49 from pancreatic cancer, and a pituitary tumor in her sister at age 16.
- Her vital signs are normal. Skin findings include dermatofibroma. Her physical examination is normal with the exception of the surgical scar on her neck.
- Which of the following is the most likely diagnosis?

B – MULTIPLE ENDOCRINE NEOPLASIA TYPE 1 (MEN1)

#20 – MEN1

- Primary hyperparathyroidism in adolescents and young adults may be the first sign of multiple endocrine neoplasia syndrome (MEN) 1 & 2
- If family history reveals primary hyperparathyroidism, pituitary tumor, Zollinger-Ellison syndrome, early death from pancreatic neoplasm, pheochromocytoma, or medullary thyroid cancer, MEN is more likely and screening should be considered
- In contrast to sporadic primary hyperparathyroidism, MEN syndromes have recurrence of hyperparathyroidism due to ongoing hyperplasia in the remaining parathyroid tissue after parathyroidectomy
- MEN1 is associated with mutation of the tumor suppressor *MEN1* gene, and MEN2A is associated with mutation of the *RET* gene