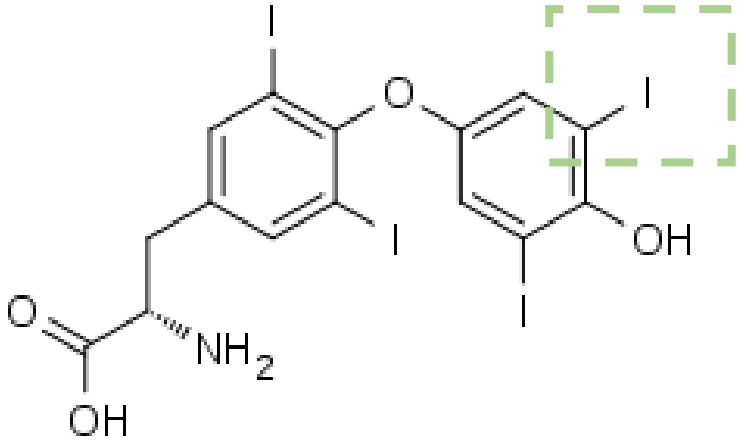
Hyperthyroidism-- Diagnosis and Management

for Visual Learners

Jeayoung Park MD

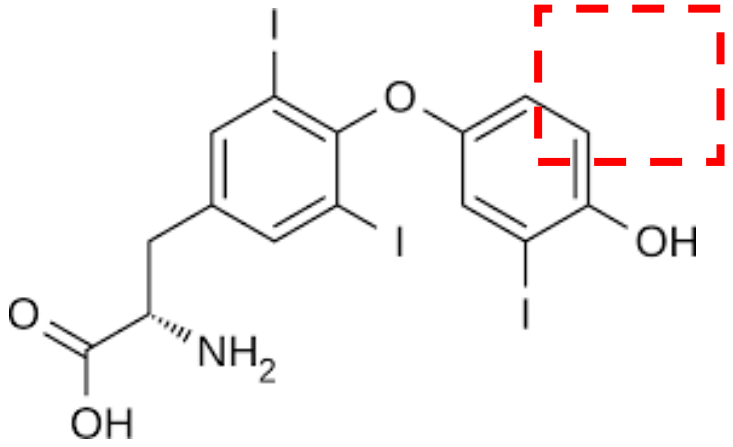
<Definitions>



Thyroxine (T4)

Weaker, less active, more numerous

>95% of T4 is bound to TBG.
Free T4 is typically measured rather than Total T4



Triiodothyronine (T3)

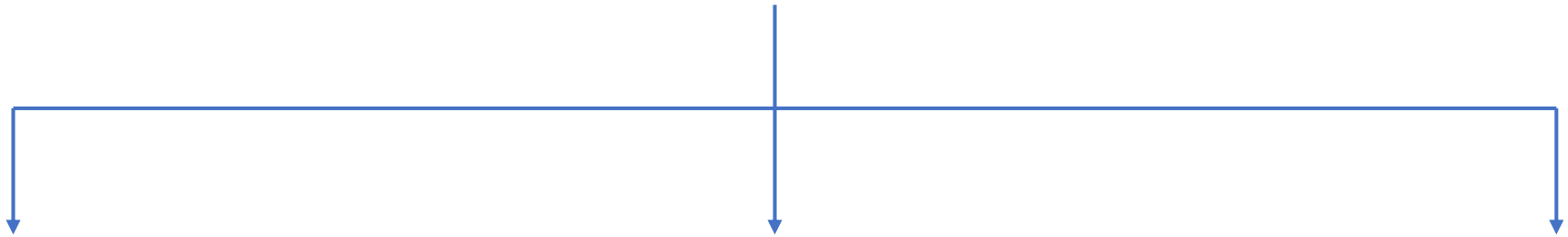
Stronger but less in quantity

Total T3 is measured
(Only because
free T3 assays are inaccurate)

<Definitions>

Thyrotoxicosis = ↑ levels of thyroxine (T4), triiodothyronine (T3), or both, for any cause.

Does not imply that a patient is markedly symptomatic or “toxic”



Hyperthyroidism

: Thyroid is actively overproducing thyroid hormone

-> Continued hyperthyroidism unless treated

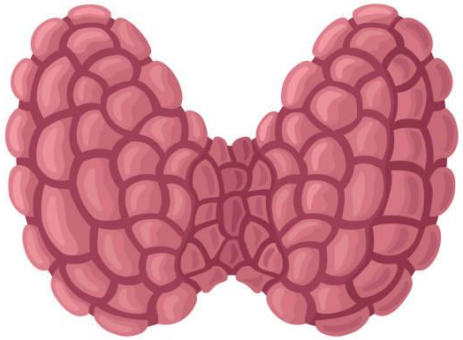
Thyroiditis

: There is leakage of pre-formed thyroid hormone due to inflammation

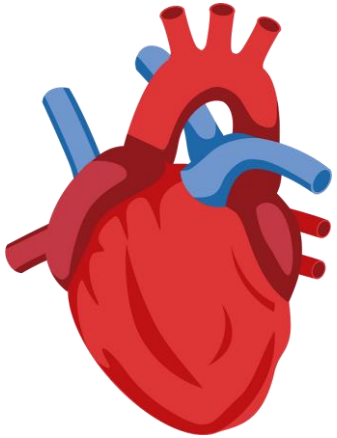
-> Spontaneous progression to hypothyroid or euthyroid state depending on degree of damage

Surreptitious/ Exogenous

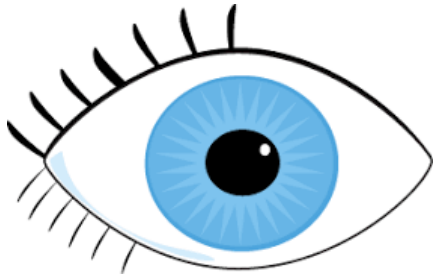
<Why do we care?>



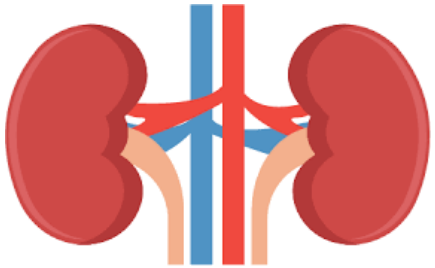
Hyperthyroidism



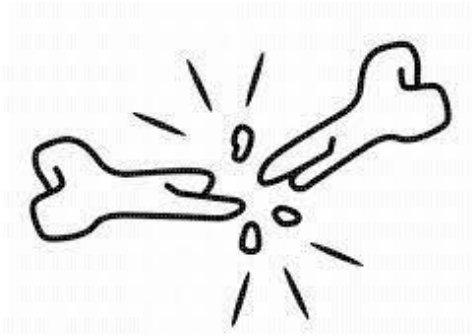
Cardiomyopathy
Atrial Fibrillation



Thyroid Eye Disease

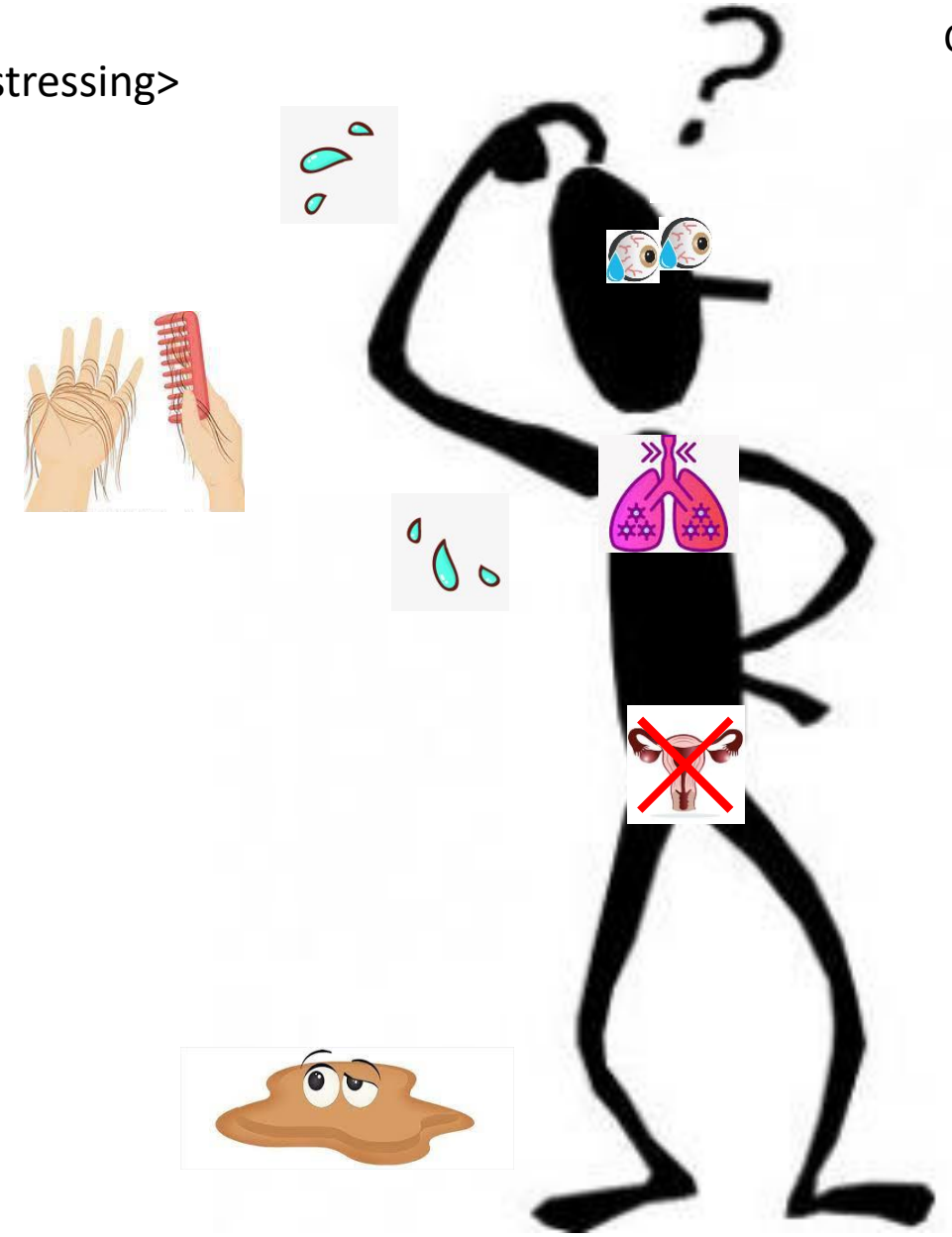


RAAS Activation
Hypertension



Osteoporosis

<Symptoms can also be distressing>



Confusion, impaired memory

Dry and bulging eyes

Insomnia, agitation

Sweating, Heat intolerance

Dyspnea

Diarrhea/hyperdefecation

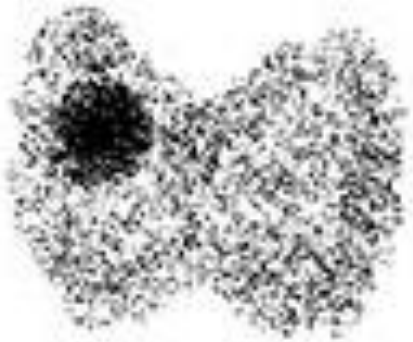
Amenorrhea/anovulation

Hair thinning/hair loss

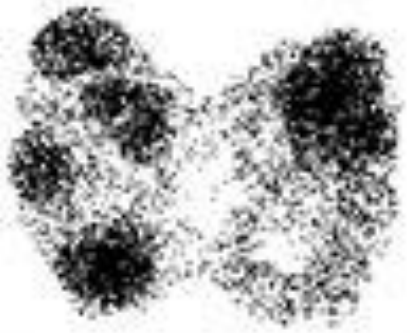
Note: neck swelling and pain is not a necessity

<3 Major Causes of Hyperthyroidism>

Graves' Disease



Toxic Adenoma

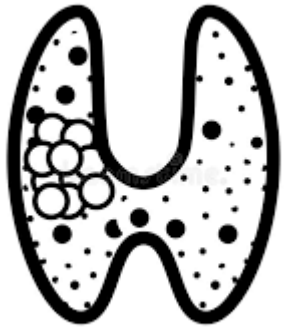


Toxic Multinodular Goiter

Path:	Autoimmune	Gain-of-function mutation of TSH receptor
Epidem:	Most common cause in 1st world (70-80%)	Most common cause in iodine-deficient countries (>50%)

<Rarer Causes of Hyperthyroidism>

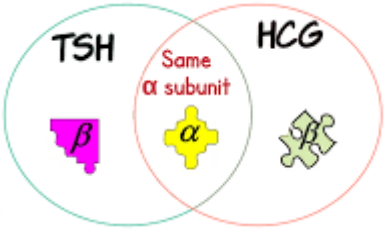
TSH-secreting Pituitary Tumor



Functional Thyroid Cancer (Follicular/Papillary)

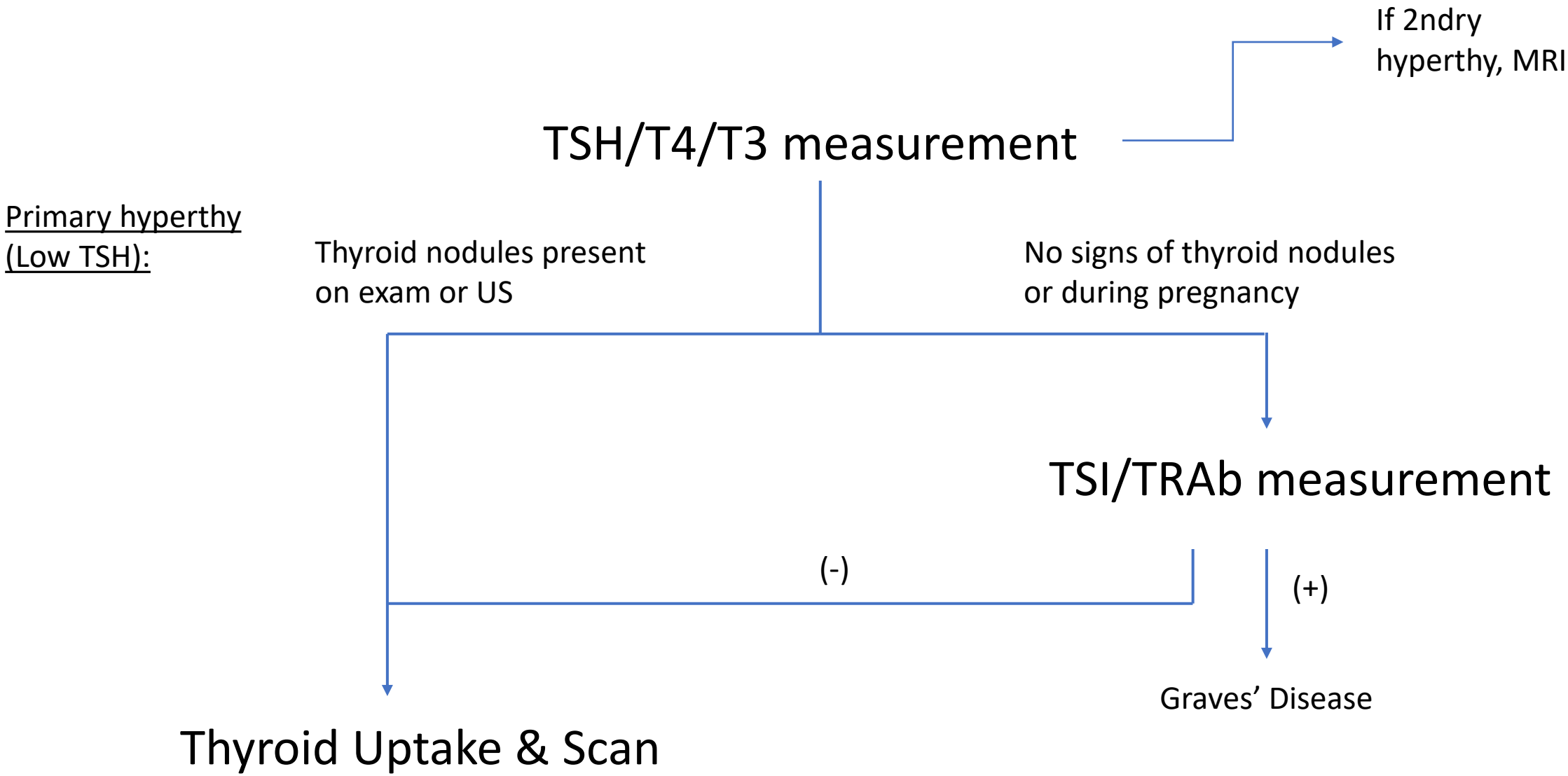
Choriocarcinoma Struma Ovarii

Germ Cell Tumor

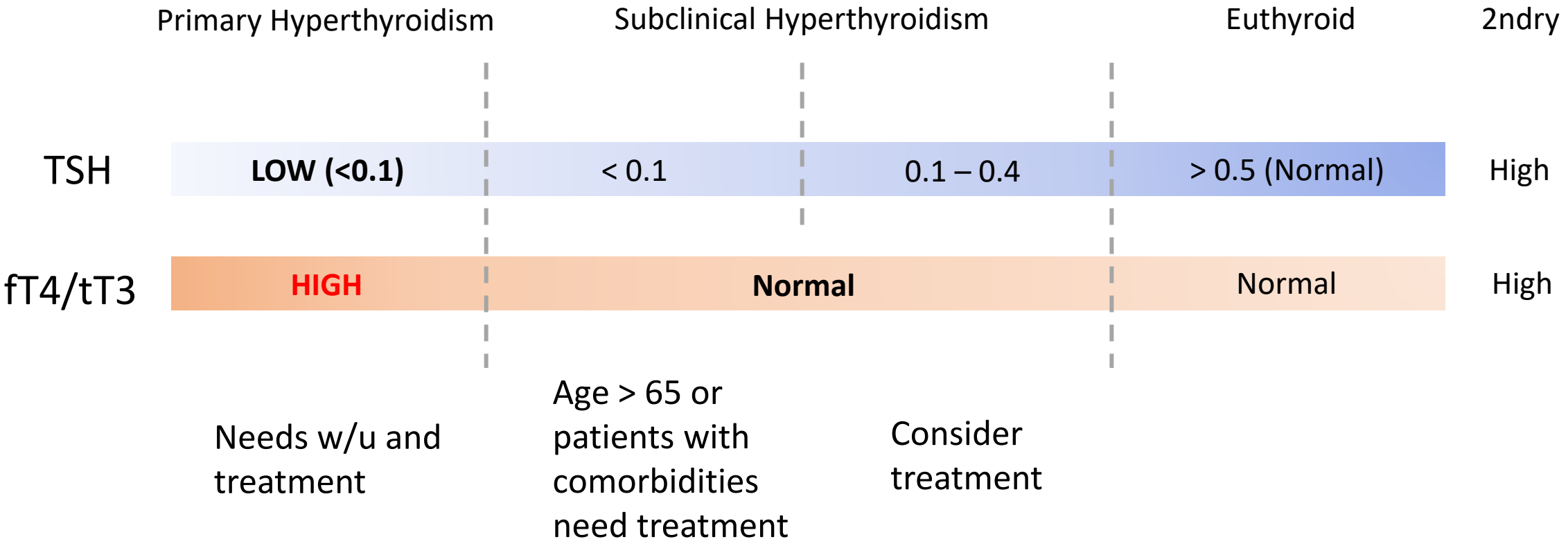


Diagnostic Workup

<Diagnostic Algorithm for Hyperthyroidism>



TSH vs T4/T3 shows the type of hyperthyroidism



T4 vs T3 rules out non-thyroidal illness

Primary Hyperthyroidism

T4

T3

Exogenous ingestion, Amiodarone, or Non-thyroidal illness

T4

~~T3~~

Exogenous: levothyroxine=T4

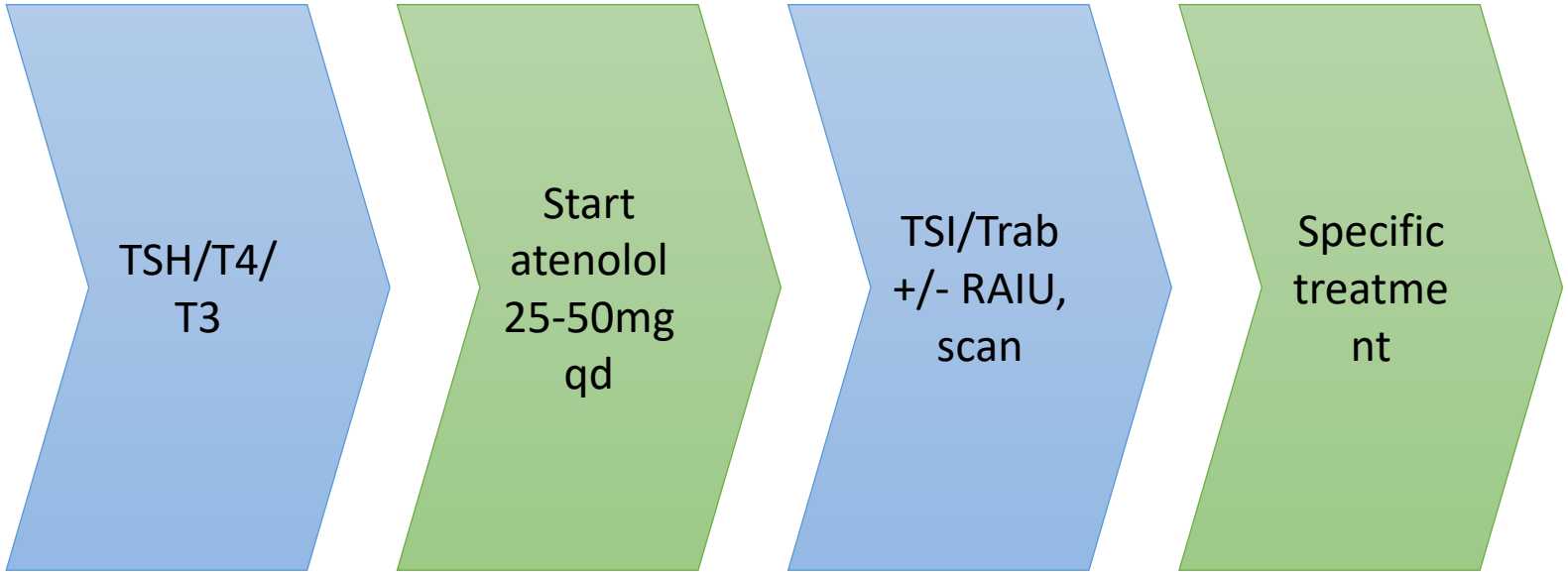
Amio/non-thy: decreased peripheral conversion

In real primary hyperthyroidism, typically both free T4 AND total T3 are elevated. Typically the T3/T4 ratio exceeds 20.

So always order TSH, free T4, and total T3.

Once the diagnosis of hyperthyroidism is established,

Start symptom control with beta-blockers (atenolol) before further workup.



If there is primary hyperthyroidism but no obvious nodules on exam…..

TSI (thyroid stimulating Ig)/TRAb(Thyroid receptor antibody) measurement

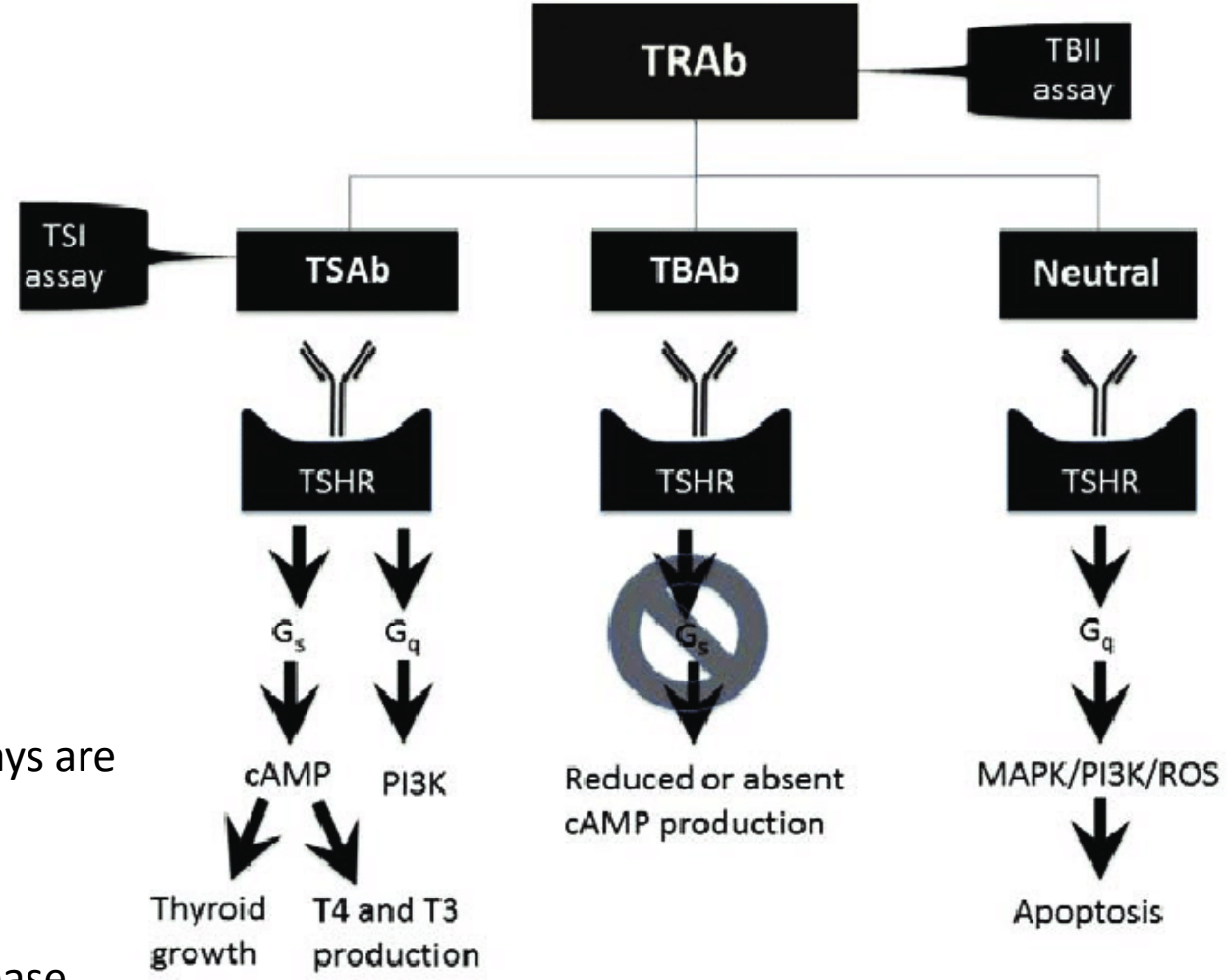
Indicated for patients without thyroid nodules on exam, or patients who are pregnant.

Or if the patient has obvious thyroid eye disease, should start with TSI/TRAb.

WHY: Can rule in/out Graves' disease ***without*** radioactive uptake and scan.
(SN=97%, SP=99%)

TSI assays:

Specific to stimulating antibodies, measures cAMP production



TBII (thyrotropin-binding inhibitory immunoglobulin) assays:

Measure ALL types of TRAb

Typically TBII and TSI assays are ordered together

Positive TBII/TSI assay is diagnostic of Graves' disease

-

Kotwal, Anupam & Stan, Marius. (2018). Thyrotropin Receptor Antibodies—An Overview. Ophthalmic Plastic and Reconstructive Surgery. 34. 1. 10.1097/IOP.0000000000001052.

If TSI/TRAb is unclear… or if there is an obvious nodule

Thyroid Uptake and Scan

…wait, what's the difference between uptake and scan?

Uptake

Quantitative measurement of uptake of ^{131}I or ^{123}I over the thyroid gland

HOT or **COLD**

= How likely is it malignant?

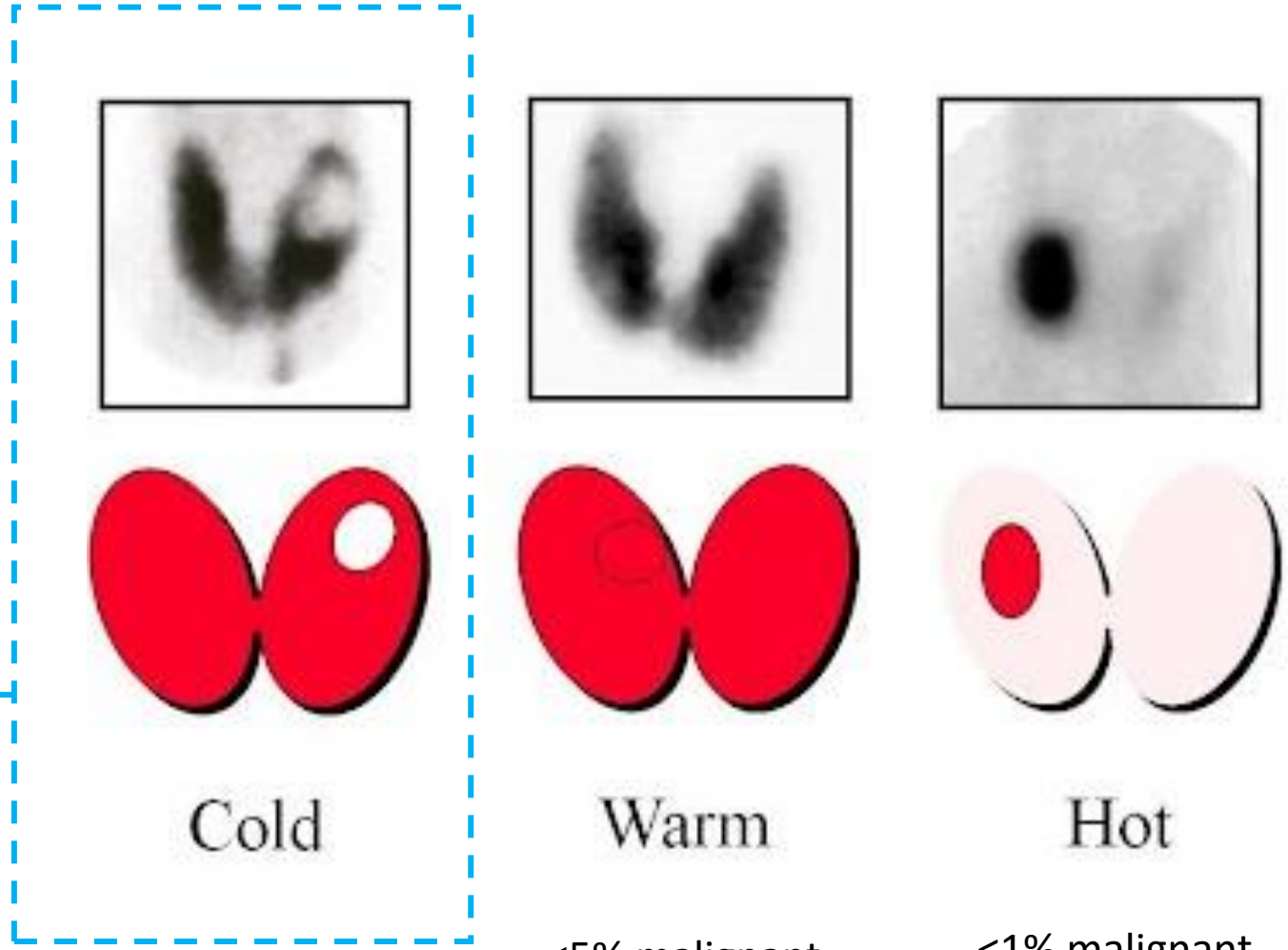
Scan

2-dimensional information for distribution of uptake over thyroid gland

Uniform vs *patchy*

= Is it Graves, TMNG, or toxic adenoma?

Thyroid Uptake

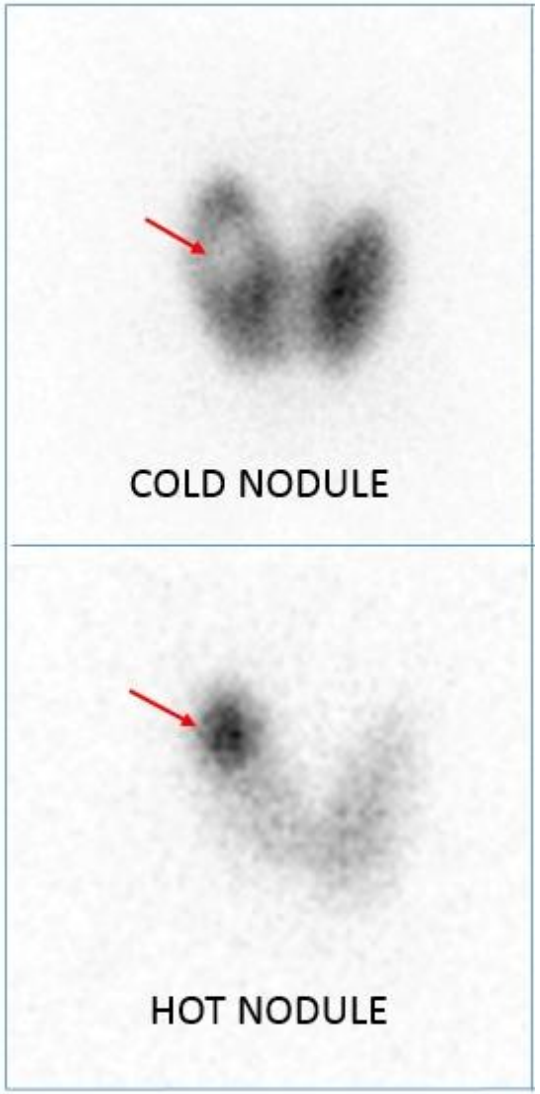


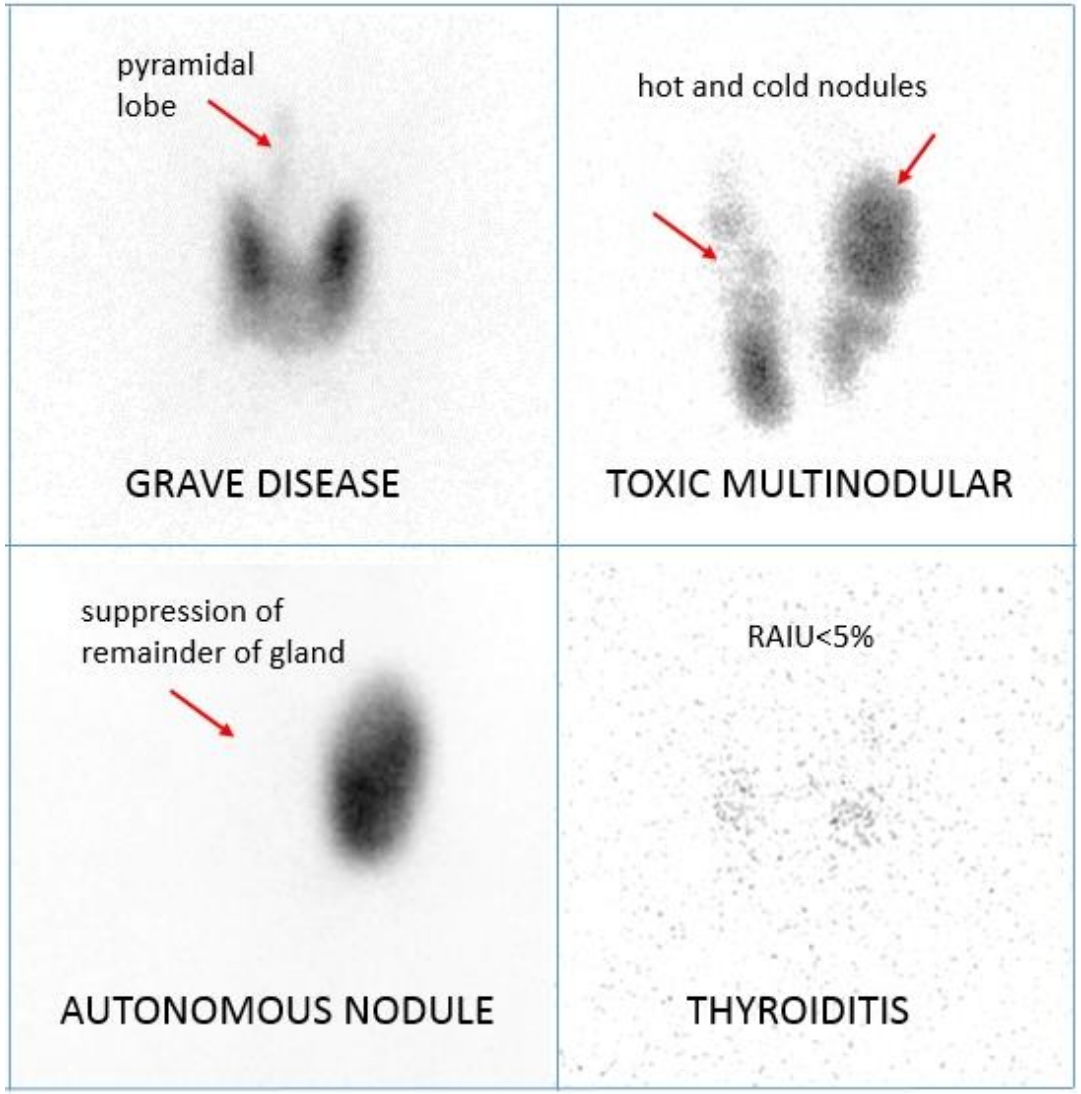
Need thyroid U/S for malignancy workup

<5% malignant

<1% malignant

Thyroid Uptake AND Scan





There is no thyroid uptake in thyroiditis!!

TSH/T4/T3 measurement

TSI/TRAb measurement

Thyroid Uptake & Scan

1) Diagnosis of hyperthyroidism made

2) Cause of hyperthyroidism identified

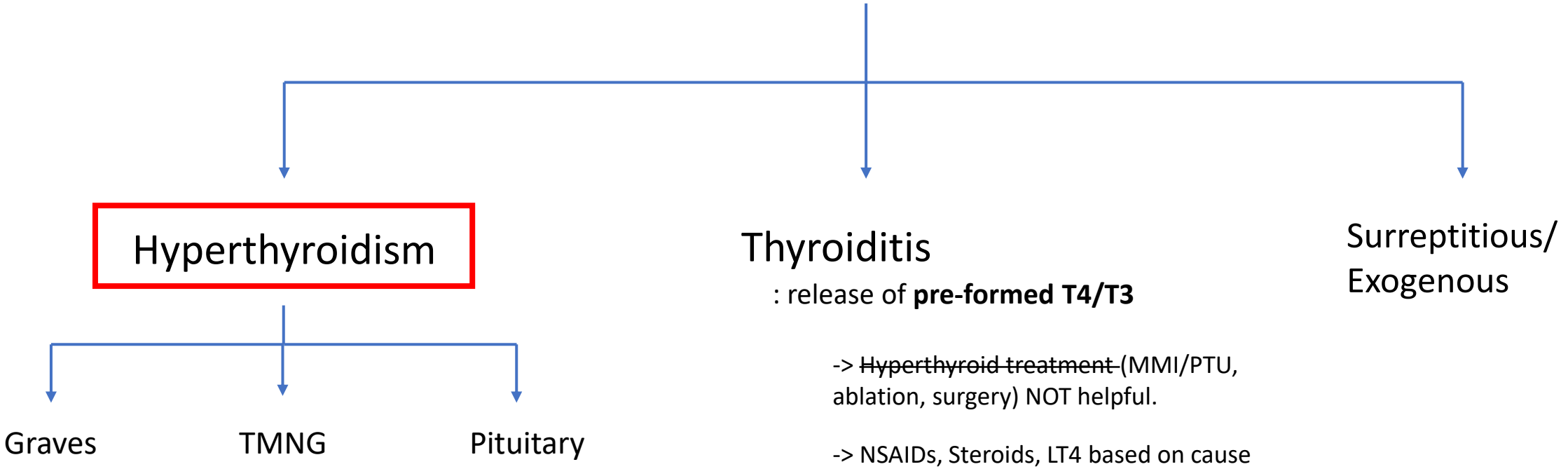
Now what?

Treatment Options

<Treatment overview>

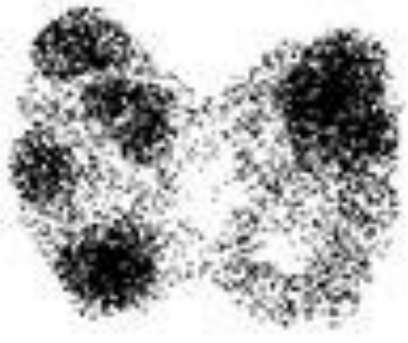
Thyrotoxicosis = ↑ levels of thyroxine (T4), triiodothyronine (T3), causes symptoms.

→ Treat with beta-blockers (atenolol preferred, beta-1 selective)



Graves' Disease

Toxic Adenoma



Toxic Multinodular Goiter

Antithyroid drugs (PTU, MMI)

Radioiodine ablation

Surgery

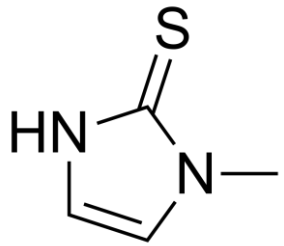
Radioiodine ablation

Surgery

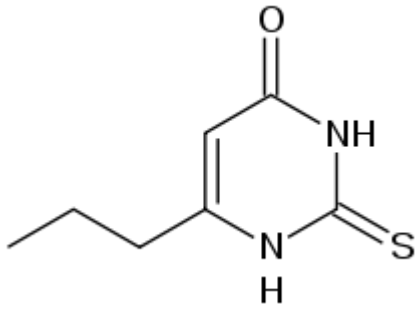
~~Antithyroid drugs~~ (PTU, MMI) only for pre-treatment prior to definitive therapy

Antithyroid medications (thionamides) are the initial treatment for Graves' disease

Graves' Disease



Methimazole (MMI)



Propylthiouracil (PTU)

MoA	Inhibition of TPO	TPO inhibition + decreased T4->T3 conversion
Indication	Always preferred	Only indicated in 1) 1st trimester pregnancy 2) Thyroid storm 3) MMI intolerance
Dosage	10-20mg qD	50-150mg TID

Graves’ Disease

Once either MMI or PTU is started,

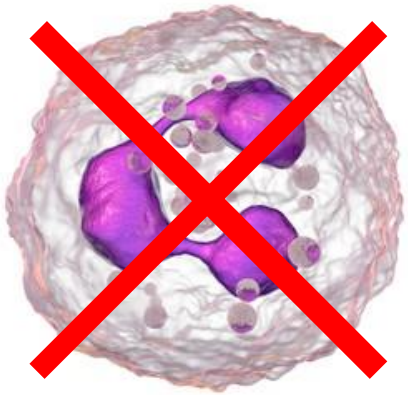
Check free T4 and total T3 every 2 weeks to titrate MMI or PTU.

Do NOT order TSH– can remain suppressed for months even with treatment.

Obtain CBC and LFTs during followup.

Side effects of Antithyroid medications:

Graves' Disease



Agranulocytosis

Hepatotoxicity

If there are significant side effects, patients may have to progress to other therapies.

Erythema Nodosum
ANCA Vasculitis

Arthropathy

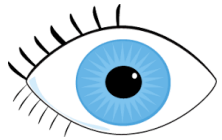
(If tolerated) Typically after 12-18 months,

Graves' Disease

30% long-term remission

20% reoccurence

50% need definitive therapy

	Radioiodine ablation (^{131}I)	**Thyroidectomy (Total)**
Indication	Preferred in non-pregnant patients without orbitopathy	 Pregnancy  Large Goiter  Thyroid Eye Disease (^{131}I WORSENS eye disease)
Side effects	Permanent hypothyroidism Concern of radiation Needs 6-18 weeks to work	Permanent hypothyroidism Higher complications Cost

Treatment Algorithm for Graves'

Graves' Disease

1) Symptom control: atenolol 25-50mg qD

+

2) Anti-thyroid medication (PTU, MMI)

↓ ⇢ (50% remission)

3) Definitive Therapy

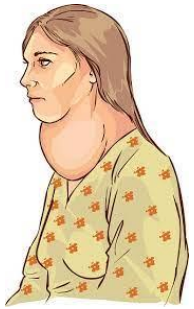
↓

Radioiodine ablation Total Thyroidectomy

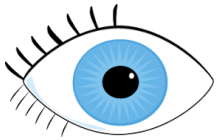
↓

Prognosis: Long-term hypothyroidism--with need for Levothyroxine supplementation

Pregnancy



Large Goiter



Thyroid Eye Disease

(^{131}I WORSENS eye disease)

Graves' Disease

Etc treatments (not commonly used):

- Iodine elixirs: mostly used 1) pre-operatively to decrease vascularity, or 2) if there is PTU/MMI intolerance.
- Glucocorticoids: used for thyroid storm, rarely used outpatient
- Cholestyramine: used as adjunct for MMI, but again mostly in thyroid storm
- ~~Rituximab~~: can cause sustained remission but cost and side effects are severe
- ~~Lithium~~: not used due to toxicity

Antithyroid medications (thionamides) are the main treatment for Graves' disease

Unlike Graves' disease, the cornerstone of TMNG and Toxic Adenoma treatment is **surgery or radioiodine ablation.**

Spontaneous resolution with ~~antithyroid medications (MMI/PTU)~~ is ***NOT*** achieved because there is an underlying mutation of the TSHR itself.

Toxic Multinodular Goiter

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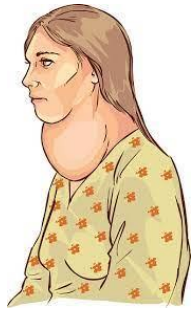
Autonomous Toxic Nodule

Surgery



Obstructive or very large goiters

Coexisting malignancy or hyperparathyroidism

Pregnancy
Need for rapid correction of hyperthyroidism

Radioiodine ablation

Patients who do not meet criteria for surgery

More commonly used than surgery due to lower cost and less side effects

Treatment Algorithm for TMNG/AFTN

Toxic Multinodular Goiter

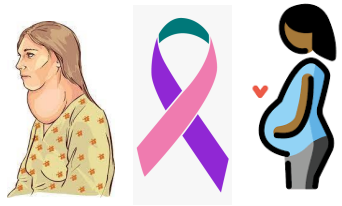
+

Autonomous Toxic Nodule

Symptom control: atenolol 25-50mg qD

+/- Pre-treatment with PTU/MMI if severe hyperthyroidism

Thyroidectomy



Radioiodine ablation

For Multinodular goiter:

Total thyroidectomy

For Toxic adenoma:

Ipsilateral lobectomy

^{131}I preferentially accumulates in the active thyroid nodules

Oftentimes the remaining thyroid remain intact

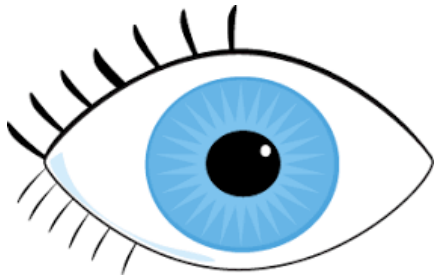
Prognosis:

Long-term hypothyroidism

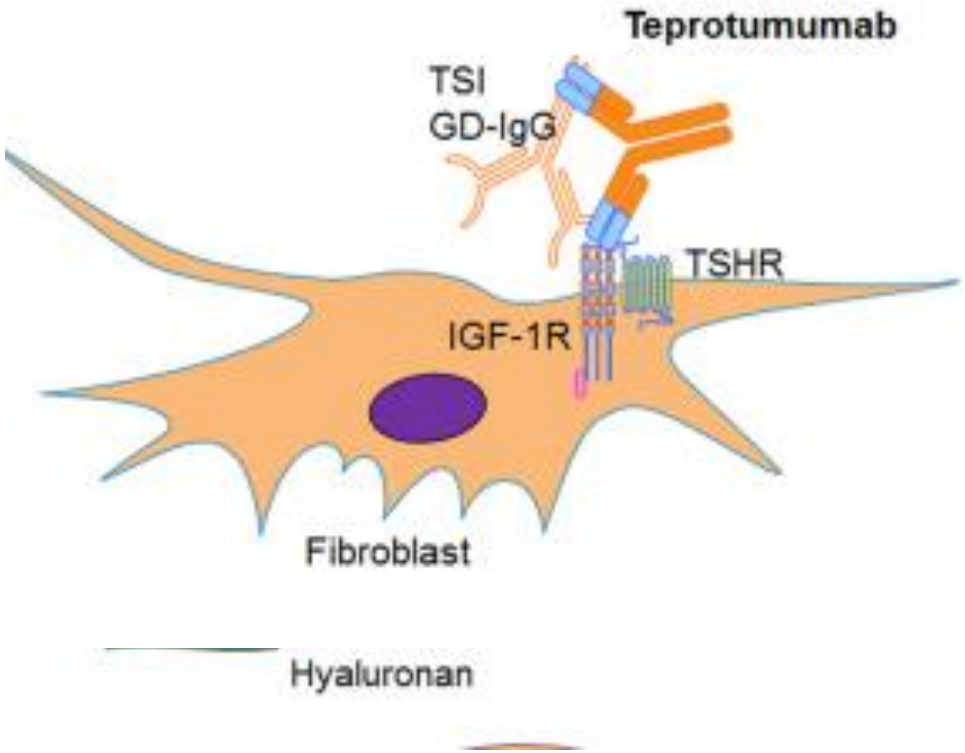
Higher chance of euthyroid

Teprotumumab (tepezza): fully human monoclonal antibody against IGF-1.

Approved by FDA in January 2020 for treatment of thyroid eye disease.



Thyroid Eye Disease



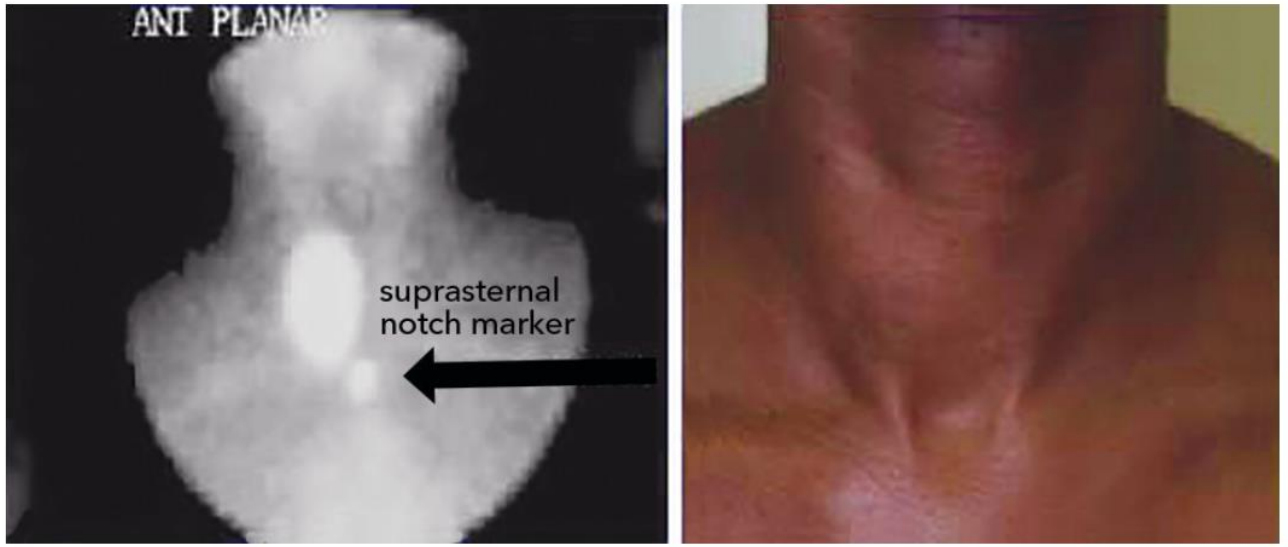
Steroids, surgery decompression, or conservative therapy with smoking cessation and oral PTU/MMI are other options.

MKSAP 2018 Question:

A 55-year-old woman is seen during a follow-up evaluation for hyperthyroidism that was diagnosed 1 week ago. Thyroid examination revealed a palpable right thyroid nodule.

Thyroid-stimulating hormone (TSH) was less than **0.01 µU/mL (0.01 mU/L),** free thyroxine (T4) and total triiodothyronine (T3) were **2.1 ng/dL (27.1 pmol/L)** and **210 ng/dL (3.2 nmol/L)**, respectively. Atenolol was prescribed, and thyroid scintigraphy with determination of radioactive iodine uptake was ordered.

On physical examination, vital signs are normal. The neck and corresponding thyroid technetium-99 scan is shown. **Uptake at 24 hours was 30% (normal 14% to 30%).**



Which of the following is the most appropriate management?

A. Fine-needle aspiration
B. Increase atenolol dose
C. Methimazole
D. Radioactive iodine (^{131}I) therapy

Which of the following is the most appropriate management?

A. Fine-needle aspiration
B. Increase atenolol dose
C. Methimazole
D. Radioactive iodine (^{131}I) therapy

Toxic adenoma and multinodular goiter are the second most common cause of hyperthyroidism overall and are most frequently seen in older adults. They are usually large and can be easily palpated on examination. **First-line treatment options include radioactive iodine therapy or surgery.** Radioactive iodine is the most commonly used first-line treatment.

Antithyroid drugs (methimazole) are **not** first line for managing hyperthyroidism because spontaneous remission does not occur and treatment would have to be continued indefinitely.

Autonomous nodules are associated with a very low risk of malignancy (<1%), and fine-needle aspiration biopsy is not indicated. Biopsies are often indeterminate and leads to unnecessary followup studies.

Increasing the atenolol dose is not the best management option. While β-blockers ameliorate adrenergic symptoms, they do not address the underlying cause. The patient had a normal BP and heart rate.

Summary

<Diagnosis>

- Obtain TSH, free T4, total T3. Isolated T4 elevation with normal TSH can be non-thyroidal illness.
- If the patient has nodules on exam, need uptake and scan.
- If the patient does not have obvious nodules and/or is pregnant, TSI/TRab studies should be done first.
- Finding the correct cause of hyperthyroidism is important as it changes management.

<Treatment>

- For symptomatic hyperthyroidism, beta-blockers can/should be started before completion of workup.
- Anithyroid medications are the cornerstone of Graves' treatment, and free T4, total T3, CBC, LFTs should be ordered to monitor response.
- Radioiodine ablation or thyroidectomy are the cornerstone of toxic adenoma or multinodular goiter treatment.
- Thyroidectomy is typically necessary for large goiters, concurrent malignancy, and pregnancy.

THANK YOU!

Any questions?