Navigating Through Common Thyroid Disorders

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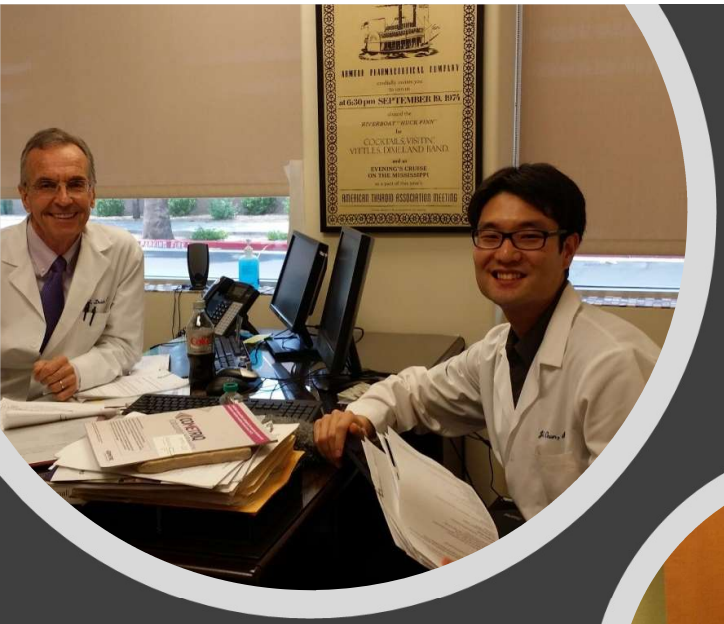
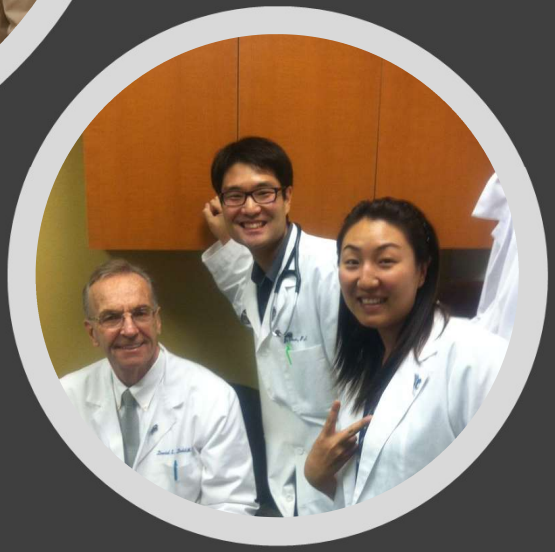
Disclosure

- None

*Employee of Corcept Therapeutics. No conflict of interest related to this topic.





Tribute

Daniel Duick, MD, MACE

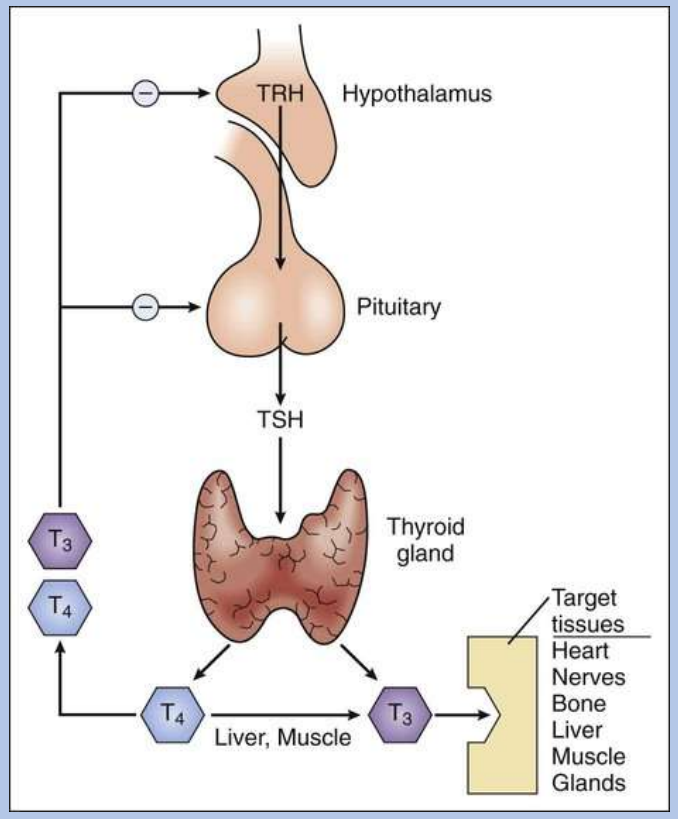
1941 – 2022

Objectives

- Review different thyroid function tests and order appropriate panel
- Understand the differences between synthetic (i.e., Levothyroxine) vs desiccated thyroid hormones (i.e., Armour thyroid)
- Strengthen your skills on working up low TSH
- Differentiate thyroid nodule(s) that can be monitored vs further evaluated

Common Thyroid Disorders

Hypothalamic-Pituitary-Thyroid Axis



- **Hypothyroidism**
  - Affects ~5% of the US population
  - 10x more common in women
  - More common after age 60 years
- **Hyperthyroidism (thyrotoxicosis)**
  - Affects ~1.2% of the US population
  - 2-10x more common in women
- **Nodular thyroid disease**
  - Affects 4-7% (as detected by palpation); 19–68% (as detected on ultrasound)
  - Malignant in 4.0% to 6.5%

T3 = triiodothyronine; T4 = thyroxine; TRH = thyrotropin releasing hormone; TSH = thyroid stimulating hormone

Case: 46yo female, annual exam

- Medical hx:
  - Hypothyroid diagnosed in her 20s
  - Lately, she's been noticing fatigue, hair thinning, dry skin, and trouble losing weight
  - Otherwise, non-contributory
- Current meds/OTC
  - Levothyroxine 50mcg, MVI, biotin
- Family hx:
  - Mom and maternal grandmother with hypothyroidism
- Physical examination
  - Normal thyroid exam, BMI 27. Otherwise, non-contributory

Q

- Which of the following thyroid tests would be least helpful for evaluating hypothyroidism?
  1. TSH
  2. Free T4
  3. Free T3
  4. Anti-thyroid peroxidase (TPO) antibodies

Thyroid Tests

- TSH
- Free T4
- Total T4
- Free T3
- Total T3
- T3 resin uptake
- Free thyroxine index (FTI)
- Reverse T3
- Urinary iodine

- Thyroglobulin
- Thyroglobulin ab
- Anti-TPO ab
- Thyroid stimulating immunoglobulin (TSI)
- Thyrotropin receptor antibody (TRAb)
- Thyroid binding inhibitory immunoglobulin (TBII)

- Thyroid ultrasound
- Radioactive iodine uptake (RAIU). Aka Thyroid uptake
- Thyroid scan (scintigraphy)
- Fine Needle Aspiration (FNA)
- Core biopsy
- Molecular testing

Tests for Common Thyroid Diseases

Hypothyroidism	Hyperthyroidism/ Thyrotoxicosis	Nodular Thyroid Disease
• TSH • Free T4 – During pregnancy, check FTI or total T4 (x 1.5 reference range) • Anti-TPO Ab - If needed	• TSH • Free T4 • Total T3 • TRAb or TSI – ESR/CRP if subacute thyroiditis is suspected – Thyroid ultrasound, uptake/scan if needed	• TSH (if low, follow hyperthyroid evaluation) • Thyroid/neck ultrasound • FNA/core biopsy if criteria are met

CRP = C–reactive protein; FNA = fine-needle aspiration; FTI = free thyroxine index; TPO = thyroid peroxidase; TRAb = thyroid stimulating hormone receptor antibody; TSH = thyroid stimulating hormone; TSI = thyroid stimulating immunoglobulin; ESR = erythrocyte sedimentation rate.

Adapted from Garber J, et al. *Endocr Pract*. 2012;18:988-1028.

Case (cont.)

- Current labs:
  - TSH 7.5 mIU/L (0.45-4.5)
  - FT4 2.5 ng/dL (0.8-1.8)
  - CBC/CMP/UA/iron/B12/vitD all WNL

Q

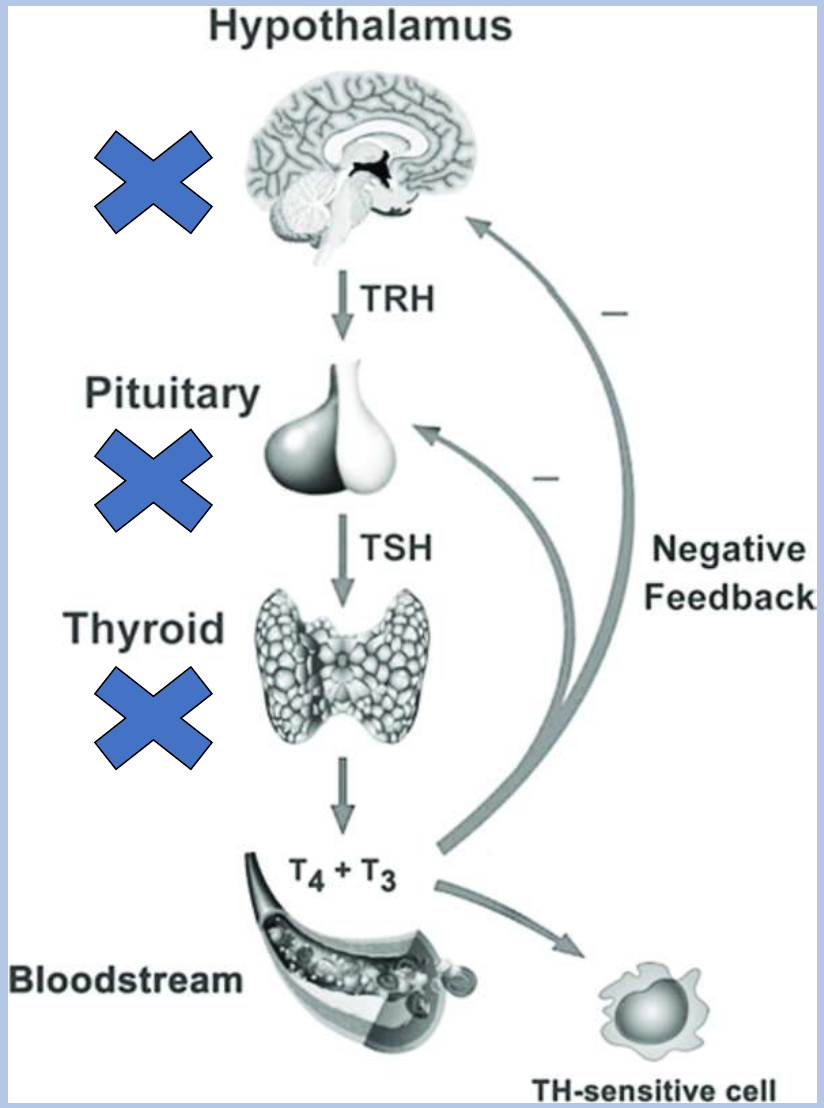
- Based on Emily's available thyroid labs, which of the following is the most likely diagnosis at this time?
  - TSH 7.5 mIU/L (0.45-4.5)
  - FT4 2.5 ng/dL (0.8-1.8)

A. Primary hypothyroidism
B. Primary hyperthyroidism
C. Secondary hypothyroidism
D. Secondary hyperthyroidism

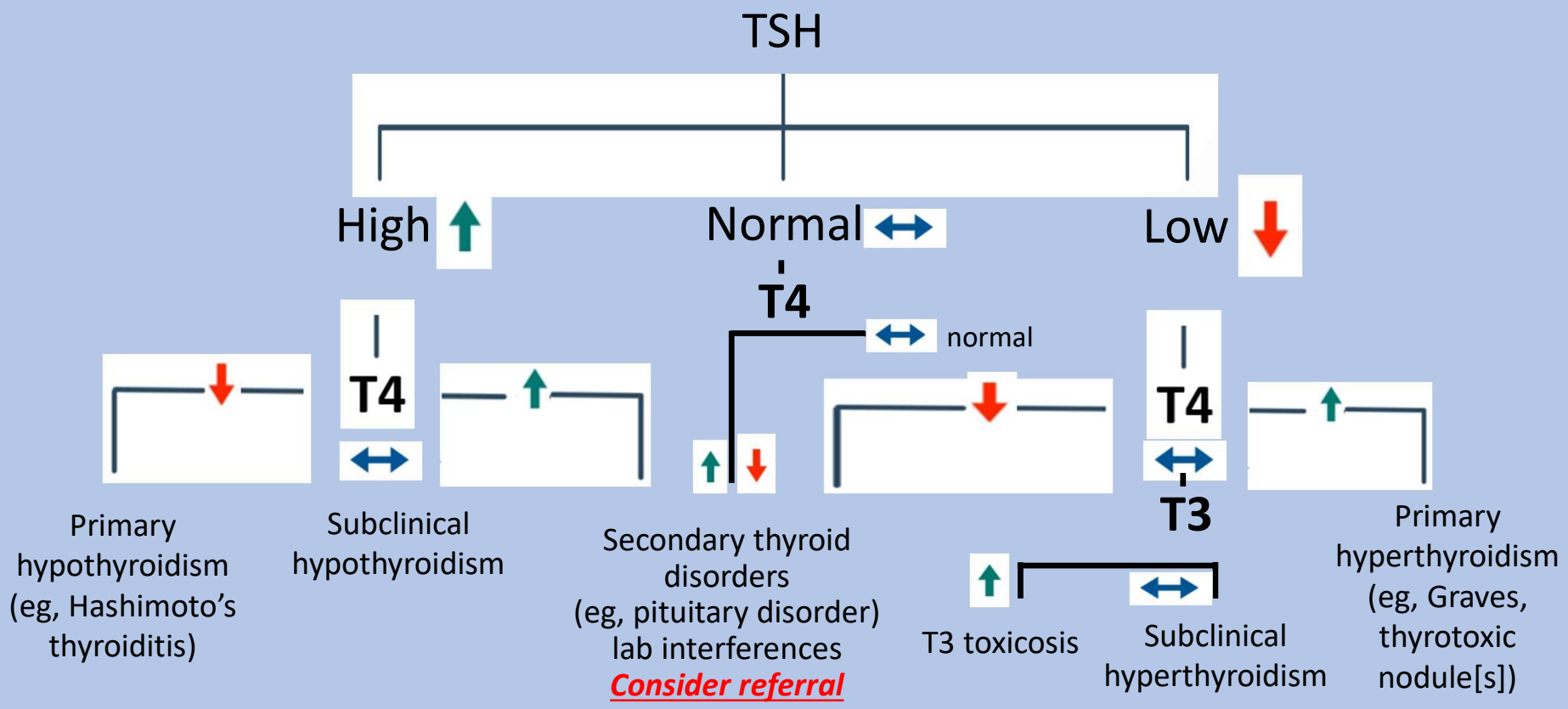
Tertiary

Secondary

Primary



Lab Interpretation



Case (cont.)

- Current labs:
  - TSH 7.5 mIU/L (0.45-4.5)
  - FT4 2.5 ng/dL (0.8-1.8)

  → Secondary hyperthyroidism
  → consider endocrine referral?

Q

Which vitamin B can interfere with thyroid lab assays?

A. Vitamin B1 (thiamine)

B. Vitamin B3 (niacin)

C. Vitamin B5 (pantothenic acid)

D. Vitamin B7 (biotin)

Biotin Interference in Thyroid Tests

- Daily requirement: 30 μg. OTC dose - up to 100 mg (3000x)
- Favorable safety reports with dose of 300 mg/d
- Interferes with many different lab tests (thyroid/steroid/polypeptide hormones, tumor markers, vitamins, infectious disease serologies)
- Interference in thyroid tests
  - May falsely lower TSH, PTH
  - May falsely elevate free T4, free T3
- Be aware! Ask the patient!
- For patients taking < 100 mg/day, stop biotin 48 h before testing (longer for higher doses)

Samarasinghe S, et al. *Endocr Pract*. 2017;23(8):989-998.

Case (cont.)

- Emily was asked to hold her MVI and biotin for 1 week and repeat her thyroid labs
- New labs:
  - TSH 1.7 mIU/L (0.45-4.5)
  - FT4 1.4 ng/dL (0.8-1.8)
- Emily asks about “natural thyroid hormones” as she has read on internet that it is better to take natural products

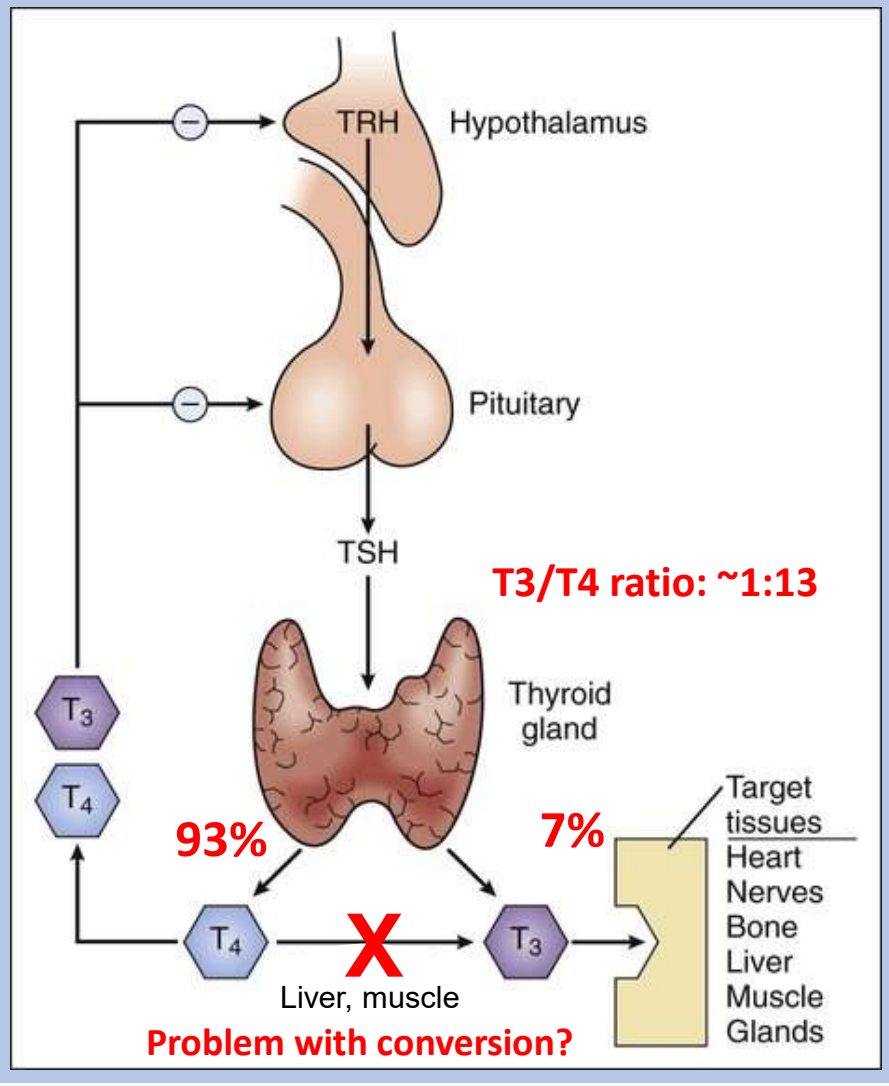
Hypothyroidism

- Common causes
  - Autoimmune disease (Hashimoto thyroiditis)–most common in US
  - Iodine deficiency–most common worldwide
  - Surgery/radiation therapy
  - Medications (eg, lithium)
- Treatment of choice: levothyroxine (LT4)*
  - What about T3?
  - Evidence does not support use of LT3/LT4 combinations†

*LT3 = liothyronin*e

*Strong recommedation. Moderate quality evidence (Jonklaas J et al. *Thyroid*. 2014;24(12):1670-1751).

†Grade B recommendation because of unresolved issues raised by studies that report some patients prefer, and some patient subgroups may benefit from, LT4 and LT3 combination (Garber J, et al. *Endocr Pract*. 2012;18(6):988-1028).



T3-T4 Pharmacology

- Thyroxine (T4)
  - Half life = 7 days
  - Stable/long acting
- Triiodothyronine (T3)
  - 4x potent than T4
  - Half life = 0.75 days
  - Onset of action: 2–4 hours
  - Rapidly absorbed
  - Marked blood level fluctuations
  - May falsely suppress TSH if taken close to bloodwork

Q

- The T3:T4 ratio in humans is about 1:13.
  What is the T3:T4 ratio in desiccated thyroid hormones (eg, Armour Thyroid, Nature-Throid)?

A. 1:1
B. 1:4
C. 1:10
D. 1:20

T3/T4

- Armour thyroid
  - 1grain=60mg: contains T3 9mcg, T4 38mcg
- Nature-throid & Westhroid
  - 1grain=65mg: contains T3 9mcg, T4 38mcg

* T3:T4 ratio in desiccated thyroid= 1:4

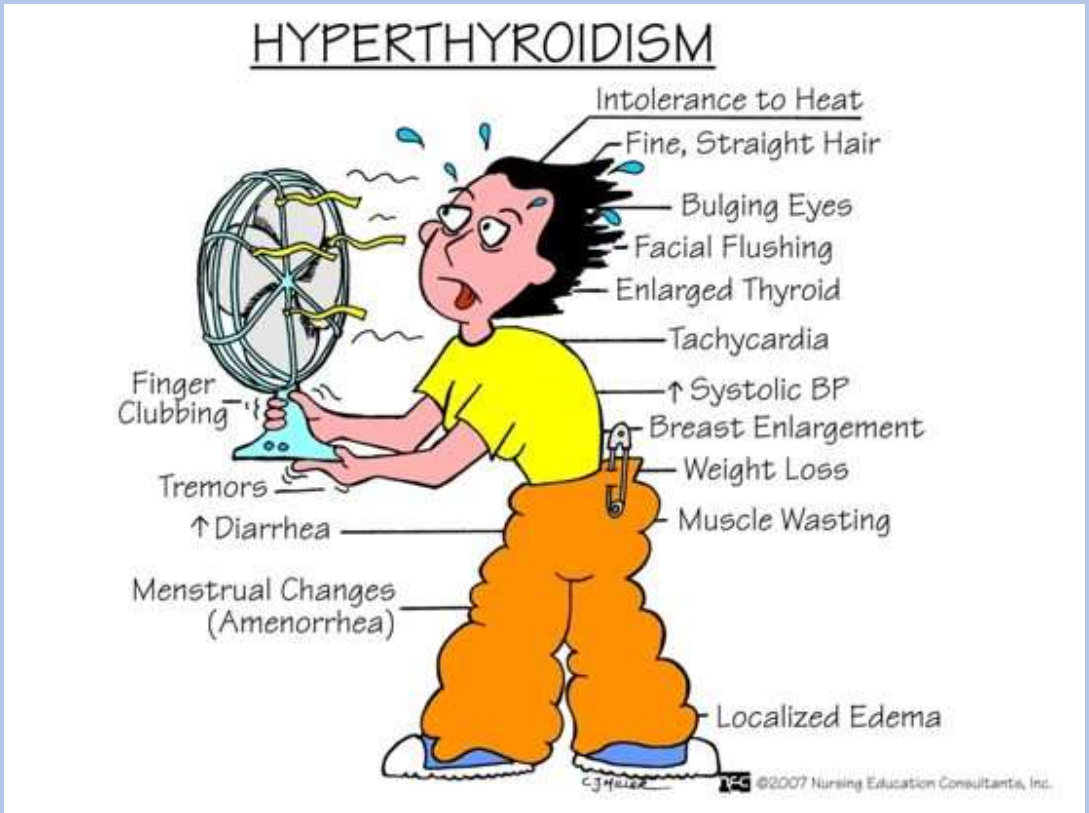
Approach

- Levothyroxine is the choice of treatment for hypothyroidism
- If patient remains symptomatic even with TSH in target AND thorough history and exam have r/o other concomitant conditions (depression, sleep disturbance, nutrition, anemia, subtle chronic infection, stress, etc)

→ Careful consideration of adding T3 or switching to desiccated thyroid hormone

* Evidence does not support **routine** use
* 1 grain desiccated thyroid → ~90-100mcg LT4

Thyrotoxicosis



Low TSH

- How to work it up

Q

- What is the most common cause of hyperthyroidism?
  1. Graves' disease
  2. Toxic (single) adenoma
  3. Toxic multinodular goiter
  4. TSH producing pituitary adenoma
  5. Thyroiditis (acute/subacute/painless)

Common causes of low TSH

- Iatrogenic/factitious
- Graves' disease
- Thyrotoxic nodule(s)
- Subacute thyroiditis
- Acute illness (euthyroid sick syndrome)

Common causes of low TSH

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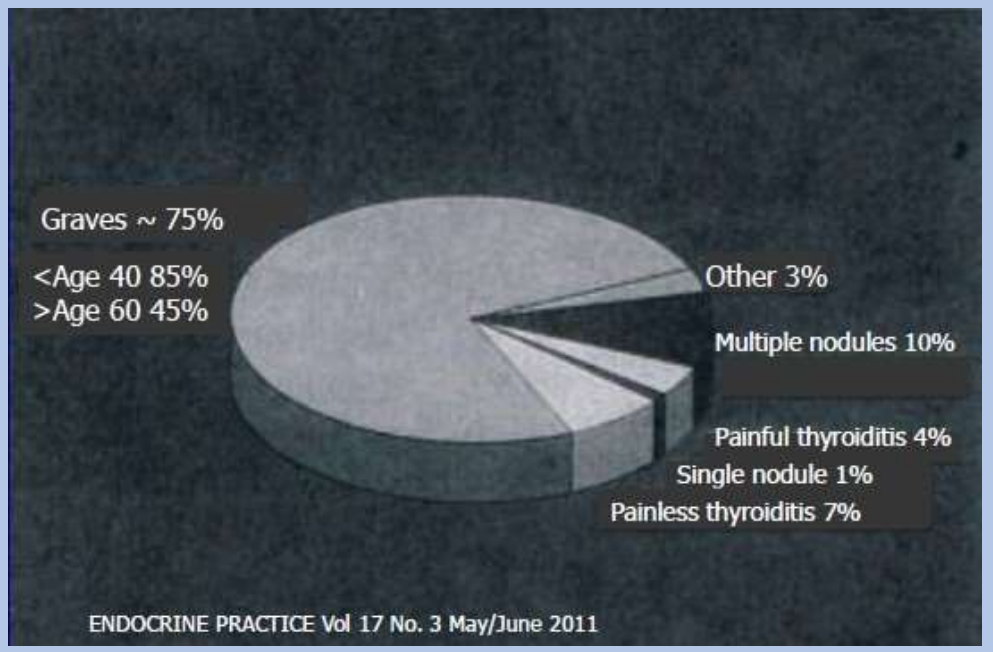
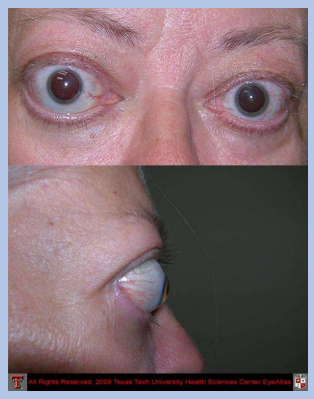


Low TSH



- Clues from HPI
  - Graves' orbitopathy / dermopathy
    → Graves' disease
  - Goiter
    → Graves' disease / toxic nodule(s)
  - Recent URI followed by pain in thyroid area
    → subacute thyroiditis

Low TSH

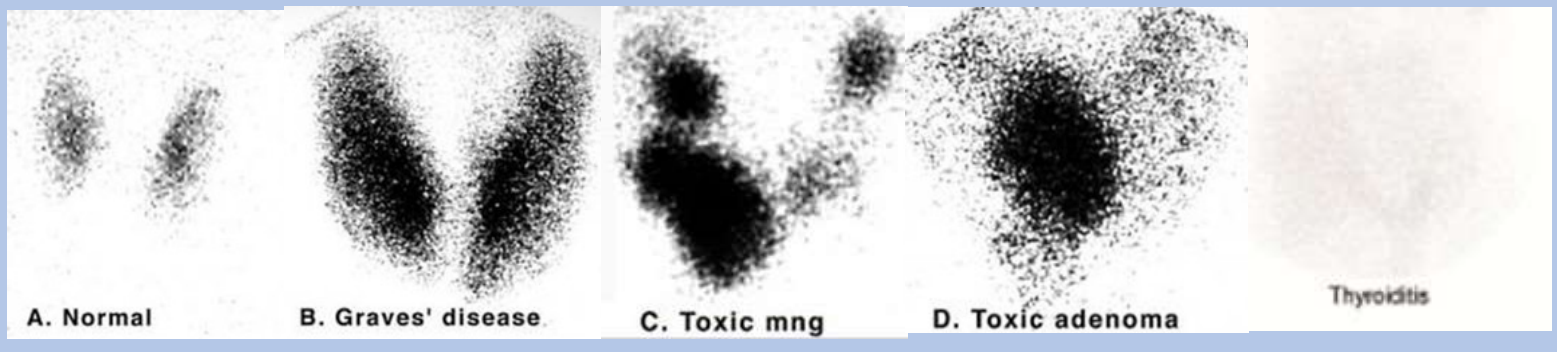
Repeat TSH with:

- Free T4
- Total T3
- TSI or TRAb (thyrotropin receptor ab)
- ESR/CRP (if suspecting subacute thyroiditis)

- Thyroid ultrasound (if suspecting toxic nodule(s))
- Uptake/scan (if diagnosis is unclear or planning RAI treatment)

Low TSH

	Graves'	Toxic nodule(s)	Thyroiditis
T3 and/or T4	↑	↑	↑
TRAb / TSI	(+)	(-)	(-)
ESR			↑
Thyroid US	Diffusely enlarged gland with hypervascularity	Nodular thyroid	
Uptake/scan	Diffusely increased uptake	Localized single or multiple increased uptake: "hot nodule(s)"	Decreased/absent uptake



Treatment: Graves Disease and Toxic Nodule(s)

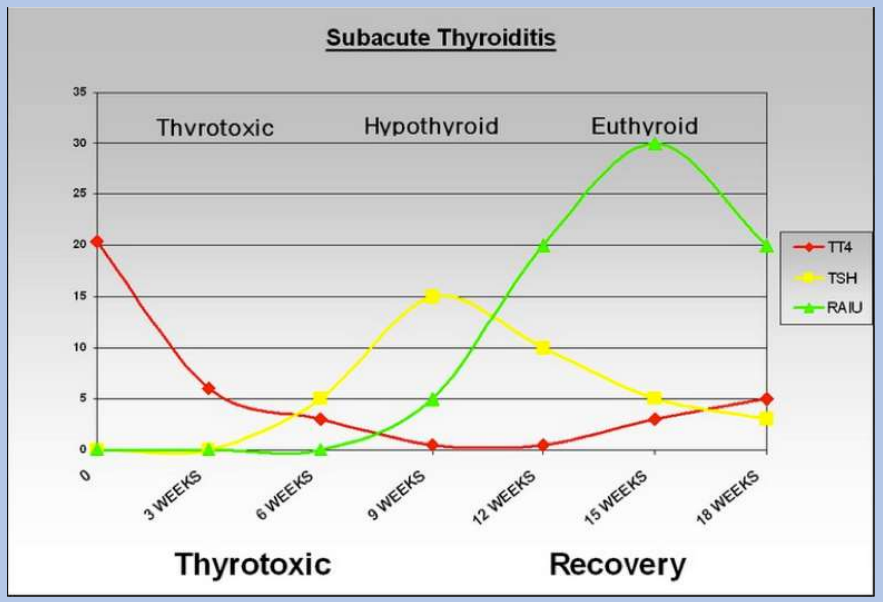
	Graves Disease	Toxic Nodule(s)
Control symptoms	Especially cardiac – beta blockers	
Control thyrotoxicosis	- Antithyroid medication [methimazole, propylthiouracil (PTU)] - Radioactive iodine ablation - Surgery	

Medications	- Methimazole
	  - Preferred over PTU except during 1st trimester pregnancy and thyroid storm
	  - Potential side effects: pruritis/rash (common), agranulocytosis/hepatotoxicity (rare)
	- PTU: second-line agent due to rare but potentially serious hepatotoxicity	

Considerations	Chance of spontaneous resolution - Consider medical therapy first	No spontaneous resolution - Consider definitive treatment

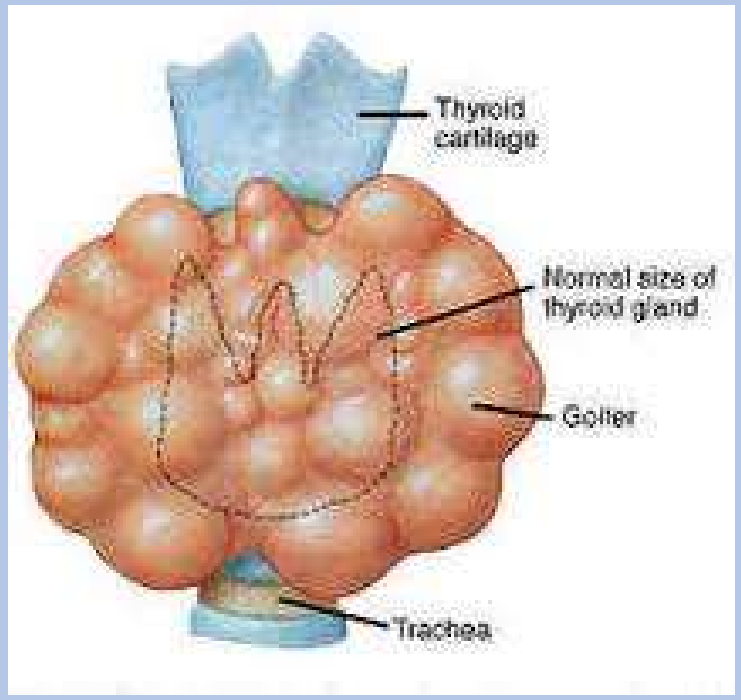
Subacute thyroiditis

- Destruction of thyroid follicular cells: often post viral (URI)
- Characterized by painful/tender thyroid
- Most cases transient
- Tx
  - Symptomatic
    - Beta blockers
    - NSAIDs, glucocorticoids



Thyroidmanager.org (accessed 9/10/2016)

Nodular thyroid disorders



Case

- 60-year-old female presents for thyroid incidentaloma that was found during her carotid ultrasound. She denies any difficulty or pain with swallowing and no history of head/neck irradiation.
- PMHx: HTN, hyperlipidemia
- Meds/OTC: statin, CCB, MVI
- FHx: no thyroid d/o including malignancy (non-contributory)
- P/E: palpable mass on right lobe w/o lymphadenopathy
- Lab 3mo ago: All wnl including TSH 3.4 mIU/L (0.45-4.5)

Prevalence

- Palpable: 5% of women, 1% of men
- On thyroid US: 19-68%
- More common in women and in elderly
- Vast majority are benign

Goal: exclude malignancy (7-15% depending on age, sex, other risk factors)

Choice of test: Fine Needle Aspiration (FNA)

Vander. Ann Intern Med. 1968 / Tunbridge. Clin Endocrinol (Oxf). 1977 / Tan Ann Intern Med. 1997 / Guth. EurJ Clin Invest. 2009 / Hegedus. NEngl J Med. 2004 / Mandel. JAMA. 2004

First step

- Thyroid nodule detected by palpation or imaging

→ HPI (risk factors) and TSH

→ If TSH is low and hyperthyroid

→ Order uptake/scan

→ If the nodule is “hot,” treat accordingly

Otherwise, further work up to r/o malignancy

Risk factors for Malignancy

- Hx of head and neck irradiation
- FHx of medullary thyroid cx, MEN 2, or papillary thyroid cx
- Age <14 or >70 years
- Male sex
- Persistent dysphonia, dysphagia, or dyspnea
- Cervical adenopathy
- Growth of the nodule
- Firm or hard nodule consistency
- Fixed nodule

Thyroid Nodule Management, Endocr Pract. 2016;22(Suppl 1)

Case (cont.)

- Ordered thyroid U/S:
  - Goiter noted with 1.8cm nodule in right thyroid lobe
  - Rest of the gland looked unremarkable

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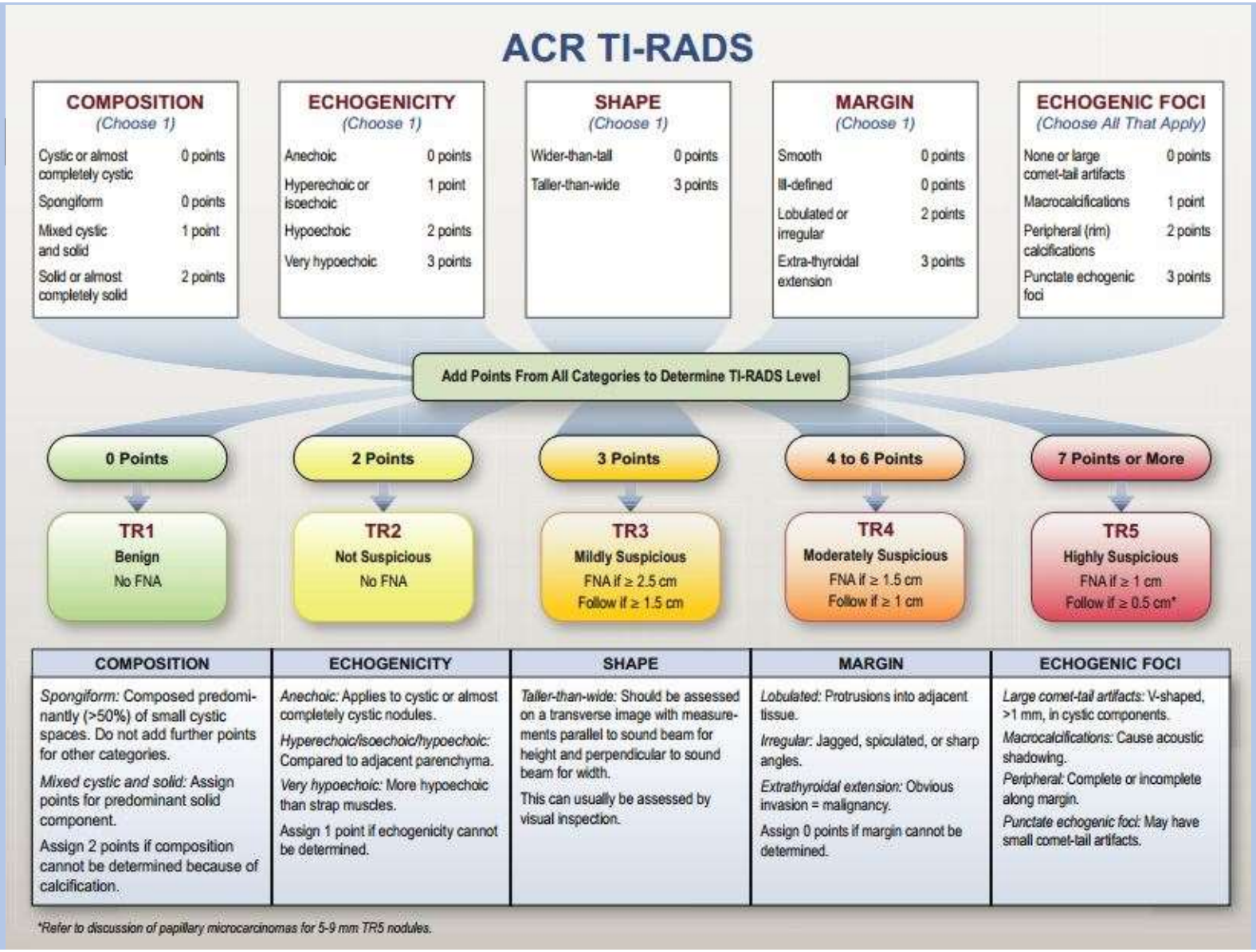

ACR TI-RADS
COMPOSITION
(Choose 1)
Cystic or almost completely cystic 0 points
Spongiform 0 points
Mixed cystic and solid 1 point
Solid or almost completely solid 2 points
ECHOGENICITY
(Choose 1)
Anechoic 0 points
Hyperechoic or isoechoic 1 point
Hypoechoic 2 points
Very hypoechoic 3 points
SHAPE
(Choose 1)
Wider-than-tall 0 points
Taller-than-wide 3 points
MARGIN
(Choose 1)
Smooth 0 points
Ill-defined 0 points
Lobulated or irregular 2 points
Extra-thyroidal extension 3 points
ECHOGENIC FOCI
(Choose All That Apply)
None or large comet-tail artifacts 0 points
Macrocalcifications 1 point
Peripheral (rim) calcifications 2 points
Punctate echogenic foci 3 points
Add Points From All Categories to Determine TI-RADS Level
0 Points
TR1
Benign
No FNA
2 Points
TR2
Not Suspicious
No FNA
3 Points
TR3
Mildly Suspicious
FNA if ≥ 2.5 cm
Follow if ≥ 1.5 cm
4 to 6 Points
TR4
Moderately Suspicious
FNA if ≥ 1.5 cm
Follow if ≥ 1 cm
7 Points or More
TR5
Highly Suspicious
FNA if ≥ 1 cm
Follow if ≥ 0.5 cm*
COMPOSITION
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.
ECHOGENICITY
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.
SHAPE
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.
MARGIN
Lobulated: Protrusions into adjacent tissue.
Irregular: Jagged, spiculated, or sharp angles.
Extrathyroidal extension: Obvious invasion = malignancy.
Assign 0 points if margin cannot be determined.
ECHOGENIC FOCI
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.

Case (cont.)

- Called radiology and requested to describe the nodule more in detail and to report according to the TI-RADS
  - Thyroid nodule on right superior lobe measuring 1.8x1.5x0.9cm
  - Composition – solid (2 pts)
  - Echogenicity – hypoechoic (2pts)
  - Shape – wider than tall (0 pts)
  - Margin – ill-defined (0 pt)
  - Echogenic foci – peripheral rim calcification (2 pts)
  - TR 4 (6 points) – moderately suspicious
  - Consider FNA if ≥ 1.5cm, monitor if ≥ 1cm

Table 7. The Bethesda system for reporting thyroid cytopathology: Diagnostic categories and risk of malignancy[1]

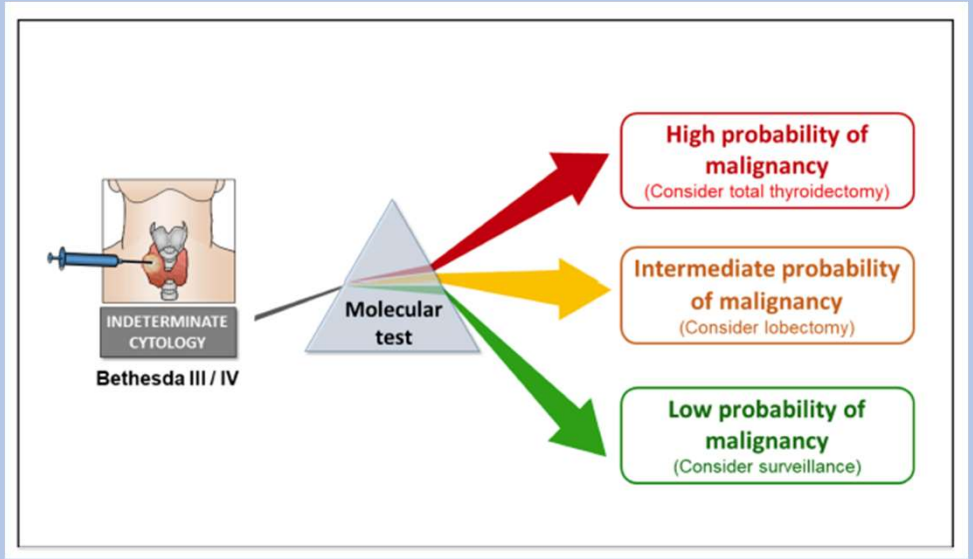
Diagnostic category	Estimated/predicted risk of malignancy by the Bethesda system (%)[1]	Actual risk of malignancy in nodules surgically excised (%, median (range))[2]
Nondiagnostic or Unsatisfactory	1-4	20 (9-32)
Benign	0-3	2.5 (1-10)
Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance (AUS/FLUS)	5-15	14 (6-48)
Follicular Neoplasm or Suspicious for a Follicular Neoplasm (FN/SFN)	15-30	25 (14-34)
Suspicious for Malignancy (SUSP)	60-75	70 (53-97)
Malignant	97-99	99 (94-100)

"indeterminant"

Haugen. Thyroid 2016

Molecular Diagnostics[1,2]

	Afirma GSC	ThyGenX/Thyra MIR	ThyroSeq v3
Sensitivity	91.1%	89%	94.1%
Specificity	68.3%	85%	81.6%
Negative predictive value	96.1%	94%	97.3%
Positive predictive value	47.1%	74%	65.9%



1. Nikiforov YE, Baloch ZW. *Cancer Cytopathol*. 2019:27(4):225-230.
2. Nishino M, Nikiforov M. *Arch Pathol Lab Med*. 2018;142:446-457.

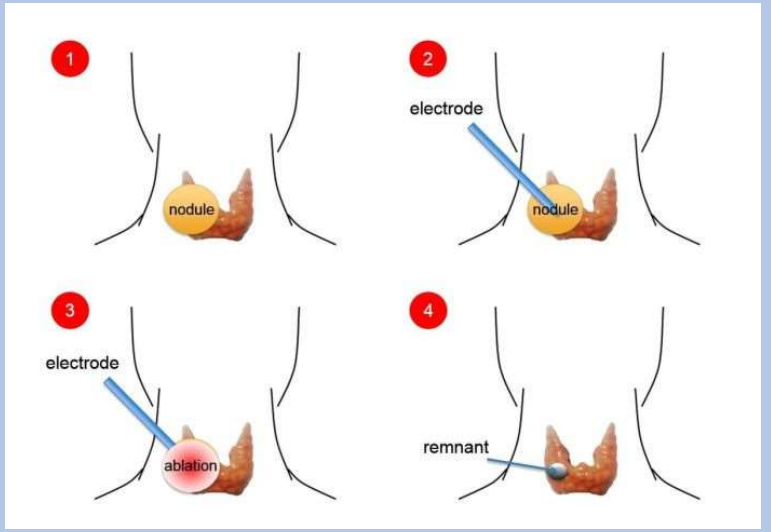
Monitoring

- TR5: 1, 2, 3, 4, 5 yr
- TR4: 1, 2, 3, 5 yr
- TR3: 1, 3, 5 yr
- Imaging can stop after 5yrs if no change.

- Consider biopsy/re-biopsy if it grows
  - > 50% increase in volume
  - > 20% increase in at least two nodule dimensions with minimal increase of 2mm

Tessler FN et al. JACR 2017. dx.doi.org/10.1016/j.jacr.2017.01.046

Radiofrequency ablation (RFA)



- Minimally invasive thermal ablative treatment can reduce morbidity associated with thyroidectomy
  - Benign nodule causing symptoms or cosmetic concern
  - thyrotoxic nodule(s)
  - Clinical value for thyroid cancers is currently being evaluated

Key Takeaways

- T3 has low value in diagnosis of hypothyroidism
- Evidence does not support ***routine*** use of LT3/LT4 combination therapy
- Methimazole is preferred antithyroid medication over PTU except in 1st trimester of pregnancy
- ACR TI-RADS may reduce unnecessary biopsies and referrals
- Molecular testing may reduce the need for surgical intervention thyroid nodules with indeterminant biopsy results

ACR = American College of Radiology; TI-RADS: Thyroid Imaging Reporting and Data System.

Q / A

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