Thyroid Disorders

Hyperthyroidism

General manifestations of hyperthyroidism	
Symptoms	• Anxiety & insomnia • Palpitations • Heat intolerance • Increased perspiration • Weight loss without decreased appetite
Physical examination	• Goiter • Hypertension • Tremors involving fingers/hands • Hyperreflexia • Proximal muscle weakness • Lid lag • Atrial fibrillation

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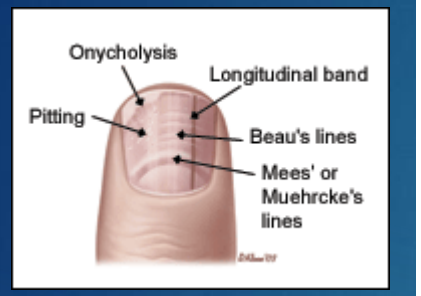


Table 2. Signs and Symptoms of Hyperthyroidism

Adrenergic

Palpitations, tachycardia, anxiety, tremor, jitteriness, diaphoresis, heat intolerance, stare, lid lag, hyperdefecation (not diarrhea)

Cardiovascular

Tachycardia, irregular pulse (in atrial fibrillation), dyspnea, orthopnea and peripheral edema (in heart failure)

Cutaneous

Onycholysis (Plummer nails), patchy or generalized hyperpigmentation (especially of the face and neck)

Symptoms pathognomonic for Graves disease: pretibial myxedema (thyroid dermopathy) and thyroid acropachy (clubbing of fingers and toes accompanied by soft-tissue swelling of the hands and feet)

Patchy vitiligo can also be observed in Graves disease

Hypermetabolism

Weight loss in spite of increased appetite, fever (in thyroid storm)

Neuromuscular

Brisk peripheral reflexes with accelerated relaxation phase and weakness of proximal muscles

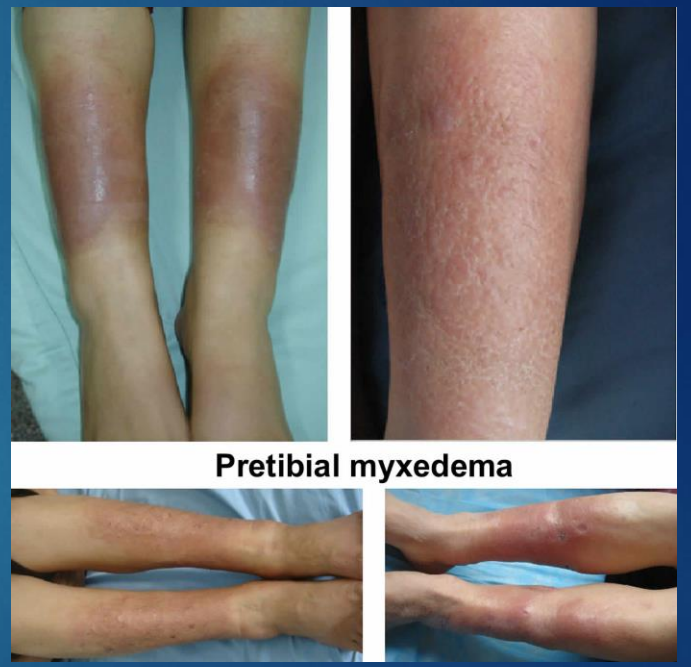
Neuropsychiatric

Anxiety, rapid and pressured speech, insomnia, psychosis (if hyperthyroidism is severe)

Ocular

Increased lacrimation, incomplete closure of the eyes when sleeping reported by the patient's partner, photophobia, increased eye sensitivity to wind or smoke, grittiness or sensation of a foreign body or sand in the eyes

Symptoms pathognomonic for Graves disease: exophthalmos, periorbital edema, diplopia, blurred vision, reduced color perception



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Cardiovascular effects of thyrotoxicosis	
Rhythm	• Sinus tachycardia • Premature atrial & ventricular complexes • **Atrial fibrillation**/flutter
Hemodynamic effects	• **Systolic hypertension** & ↑pulse pressure • ↑Contractility & cardiac output • ↓Systemic vascular resistance • ↑**Myocardial oxygen demand**
Heart failure	• High-output failure • Exacerbation of pre-existing low-output failure
Angina symptoms	• Coronary vasospasm • Pre-existing coronary atherosclerosis

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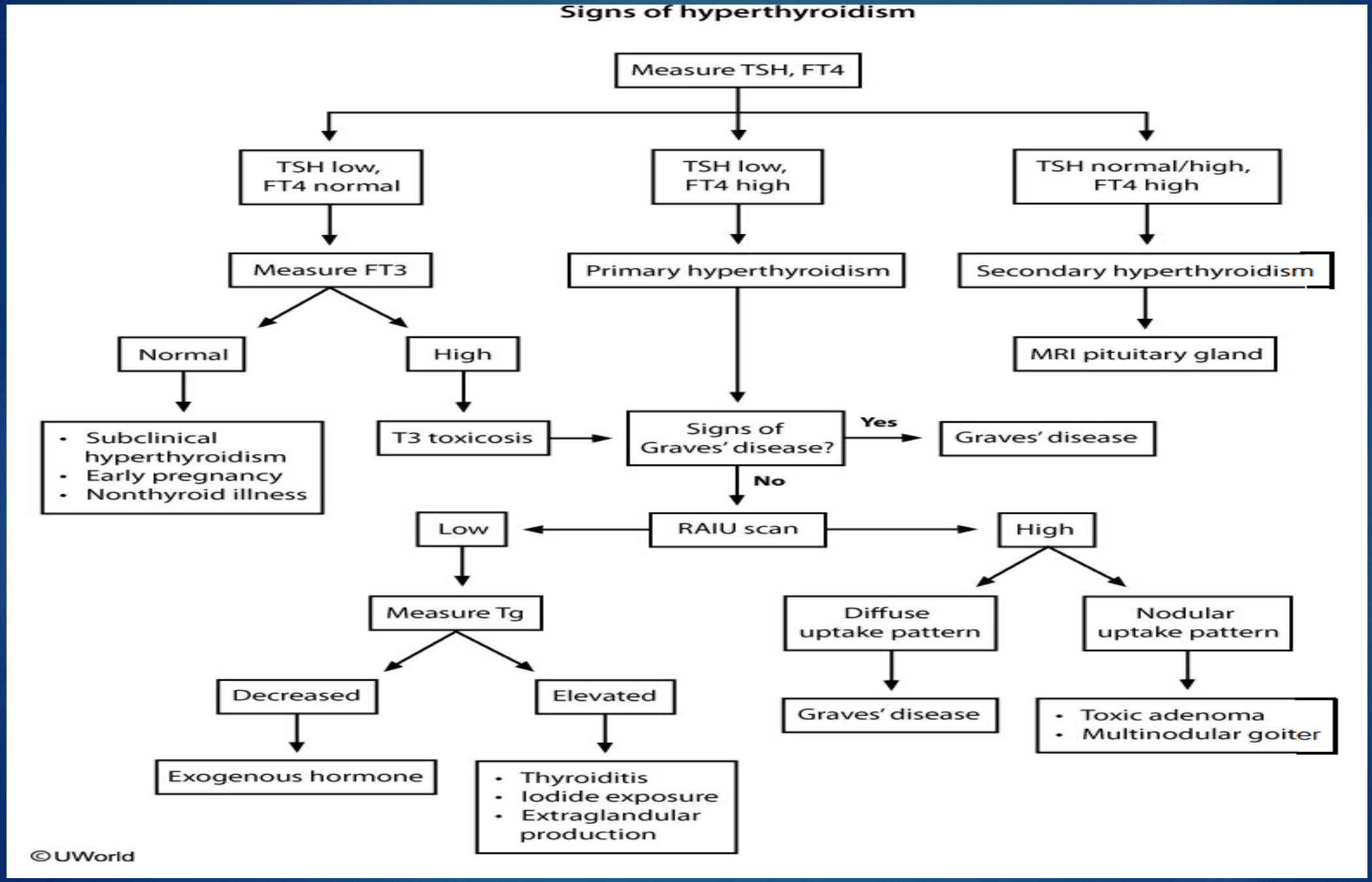
Diagnosis

- In patients in whom hyperthyroidism is suspected, serum TSH is the best initial test.
- If subnormal, serum free T4 and T3 concentrations are run by most laboratories.
- If serum free T4 and T3 are not automatically measured when a low serum TSH value is obtained but the index of suspicion for hyperthyroidism is high, a free T4 and T3 should be ordered with the initial TSH measurement.
- Some physicians first order a TSH test, which has the highest sensitivity and specificity for hyperthyroidism, and then subsequently obtain free thyroxine (T4) and total triiodothyronine (T3) levels (free T3 assays are poorly validated) if the TSH level is low. Others prefer to order all three tests if hyperthyroidism is suspected to make the diagnosis more efficiently.
- The serum level of thyroid-stimulating immunoglobulins or TSH receptor antibodies helps distinguish Graves disease from other causes of hyperthyroidism in patients who lack signs pathognomonic of Graves disease and have a contraindication to radioactive iodine uptake and scan.



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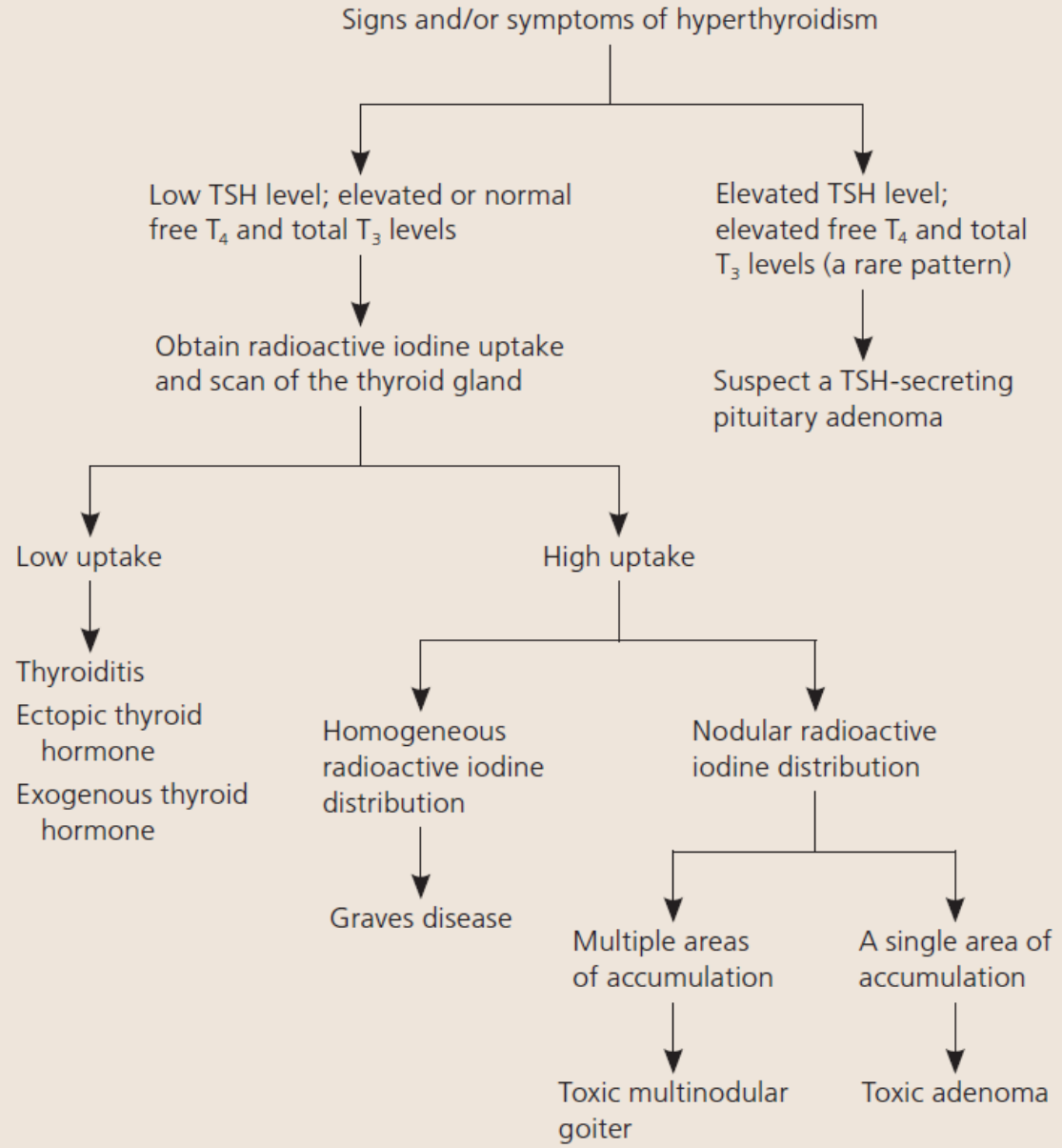
Diagnostic Workup of Hyperthyroidism



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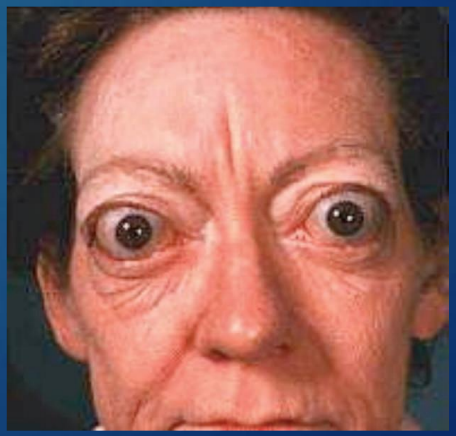
Etiology/"What Is the Most Likely Diagnosis?"	
Diagnosis	**Unique feature**
Graves disease	Eye (proptosis) (20%–40%) and skin (5%) findings
Subacute thyroiditis	Tender thyroid
Painless "silent" thyroiditis	Nontender, normal exam results
Exogenous thyroid hormone use	Involuted gland is not palpable
Pituitary adenoma	High TSH level

Only Graves disease has eye and skin abnormalities.



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Lab Findings in Hyperthyroidism

Diagnosis	TSH	RAIU*	Confirmatory
Graves disease	Low	Elevated	Positive antibody testing
Subacute thyroiditis	Low	Decreased	Tenderness
Painless "silent" thyroiditis	Low	Decreased	None
Exogenous thyroid hormone use	Low	Decreased	History and involuted, nonpalpable gland
Pituitary adenoma	High	Not done	MRI of head

*RAIU = radioactive iodine uptake

Only Graves disease has TSH receptor antibodies.

Treatment

- Use propylthiouracil (PTU) or methimazole acutely to bring the gland under control.
- Then use radioactive iodine to ablate the gland.
- Use propranolol to treat sympathetic symptoms, such as tremors, palpitations, etc. "first step"
- After ablative therapy, the patient will become hypothyroid and hormone replacement treatment is indicated.
- Subtotal thyroidectomy is only indicated in pregnancy (2nd trimester) and in children.
- Surgery is also used if the thyroid is so large that there are compressive symptoms. PTU is not curative.

Monitoring

- Free T4 and total T3 should be obtained four weeks after starting a thionamide and every four to eight weeks thereafter with the dosage adjusted based on results.
- Once free T4 and total T3 levels normalize, they should be monitored every three months.
- Serum TSH is of limited value early in the treatment course because levels may remain suppressed for several months after treatment is started.
- An antithyroid medication should be continued for 12 to 18 months, then tapered or discontinued if the TSH level is normal at the time.

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Treatment	
Diagnosis	**Treatment**
Graves disease	Radioactive iodine
Subacute thyroiditis	Aspirin
Painless "silent" thyroiditis	None
Exogenous thyroid hormone use	Stop use
Pituitary adenoma	Surgery

Methimazole is preferred over propylthiouracil.

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Treatment of Graves' disease	
Treatment	**Adverse effects**
Antithyroid drugs (thionamides)	• **Agranulocytosis** • Methimazole: 1st-trimester teratogen, cholestasis • Propylthiouracil: **Hepatic failure**, ANCA-associated vasculitis
Radioiodine ablation	• Permanent hypothyroidism • Worsening of ophthalmopathy • Possible radiation side effects
Surgery	• Permanent hypothyroidism • Risk of recurrent laryngeal nerve damage • Risk of hypoparathyroidism

ANCA = antineutrophilic cytoplasmic antibodies.

Radioactive iodine ablation

- It is contraindicated in pregnancy.
- Moderate to severe Graves orbitopathy is a relative contraindication, especially in patients who smoke, because radioactive iodine may exacerbate the eye disease.
- In mild cases of Graves orbitopathy, radioactive iodine ablation can be performed with concomitant glucocorticoid therapy.
- Nonradioactive iodine impedes radioactive iodine uptake by iodide transporter; therefore, exposure to large amounts of nonradioactive iodine (e.g., iodinated contrast, amiodarone) should be avoided within three months before radioactive iodine ablation.
- Pregnancy should be ruled out within 48 hours before radioactive iodine ablation and avoided for six months thereafter.
- A thionamide should be discontinued at least five days before the treatment but can be restarted three to five days after to maintain control of thyroid function, because it may take up to 12 weeks to achieve the full effect of radioactive iodine.

Radioactive Iodine ablation

- Most patients develop permanent hypothyroidism between two and six months after radioactive iodine ablation and require thyroid hormone supplementation.

- Free T4 and total T3 should be measured four to eight weeks after ablation; if hyperthyroidism persists, these indices should be monitored every four to six weeks and thyroid hormone replacement started in the early stages of hypothyroidism.

Thyroidectomy

- This treatment option is preferred in patients with goiter-induced compressive symptoms and in patients with contraindications to radioactive iodine ablation or thionamides.

DRUG-ASSOCIATED HYPERTHYROIDISM

- Amiodarone-induced thyrotoxicosis can be classified as type 1 (thyroid hormone overproduction, treated with antithyroid medications) or type 2 (thyroid tissue destruction, treated with steroids).
- Amiodarone should not be discontinued unless it can be stopped safely, without triggering cardiac complications.
- Hyperthyroidism associated with use of other medications (e.g., lithium, interferon alfa, tyrosine kinase inhibitors, highly active antiretroviral therapy) is usually self-limited.
- The physician should determine whether the medication may be discontinued safely or replaced with a different medication.

Indications for treatment of endogenous subclinical hyperthyroidism in nonpregnant adults*

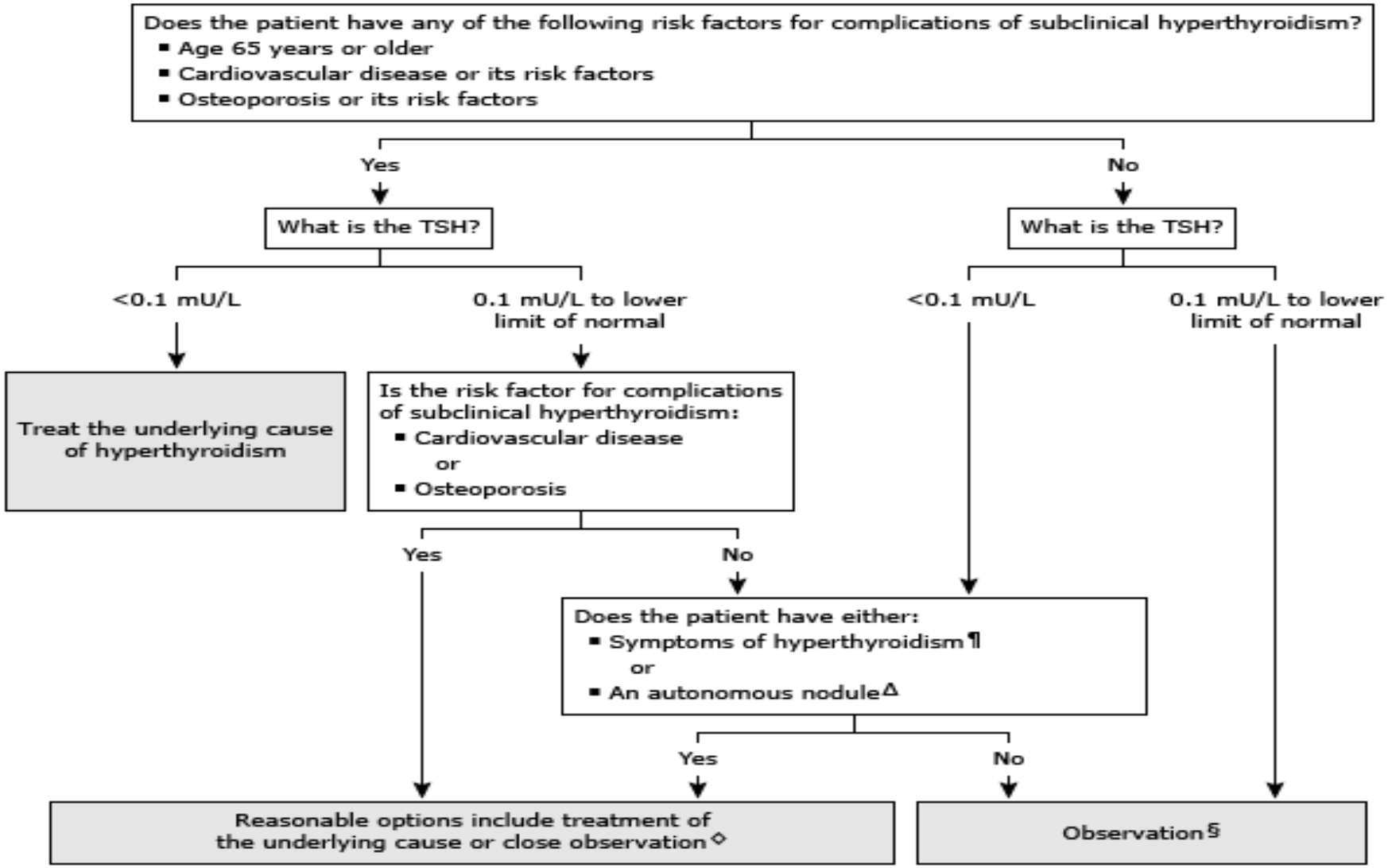

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Table 5. Pharmacologic Treatment of Hyperthyroidism

First-line agents	*Dosage*	*Adverse effects*	*Comments*
Beta blockers			
Atenolol	25 to 100 mg orally once per day	Exacerbation of congestive heart failure	Selective beta$_1$ blocker; safer than propranolol in asthma or chronic obstructive pulmonary disease; once-daily dosing improves compliance
Propranolol	Immediate release: 10 to 40 mg orally every eight hours Extended release: 80 to 160 mg orally once per day	Exacerbation of congestive heart failure or asthma	Decreases T_4 to T_3 conversion; nonselective beta blocker
Antithyroid medications			
Methimazole (Tapazole)	5 to 120 mg orally per day (can be given in divided doses)	Dose-related agranulocytosis	Contraindicated in the first trimester of pregnancy
Propylthiouracil	50 to 300 mg orally every eight hours	Agranulocytosis not related to dose; liver dysfunction; rash, including ANCA-associated vasculitis	Drug of choice in the first trimester of pregnancy; carries a higher risk of liver failure than methimazole
Radioactive iodine	Usually 10 to 30 millicurie, depending on uptake and the size of the thyroid gland	May aggravate hyperthyroidism in the early posttreatment period Causes hypothyroidism three to six months after treatment	Contraindicated in severe Graves orbitopathy and in patients who are pregnant or nursing

Ancillary agents			
Cholestyramine	1 to 2 g orally twice per day	Constipation or diarrhea; bloating	Binds thyroid hormones in the intestine and thus increases fecal excretion
Glucocorticoids	Prednisone: 20 to 40 mg orally per day for up to four weeks Hydrocortisone: 100 mg intravenously every eight hours with subsequent taper	Hyperglycemia in patients with diabetes mellitus, otherwise few short-term adverse effects	Used in severe hyperthyroidism or thyroid storm to reduce T_4 to T_3 conversion; also used in severe subacute thyroiditis
Nonsteroidal anti-inflammatory drugs	Depends on the specific agent	Nephrotoxicity; gastrointestinal bleeding	Treats pain in subacute thyroiditis
Supersaturated potassium iodide	5 drops orally every eight hours	May aggravate hyperthyroidism if given before an antithyroid agent	Give at least one hour after methimazole or propylthiouracil Do not give before radioactive iodine treatment

MONITORING AFTER TREATMENT

- **Thyroid function tests:** Whatever treatment is used, initial monitoring should consist of periodic clinical assessment and measurements of serum free T4 and often total T3 levels.

- Serum TSH concentrations should be interpreted with caution since they may remain low for several weeks after the patient becomes euthyroid and may even remain low transiently in patients who have become hypothyroid.

- **Thionamides:** Patients should have their thyroid function assessed at four- to six-week intervals until stabilized on maintenance thionamide therapy, then at three- to six-month intervals.

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Clinical features of thyroid storm	
Precipitating factors	• Thyroid or non-thyroid surgery • Acute illness (eg, trauma, infection), childbirth • Acute iodine load (eg, iodine contrast)
Clinical presentation	• Fever as high as 40-41.1 C (104-106 F) • Tachycardia, hypertension, congestive heart failure, cardiac arrhythmias (eg, atrial fibrillation) • Agitation, delirium, seizure, coma • Goiter, lid lag, tremor, warm & moist skin • Nausea, vomiting, diarrhea, jaundice
Treatment	• Beta blocker (eg, propranolol) to ↓ adrenergic manifestations • PTU followed by iodine solution (SSKI) to ↓ hormone synthesis & release • Glucocorticoids (eg, hydrocortisone) to ↓ peripheral T4 to T3 conversion & improve vasomotor stability • Identify trigger & treat, supportive care

PTU = propylthiouracil; **SSKI** = potassium iodide.

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Hypothyroidism

Etiology

- Hypothyroidism is almost always from a single cause: failure of the thyroid gland from burnt-out Hashimoto thyroiditis.
- The acute phase is rarely perceived.

Occasionally patients have hypothyroidism from:

- Dietary deficiency of iodine
- Amiodarone

What to Look for in Hypothyroidism and Hyperthyroidism	
Hypothyroidism	**Hyperthyroidism**
Bradycardia	Tachycardia, palpitations, arrhythmia (atrial fibrillation)
Constipation	Diarrhea (hyperdefecation)
Weight gain	Weight loss
Fatigue, lethargy, coma	Anxiety, nervousness, restlessness
Decreased reflexes	Hyperreflexia
Cold intolerance	Heat intolerance
Hypothermia (hair loss, edema)	Fever

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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

What Is the Most Likely Diagnosis?

- Hypothyroidism is characterized by almost all bodily processes being slowed down- except menstrual flow, which is increased.
- When TSH is very high (more than double the upper limit of normal) with normal T4, replace hormone.
- When TSH is less than double the normal, get antithyroid peroxidase/antithyroglobulin antibodies.
- If antibodies are positive, replace thyroid hormone.

High TSH (double normal) + normal T4 = treatment

Antithyroid peroxidase antibodies tell who needs thyroid replacement when T4 is normal and TSH is high.

Management

Diagnostic tests

- All thyroid disorders are best tested first with a TSH.
- If the TSH level is suppressed, measure free T4levels.
- TSH levels are markedly elevated if the gland has failed.

Treatment

- Replacing thyroid hormone with thyroxine (synthroid) is sufficient.

Dose and monitoring

- Initial dose: The average full replacement dose of T4 in adults is approximately 1.6 mcg/kg body weight per day (112 mcg/day in a 70-kg adult), but the range of required doses is wide, varying from 50 to ≥200 mcg/day.
- Older patients or those with coronary heart disease, in whom the duration of hypothyroidism is unknown, should be started on a lower dose (25 to 50 mcg daily).
- T4 (tablets, gel capsules, or liquid) should be taken on an empty stomach with water, ideally 30 to 60 minutes before breakfast.

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Initial monitoring and dose adjustments

- The patient with symptomatic improvement should be re-evaluated and serum TSH measured in four to six weeks.
- If the TSH remains above the reference range, the dose of T4 can be increased by 12 to 25 mcg/day in older patients, or it can be increased by a higher dose in younger patients.
- The patient will require a repeat TSH measurement in six weeks.
- The patient with persistent symptoms after two to three weeks should be reevaluated and a serum free T4 and TSH measured in three weeks.
- This process of increasing the dose of T4 every three to six weeks should continue, based upon periodic measurements of serum TSH until the high values of TSH return to the reference range.
- After identification of the proper maintenance dose, the patient should be examined and serum TSH measured once yearly or more often if there is an abnormal result or a change in the patient's status.

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Major drug interactions of levothyroxine	
↓ levothyroxine absorption	• Bile acid binding agents (eg, cholestyramine) • Iron, calcium, aluminum hydroxide • Proton pump inhibitors, sucralfate
↑ TBG concentration	• Estrogen (oral), tamoxifen, raloxifene • Heroin, methadone
↓ TBG concentration	• Androgens, glucocorticoids • Anabolic steroids • Slow-release nicotinic acid
↑ thyroid hormone metabolism	• Rifampicin • Phenytoin • Carbamazepine

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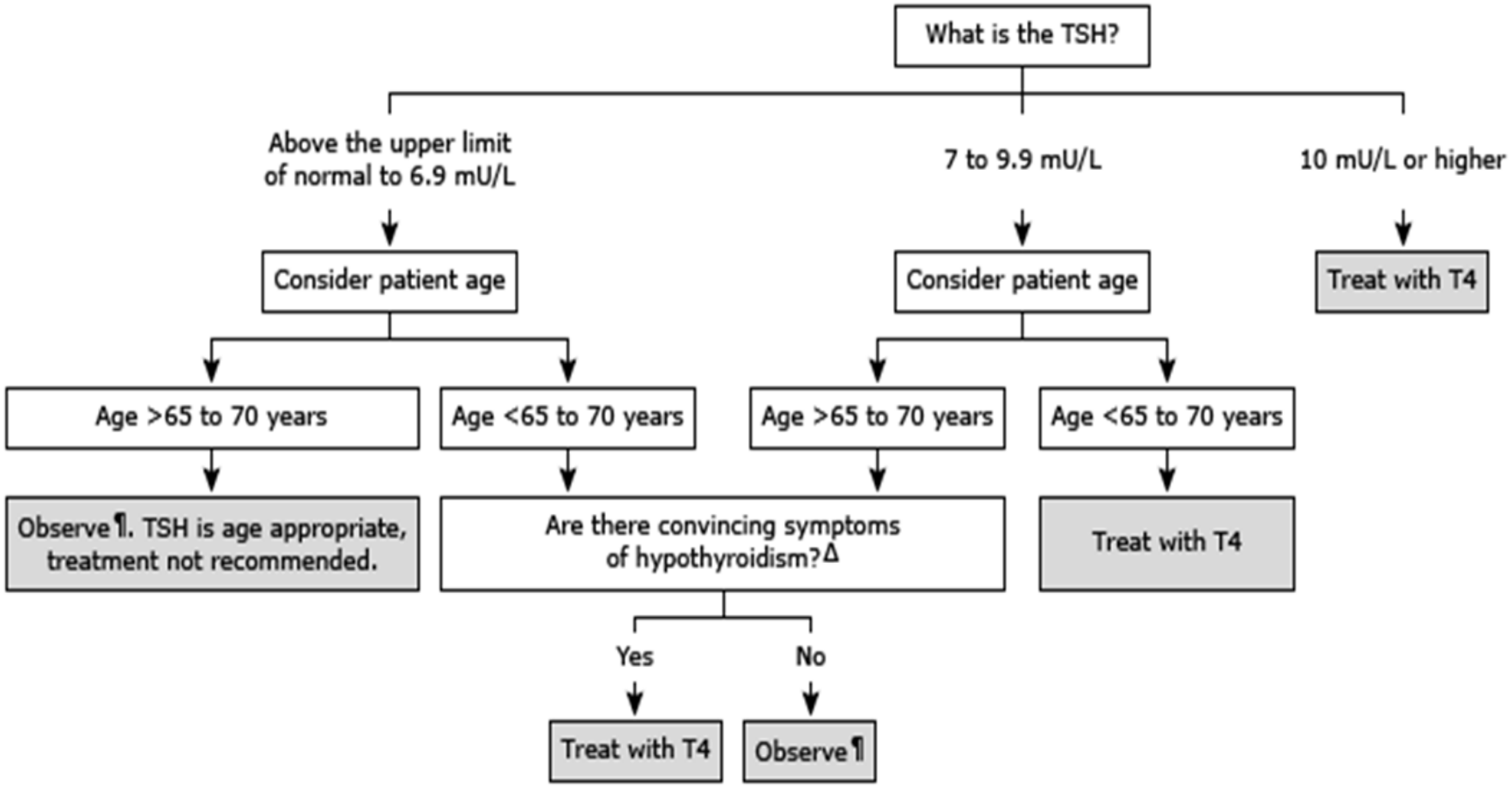
Indications for thyroid hormone replacement in nonpregnant adults with subclinical hypothyroidism*



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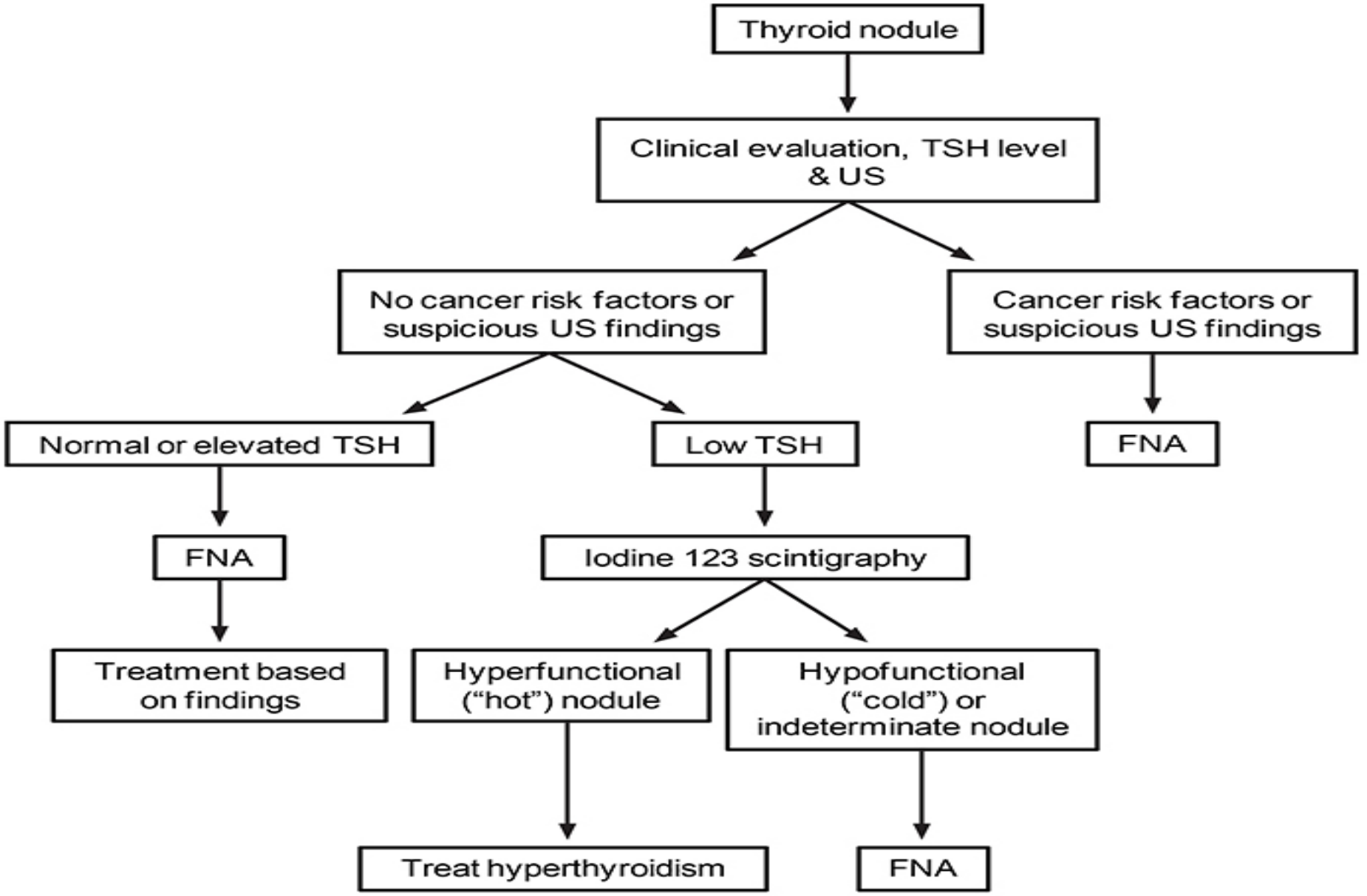

FNA = fine needle aspiration; **US** = ultrasound.

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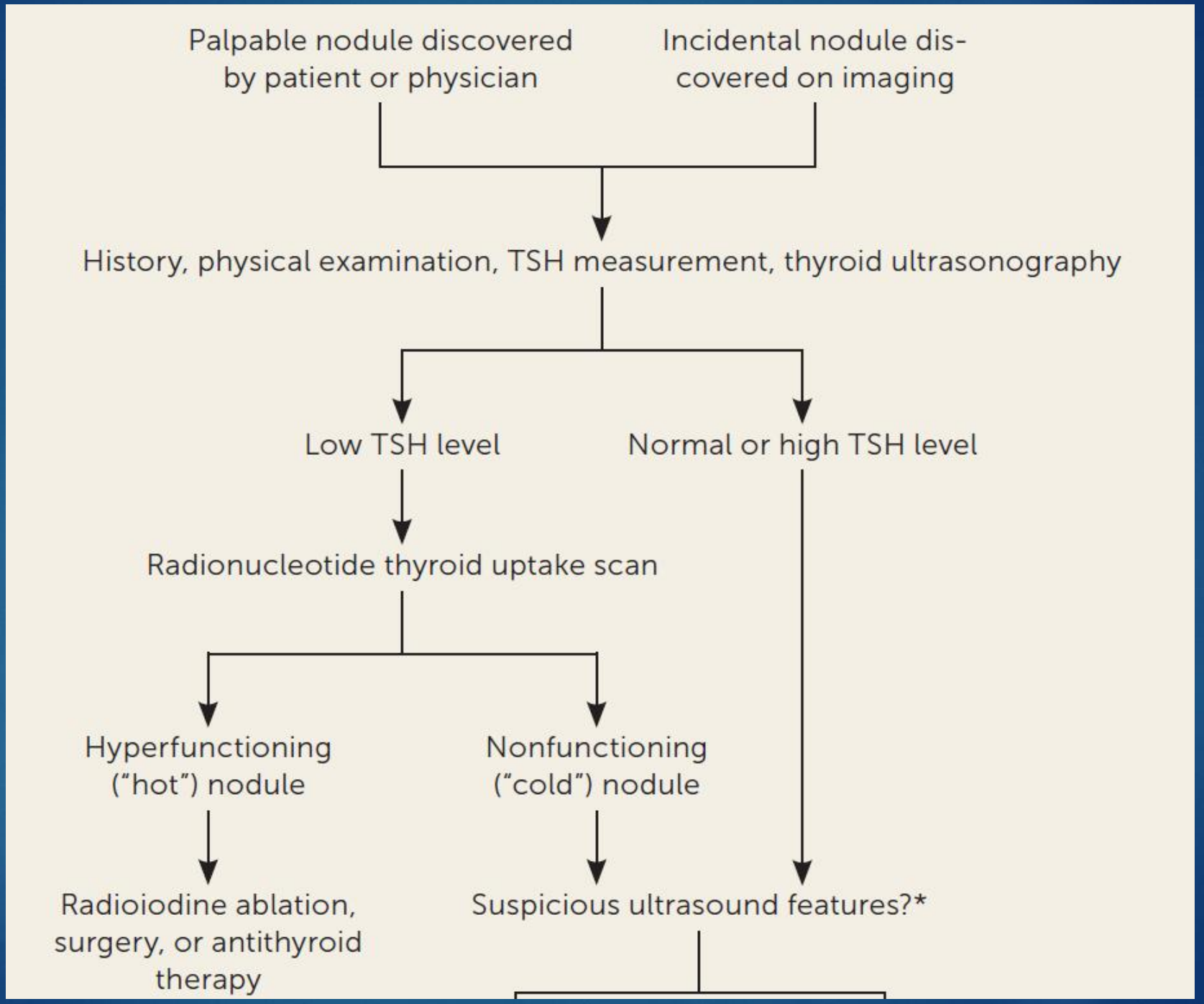
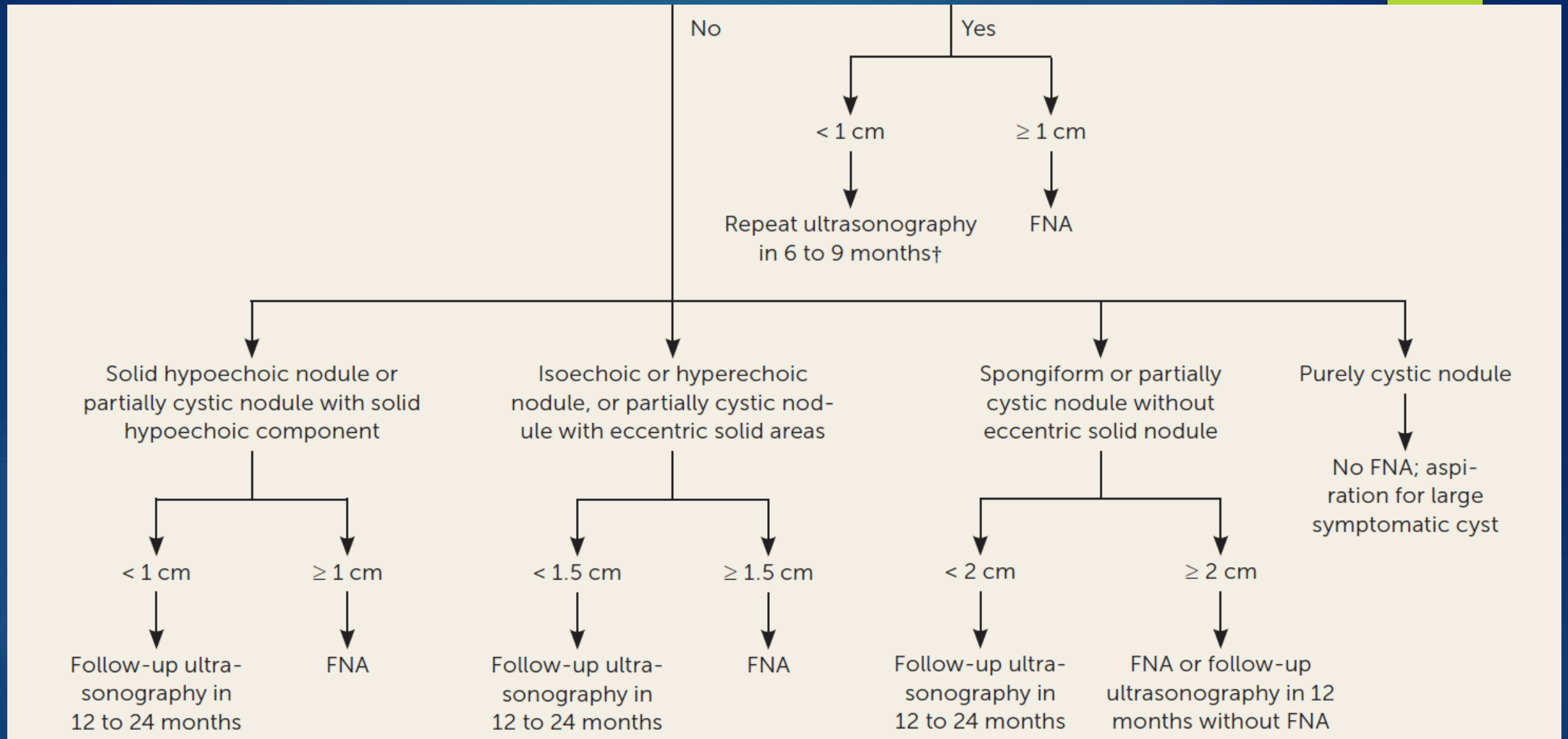

Palpable nodule discovered by patient or physician
Incidental nodule discovered on imaging
History, physical examination, TSH measurement, thyroid ultrasonography
Low TSH level
Normal or high TSH level
Radionucleotide thyroid uptake scan
Hyperfunctioning ("hot") nodule
Nonfunctioning ("cold") nodule
Radioiodine ablation, surgery, or antithyroid therapy
Suspicious ultrasound features?*



FNA = fine-needle aspiration; TSH = thyroid-stimulating hormone.

*—Irregular margins, microcalcifications, nodule taller than wide, extrathyroidal extension, disrupted rim calcification, or cervical lymphadenopathy.
†—Except when ultrasonography shows extrathyroid extension or cervical lymphadenopathy, in which case FNA should be performed. FNA can be considered for younger patients or if the patient requests it.

Bethesda System for Reporting Thyroid Cytopathology

Bethesda category	Cytologic diagnosis	Risk of malignancy (%)
1	Nondiagnostic or unsatisfactory	1 to 4
2	Benign	0 to 3
3	Atypia of undetermined significance or follicular lesion of undetermined significance	5 to 15
4	Follicular neoplasm or suspicious for follicular neoplasm	15 to 30
5	Suspicious for malignancy	60 to 75
6	Malignant	97 to 99

Clinical Scenario

- A 46-year-old woman comes to the office because of a small mass she found on palpation of her own thyroid. A small nodule is found in the thyroid. There is no tenderness. She is otherwise asymptomatic and uses no medications.
- What is the most appropriate next step in the management of this patient?

a. Fine-needle aspiration

b. Radionuclide iodine uptake scan

c. T4 and TSH levels

d. Thyroid ultrasound

e. Surgical removal (excisional biopsy)

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Types of thyroid malignancies	
Epithelial (thyroid follicular cells) (90%-95%)	• **Papillary** (>70%) • Follicular • Anaplastic
Parafollicular C-cells (3%-4%)	• Medullary thyroid cancer
Other cells (<5%)	• Lymphoma • Sarcoma • Metastatic (renal, breast, melanoma, colon)

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