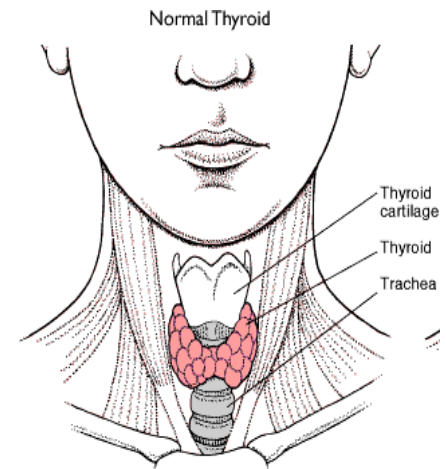


# GETTING HYPER OVER THYROID FUNCTION: AN APPROACH TO THYROID DISORDERS IN CHILDHOOD

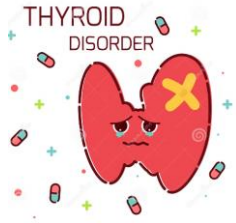
SARAH LAWRENCE, MD, FRCPC  
PEDIATRIC ENDOCRINOLOGY



# DISCLOSURE

- Nothing to disclose

# Objectives



Provide cost effective evaluation and treatment for patients with goiter and/or hypothyroidism

Manage neonatal thyroid disorders including a positive newborn screen and infants of mothers with Graves' disease

Formulate a management plan for the patient with hyperthyroidism

# How common are thyroid disorders in children?

- NHANES report: 2% of 12 –19 yrs olds in US have subclinical hypothyroidism (defined as TSH >4.5 mU/L, normal T4)

Hollowell JG, et al, *JCEM* 2002

- 3-4% of school aged children/youth will have some sort of thyroid condition on evaluation
  - Goiter is most common
  - 1-2% autoimmune hypothyroidism (4:1 female preponderance)
  - Graves 0.1-3 cases per 100,000 with geographic variation
    - 1/10,000 in US
    - 1/100,000 in the UK and Ireland

Bauer, *JAMA Pediatrics* 2015

# CLINICAL EVALUATION

# History and Physical

- Family history
- Constitutional symptoms are common to all age groups
- Unique to the pediatric age group, is impact on growth

# Hypothyroidism



## WHO GROWTH CHARTS FOR CANADA

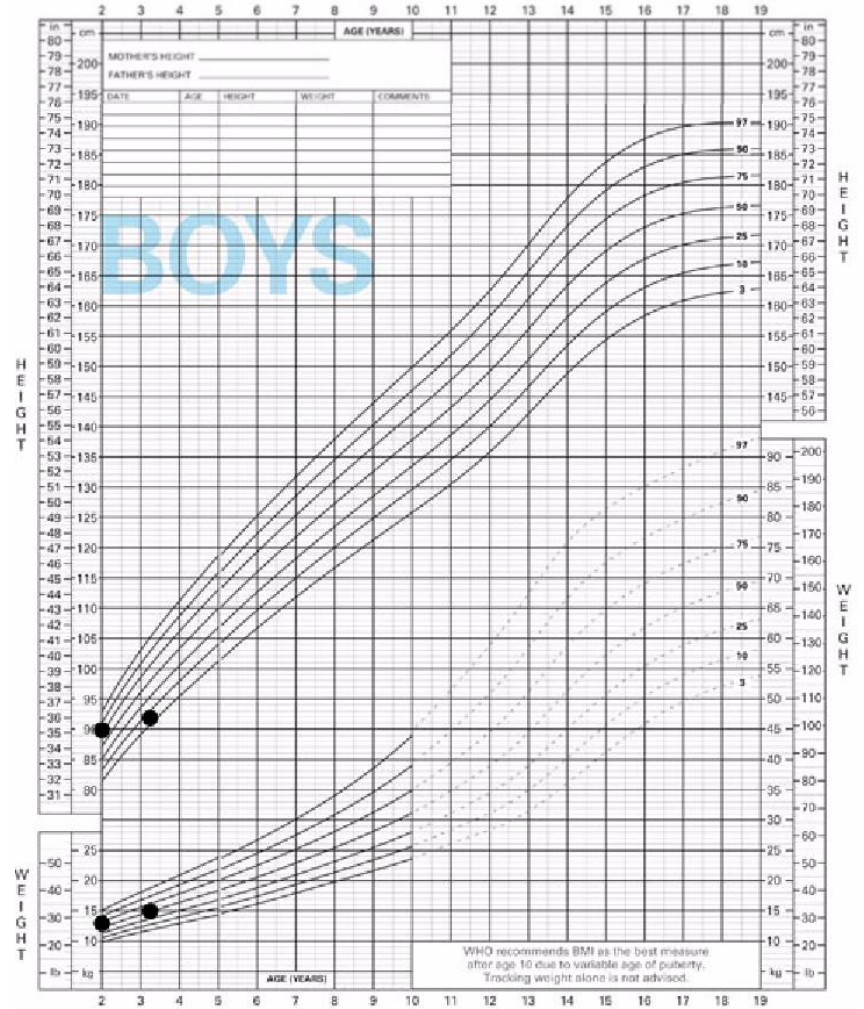
**BOYS**

### 2 TO 19 YEARS: BOYS

Height-for-age and Weight-for-age percentiles

NAME: \_\_\_\_\_

DOB: \_\_\_\_\_ RECORD # \_\_\_\_\_



# Hypothyroidism post treatment



WHO GROWTH CHARTS FOR CANADA

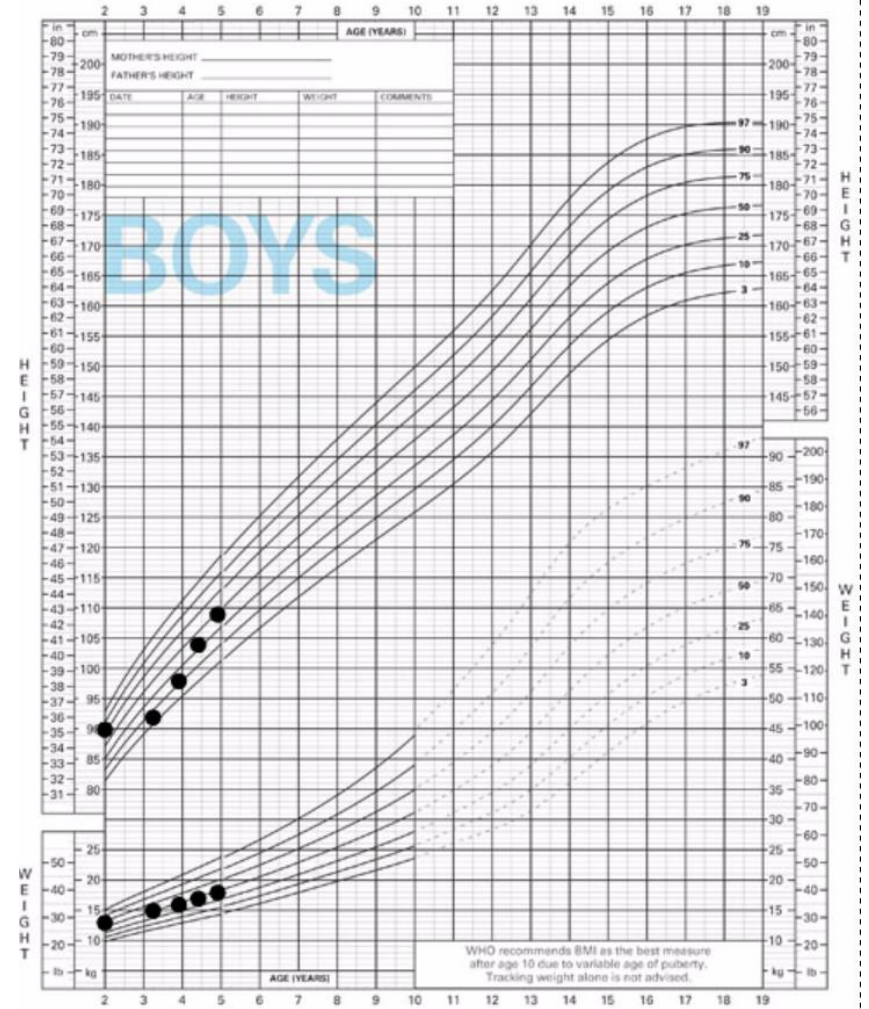
BOYS

2 TO 19 YEARS: BOYS

Height-for-age and Weight-for-age percentiles

NAME: \_\_\_\_\_

DOB: \_\_\_\_\_ RECORD # \_\_\_\_\_





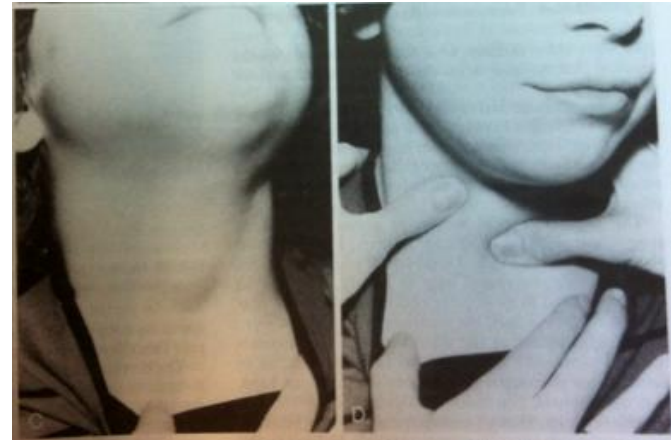
# Thyroid exam

Normal Volume:

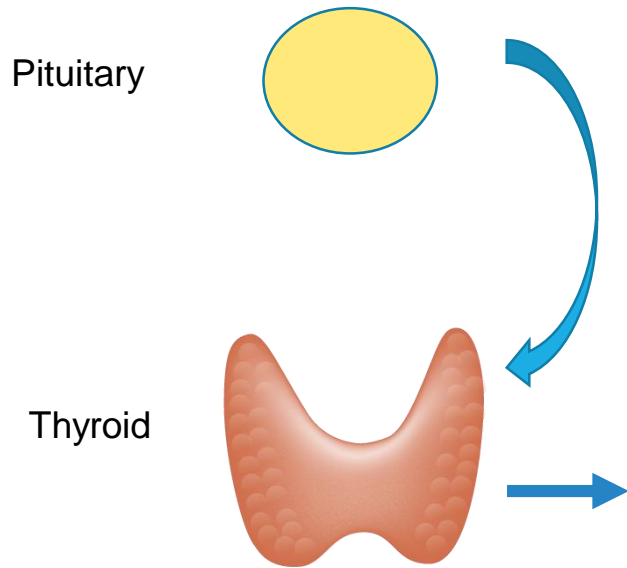
Child: 1 ml birth → 6-7 ml age 14

Clinically:

Goiter: Each lobe is > size of distal phalanx of child's thumb (1960 WHO)



# Patient education



TSH

FT4

N



N

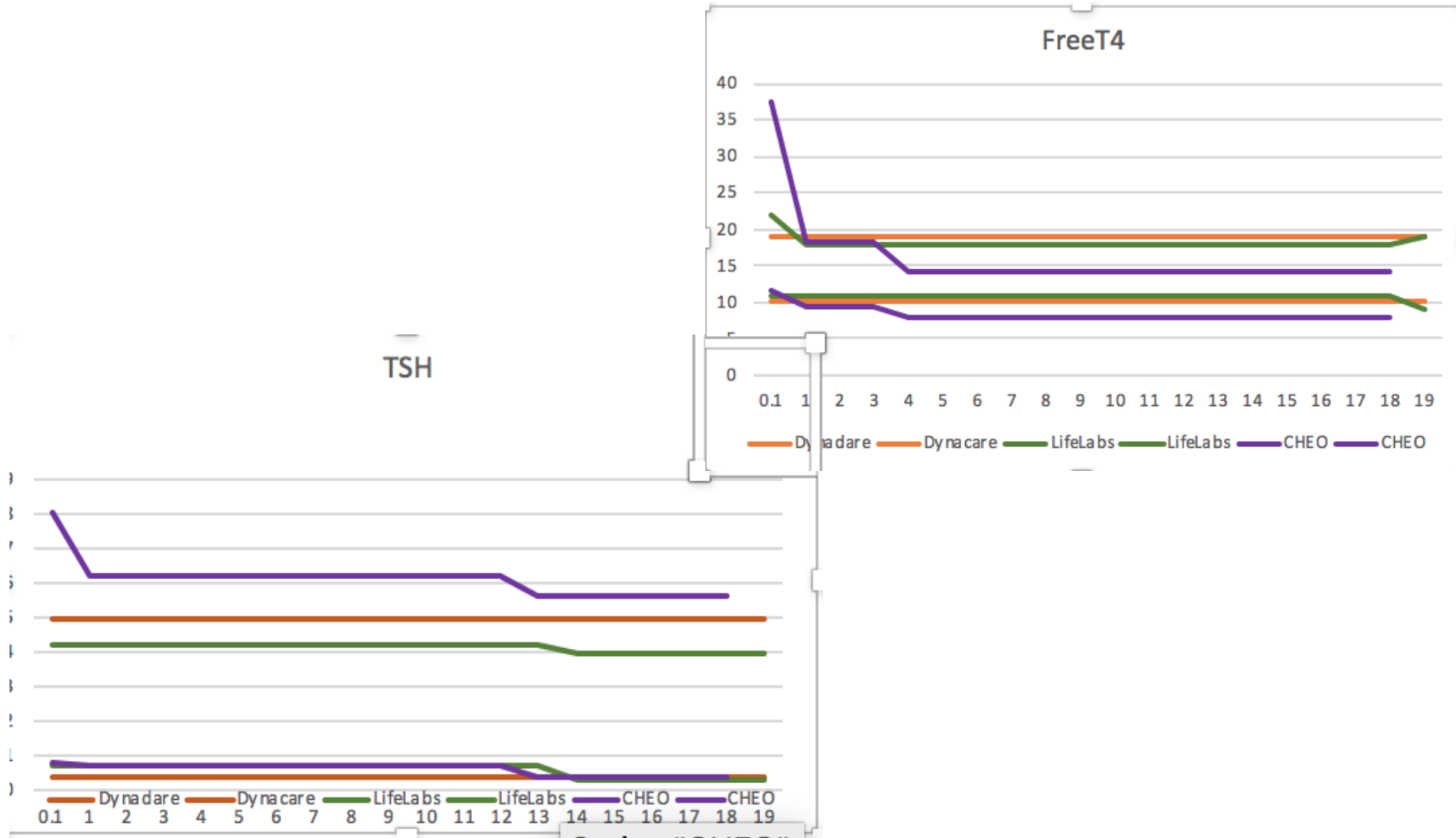
N



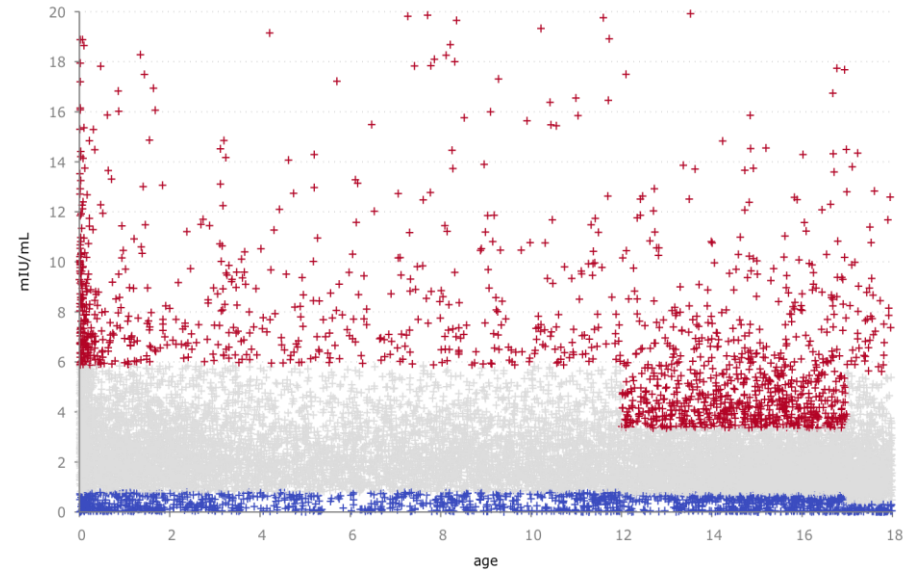
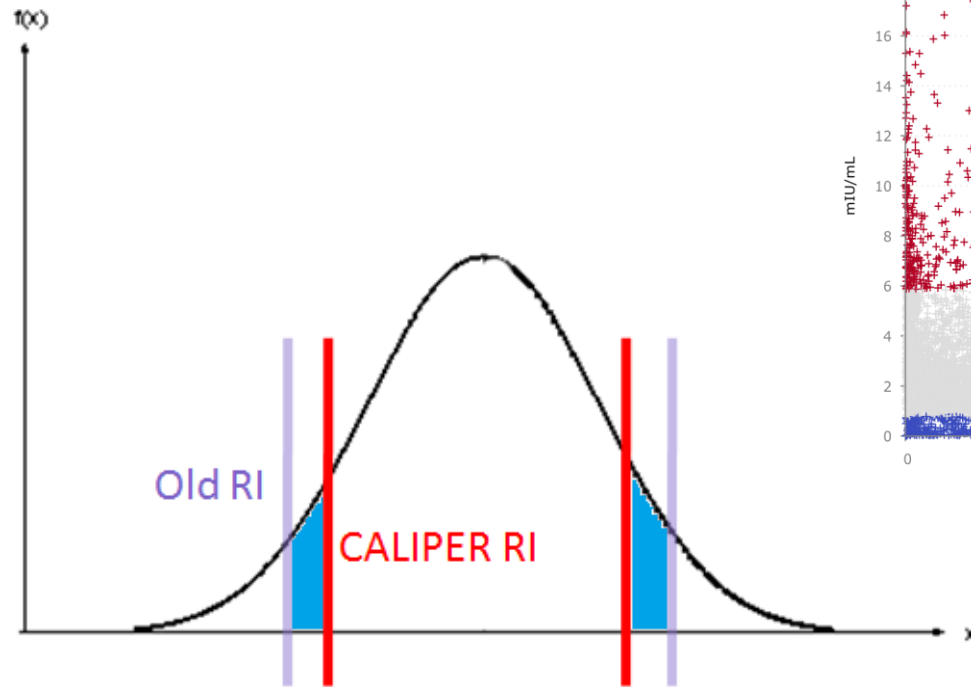
Growth  
Metabolism

Normal  
Compensated  
HYPOthyroid  
HYPERthyroid

# Reference Intervals



# Old vs New RI at CHEO



# Medication effects on TFTs

1. Glucocorticoids: low TSH, low T3 and N/slightly low free T4
2. Dopamine (prolonged use): Low TSH, low free T4 and free T3
3. Amiodarone (high iodine content):
  - Hypothyroidism 5-25%
  - Hyperthyroidism 2-10%
4. Phenytoin
  - Increases rate hepatic metabolism of T4 and T3
  - May cause decrease in free T4, effect on T3 variable

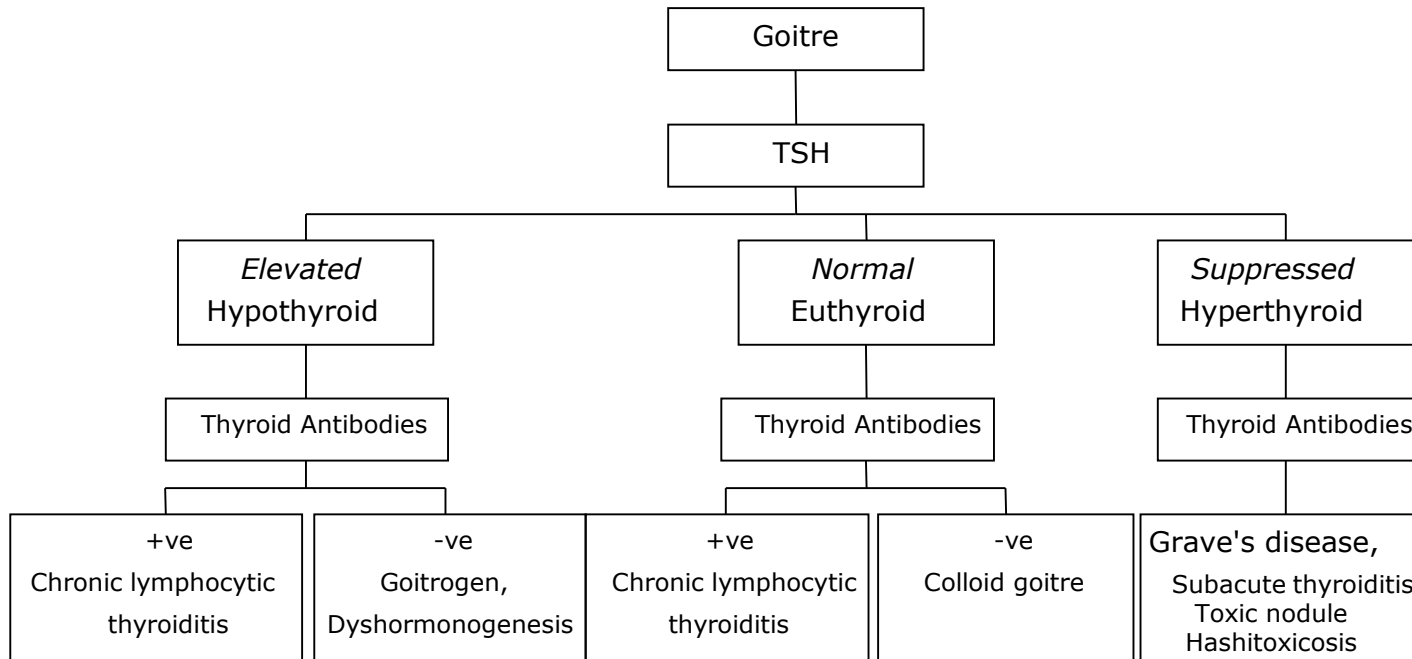
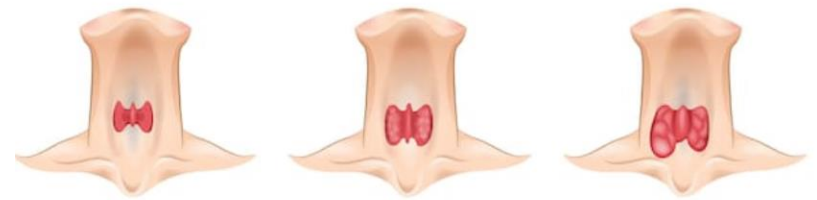
# APPROACH TO GOITER

# Question 1

A 12 year old girl presents with a goiter. What screening thyroid investigations should you order to determine the diagnosis?

- A. TSH
- B. TSH, thyroid antibodies
- C. TSH, thyroid antibodies, FreeT4
- D. TSH, thyroid antibodies, ultrasound
- E. Thyroid ultrasound

# Approach to Goitre





# APPROACH TO SUBCLINICAL (COMPENSATED) HYPOTHYROIDISM

## Question 2

11 year old girl presents with hair loss, mild to moderate weight gain with normal linear growth, normal to slightly low energy. No family history of hypothyroidism.

TSH 8.53 mIU/L (0.5-5 mIU/L)

FT4 11 pmol/L (10-18)

- A. Ultrasound of the thyroid
- B. Start treatment with L-thyroxine
- C. Repeat thyroid function tests in 1 week
- D. Repeat thyroid function tests in 2-4 weeks
- E. Follow the patient in clinic in 6 months

# How important are antibodies in determining risk of progression?

- Large cohort children (121,000) with TSH 5.5 – 10 mU/L followed for 5 years  
Lazar L, et al, JCEM 2009
- 250 children with ↑ TSH and + antibodies over 4 years follow-up:  
Radetti G, et al, Clin Endocrinol 2012

	All SCH	With AITD
Normalizes	73%	34%
Persistent SCH	25%	42%
Overt hypothyroidism	2%	24%

# What are the adverse effects if we don't treat SCH?

- Most children with SCH do not have symptoms and signs of overt hypothyroidism
- Older children: evidence for association between SCH and impaired neuropsychological development inconsistent
- SCH not associated with adverse effects on growth or bone health. It may be associated with adverse cardiovascular parameters.

Lazarus J, et al, Eur Thyroid 2012

# Why would someone without AITD have an elevated TSH?

- Altered setpoint for TSH secretion
  - TSH receptor gene “loss-of-function” mutations; requires increased TSH for N thyroid function
  - 11.8% patients with non-autoimmune elevated TSH had mutations in TSH receptor gene

Calebrio D, et al, JCEM 2012

- Laboratory test artifact,
  - e.g., heterophile antibody against TSH
- Normal thyroid function, with TSH just outside  $\pm 2$  SD
  - Age adjusted reference intervals

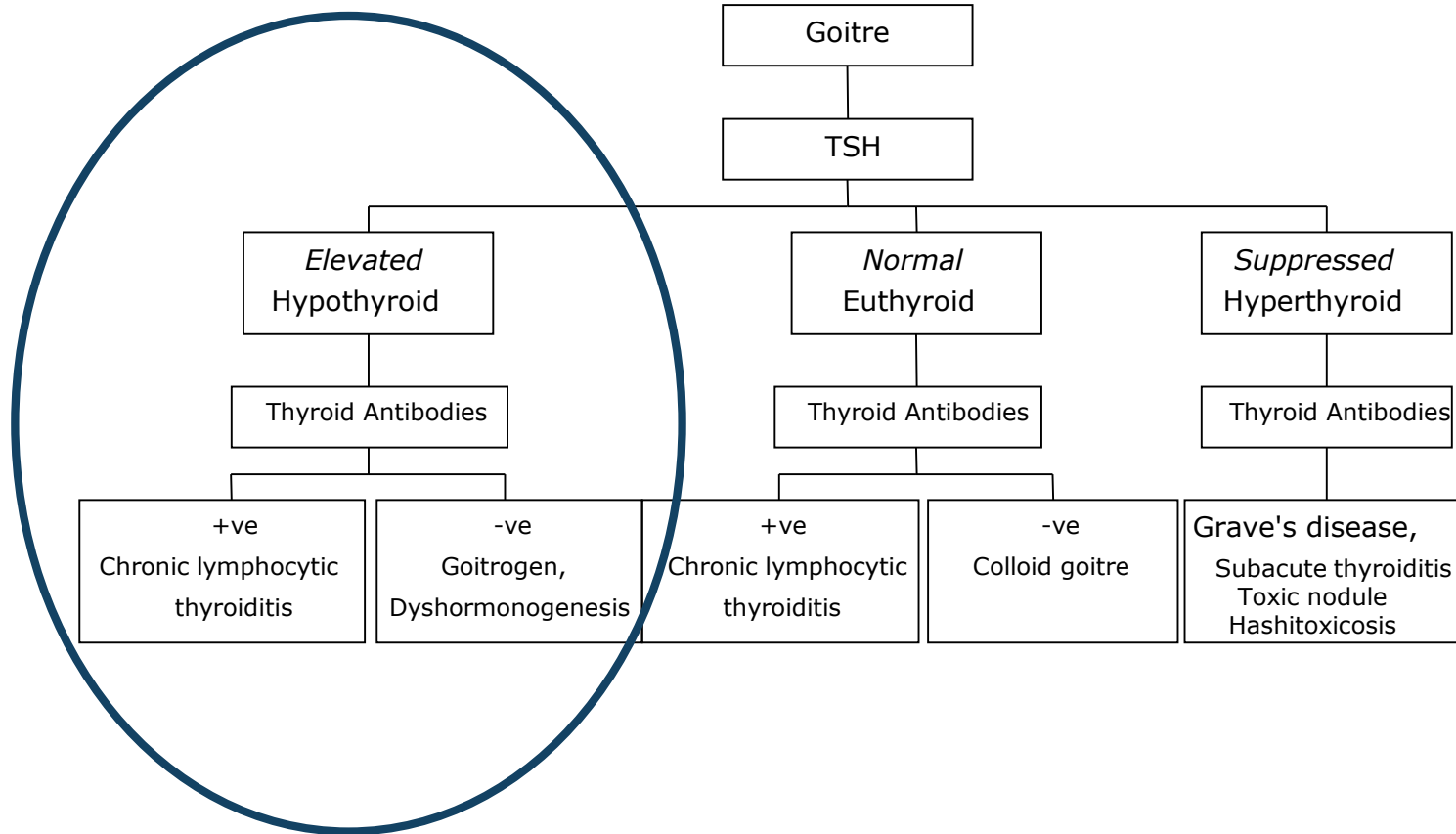
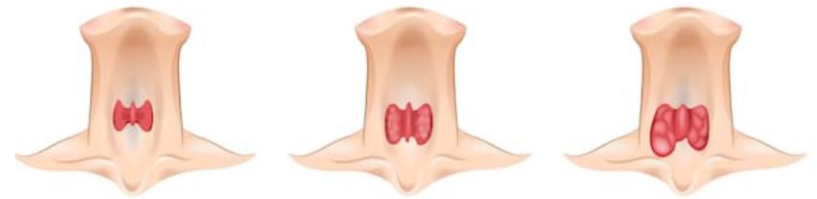
# GENERAL RECOMMENDATIONS

## Mild elevation of TSH

- Recheck in about 1 month, include TPO
- TSH q(6-)12 months or increasing symptoms
- Treat if TSH persists  $> 10$  mIU/L. (8-10)
- If strongly positive antibodies or underlying condition to increase risk (eg Turner, Diabetes), then consider starting with lower TSH threshold

# APPROACH TO OVERT HYPOTHYROIDISM

# Approach to Goitre





# Acquired Hypothyroidism - Etiology

1. Autoimmune Thyroid Disease (AITD) or Hashimoto Thyroiditis most common

2. Non-Autoimmune

Late onset thyroid dysgenesis/dyshormonogenesis

Drug induced, goitrogenic agents

Iodine deficiency (rare in developed countries)

Iatrogenic - radioiodide ablation, surgery

Infiltrative disease (cystinosis, histiocytosis)

Central hypothyroidism (secondary to head-trauma tumors)

3. Miscellaneous: Down syndrome, Turner syndrome

# Question 3

An 12 year old girl presents with growth failure and classic symptoms of hypothyroidism. Her TSH is 110 mIU/L and FreeT4 is 6 pmol/L. You diagnose overt hypothyroidism and plan to start thyroxine. Her weight is 40 kg.

**What dose of thyroxine will you start with?**

- A. 50 mcg daily
- B. 75 mcg daily
- C. 100 mcg daily
- D. 125 mcg daily

1-5 yrs:	4-6 mcg/kg/day
6-10 yrs:	3-4 mcg/kg/day
≥11 yrs:	2 mcg/kg/day
Adult:	1.6 mcg/kg/day

OR 100 mcg/m<sup>2</sup>

# Question 4

When would you recheck her labs?

- A. 4 weeks
- B. 6-8 weeks
- C. 3 months
- D. 6 months

## Question 5

What would be your plan for routine monitoring?

- A. TSH every 3 months
- B. TSH every 6 months
- C. TSH every year
- D. TSH every year
- E. TSH, FT4 every year

## Question 6

How long would you treat?

- A. 1 year
- B. Until the end of puberty
- C. Lifelong

If you challenge off treatment, there are a number of ways to do this. Our usual is:

- Stop thyroxine
- TSH, FT4 at baseline, 1,3,6 and 12 months

## Question. (no poll)

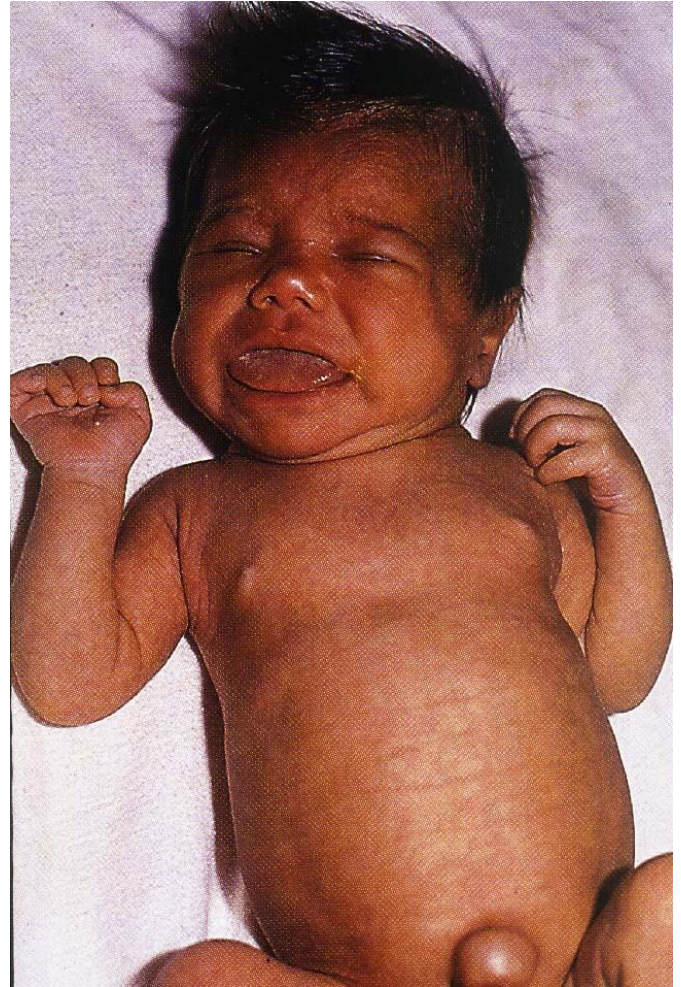
Before starting thyroxine, what other important condition should you consider?

# Down Syndrome and Hypothyroidism

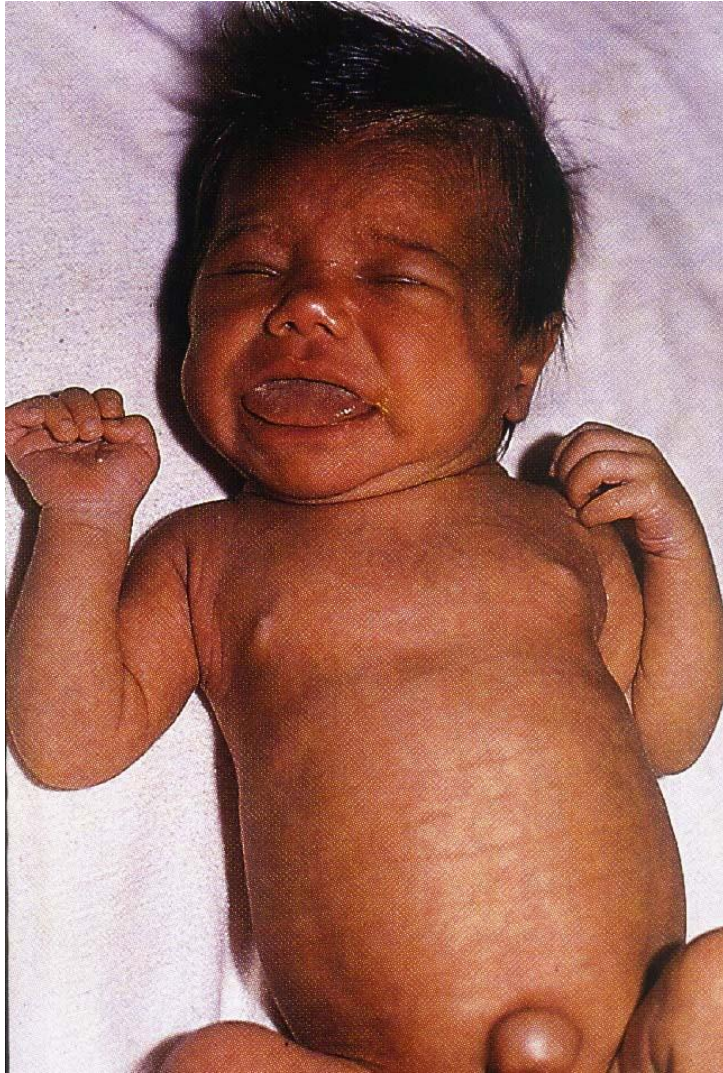
- Thyroid dysfunction common (4-18%)
- Timing and method for thyroid screening remains controversial although AAP indicates annual screening
- Patients at higher risk for congenital hypothyroidism (incidence 1/113)
- Patients at higher risk for both autoimmune hypothyroidism or Graves' disease
- RCT of infants treated with LT4 for 2 yrs (those with TSH >5) did not seem to benefit mental or motor developmental later in life (at 10 yrs) JCEM 2014

# APPROACH TO CONGENITAL HYPOTHYROIDISM





# Signs and symptoms of congenital hypothyroidism



1st week

Poor feeding, prolonged jaundice, hypothermia, cool skin, large posterior fontanelle

Week 2-4

Decreased activity, doesn't cry or demand to be fed, constipation, hoarse cry, hypotonia

1 month

peripheral cyanosis, mottling, respiratory distress, failure to gain weight, macroglossia

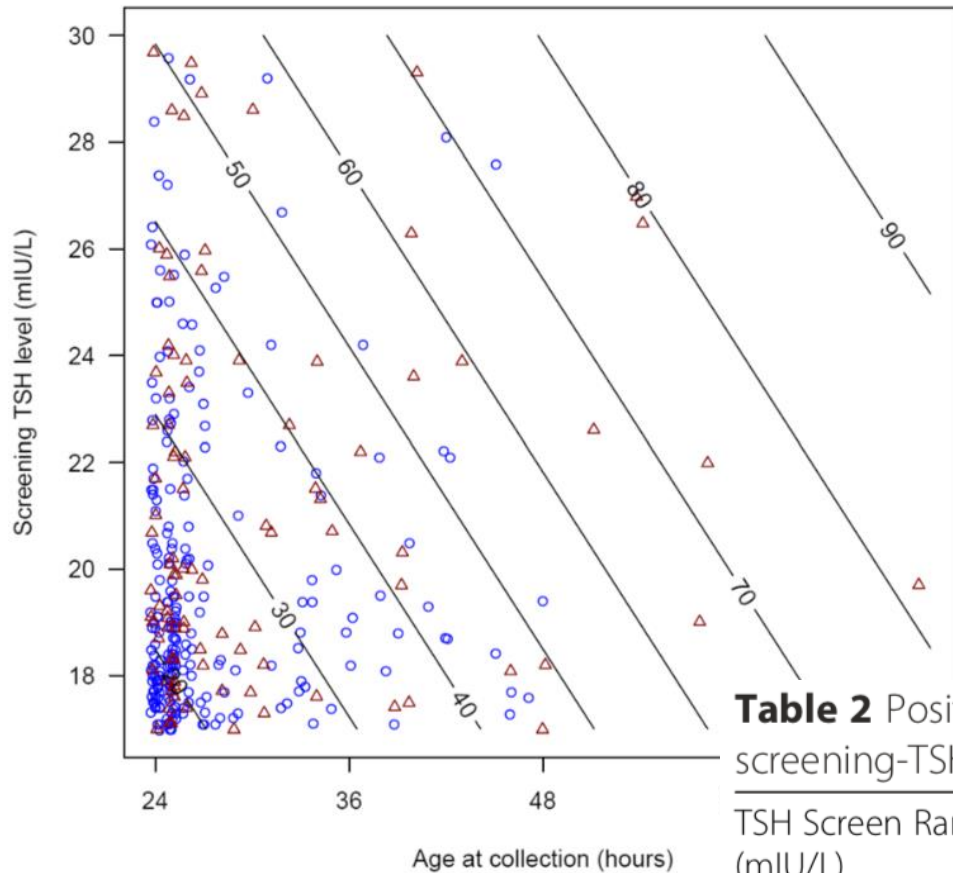
3 months

umbilical hernia, dry, pale skin, carotenemia, myxedema, growth failure

## Question 7

The most common cause of a positive newborn screen for hypothyroidism is:

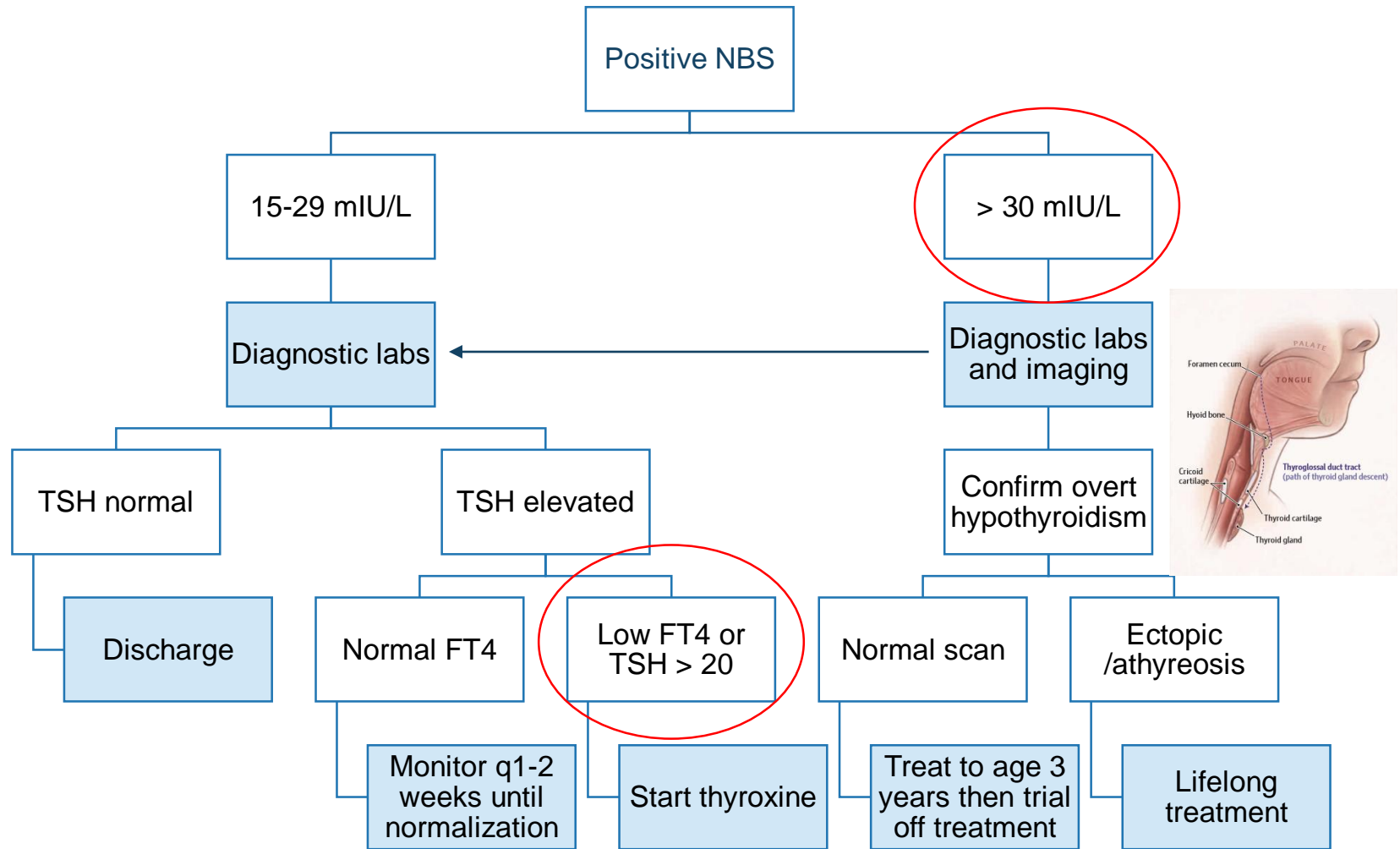
- A. Thyroid dysgenesis (Ectopic thyroid/ agenesis)
- B. Early discharge
- C. Prematurity
- D. Dyshormonogenesis
- E. Central hypothyroidism

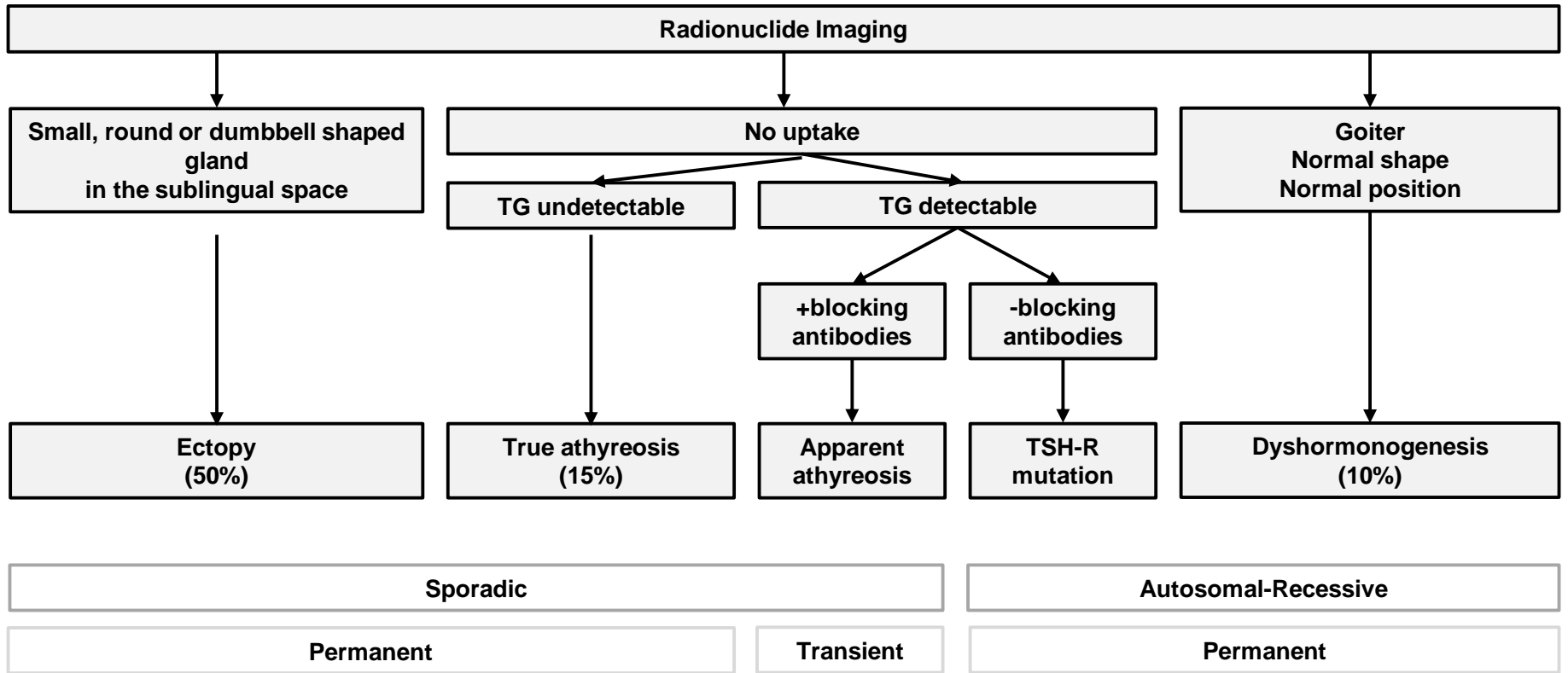


**Table 2** Positive predictive values for the CH ONSP at various screening-TSH ranges

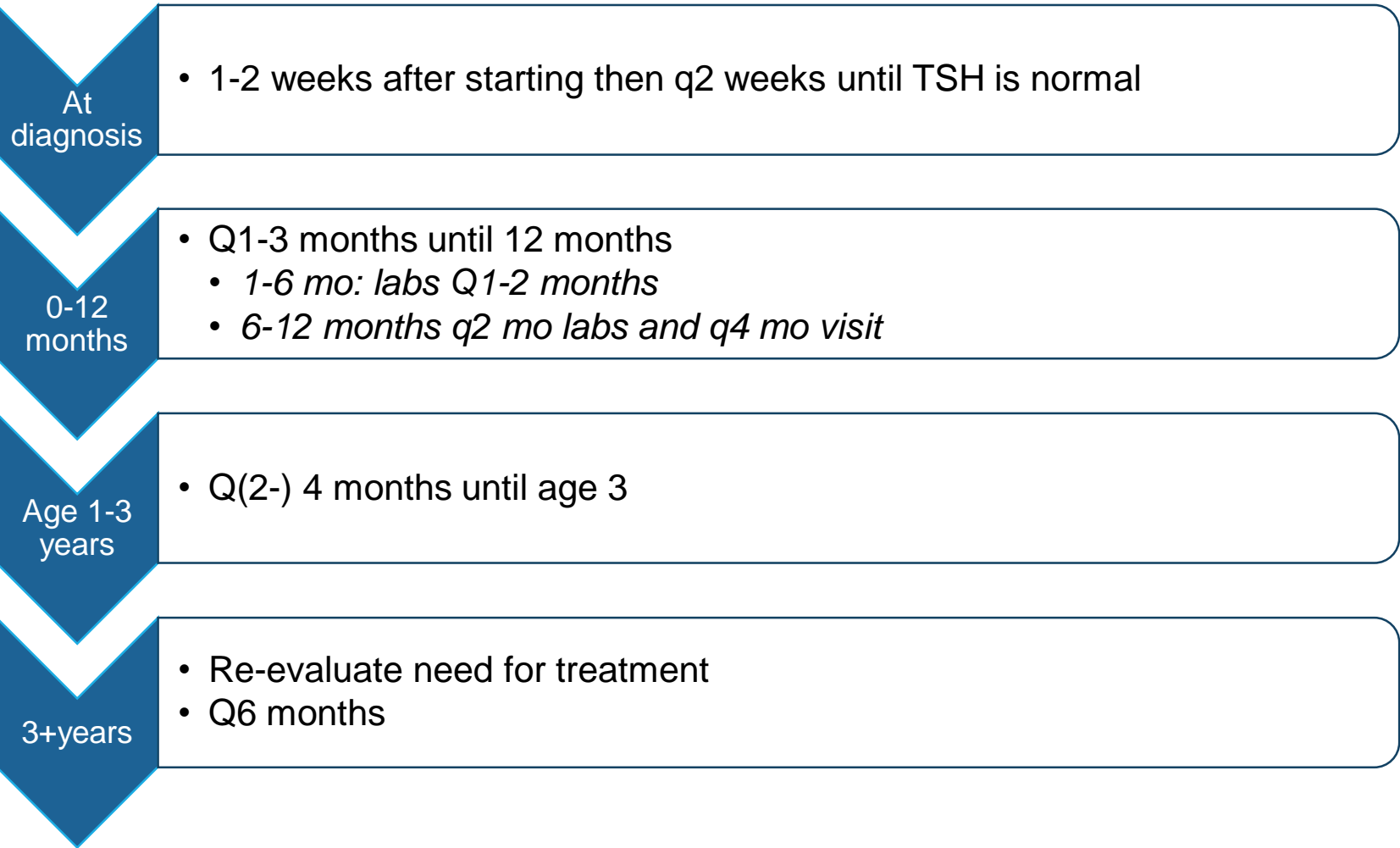
TSH Screen Range (mIU/L)	Screen Positives	True Positives	False Positives	Positive Predictive Value
17–19.9	201	48	153	24 %
20–29.9	129	50	79	39 %
30–39.9	34	26	8	76 %
≥40	177	172	5	97 %

# Approach to a positive CH newborn screen





# Management of CH



# Dosing of thyroxine

Dissolve-a-Dose™



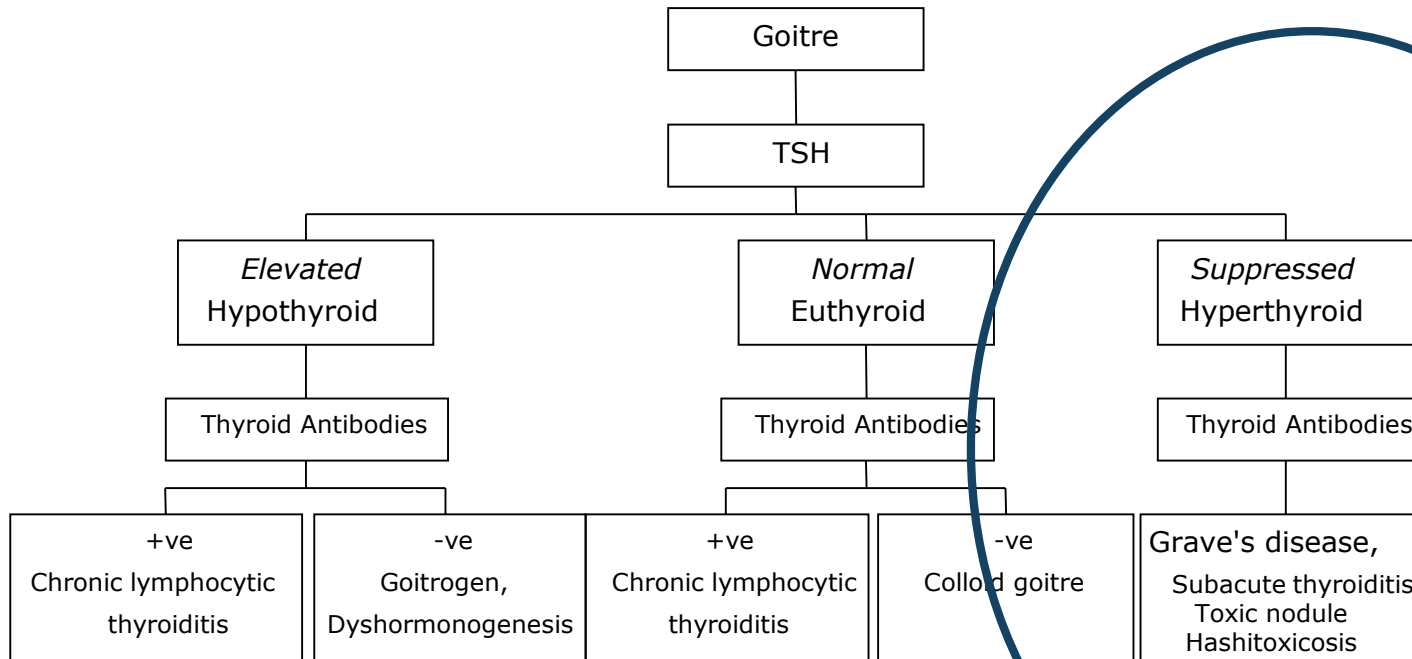
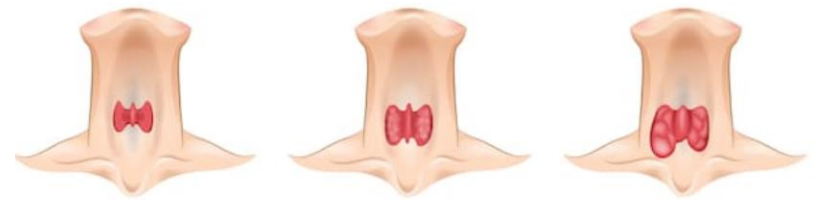
Tablet po

- Place tablet in cheek as they start to nurse/bottle



# APPROACH TO HYPERTHYROIDISM

# Approach to Goitre

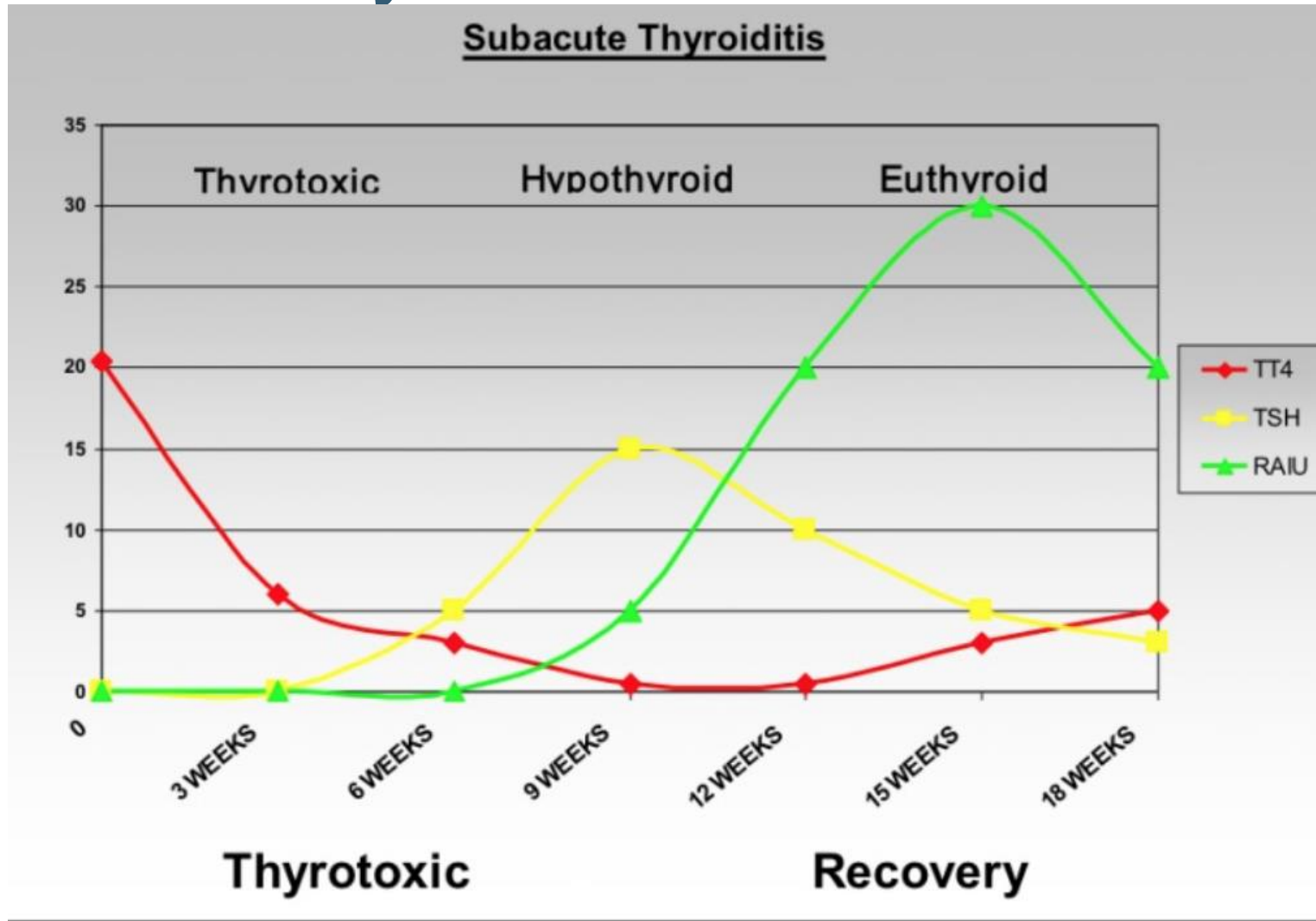


# Causes Hyperthyroidism in Pediatrics

- Graves' disease (>90%)
- Other causes
  - Hashitoxicosis
  - Subacute (deQuervain) thyroiditis
  - Nodule
    - Toxic nodular goiter
    - Toxic adenoma
  - Medications (iodine, amiodarone, lithium)
  - Factitious - Ingestion of  $T_4$
  - TSH-secreting pituitary tumor (very rare)

N Eng J Med, 2011

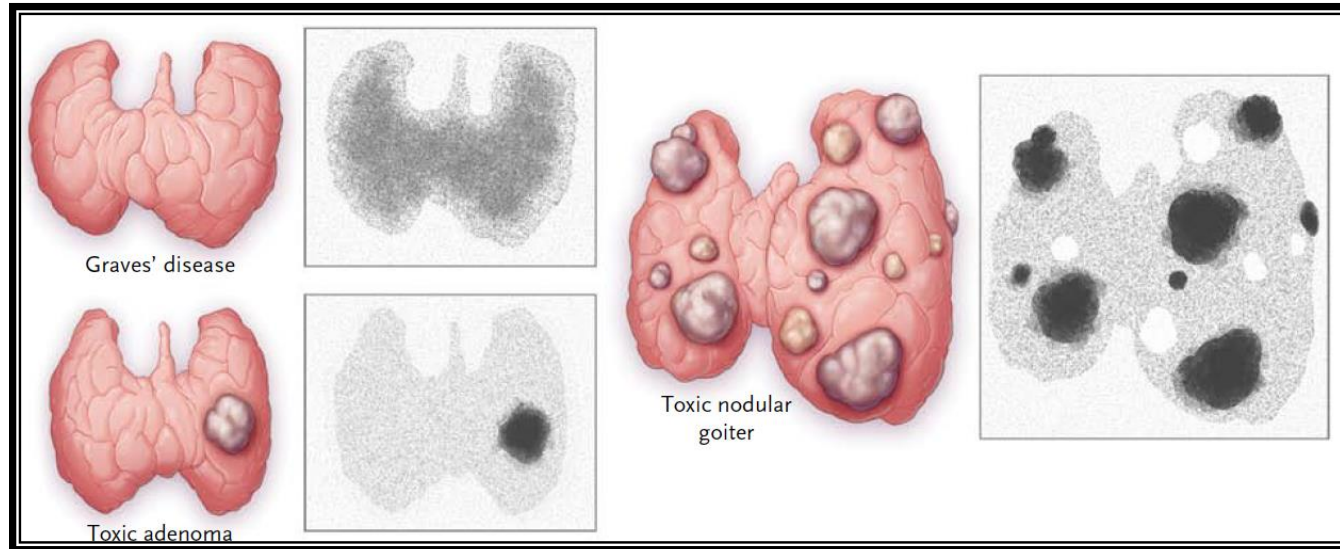
# Subacute thyroiditis



# Hashitoxicosis

- 5-10% of children with Hashimoto thyroiditis present with a transient HYPERTHYROIDISM phase
- Graves ophthalmopathy is absent
- Very high antibodies
- Lasts weeks to months (31-168 days)
  - Levels typically drop quickly after starting antithyroid drugs

# Hot nodule

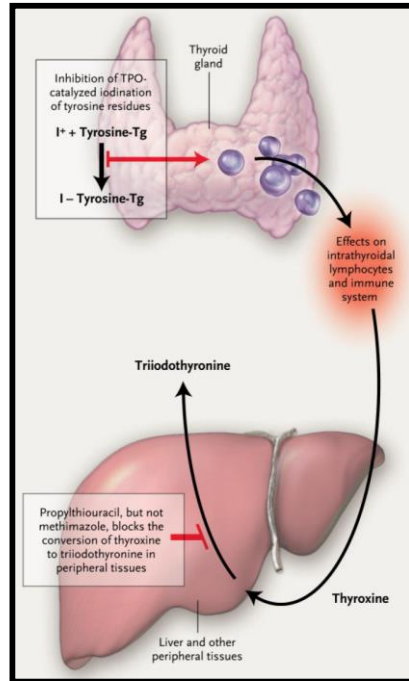


- Typically > 3 cm
- Treatment options: antithyroid medications or surgery

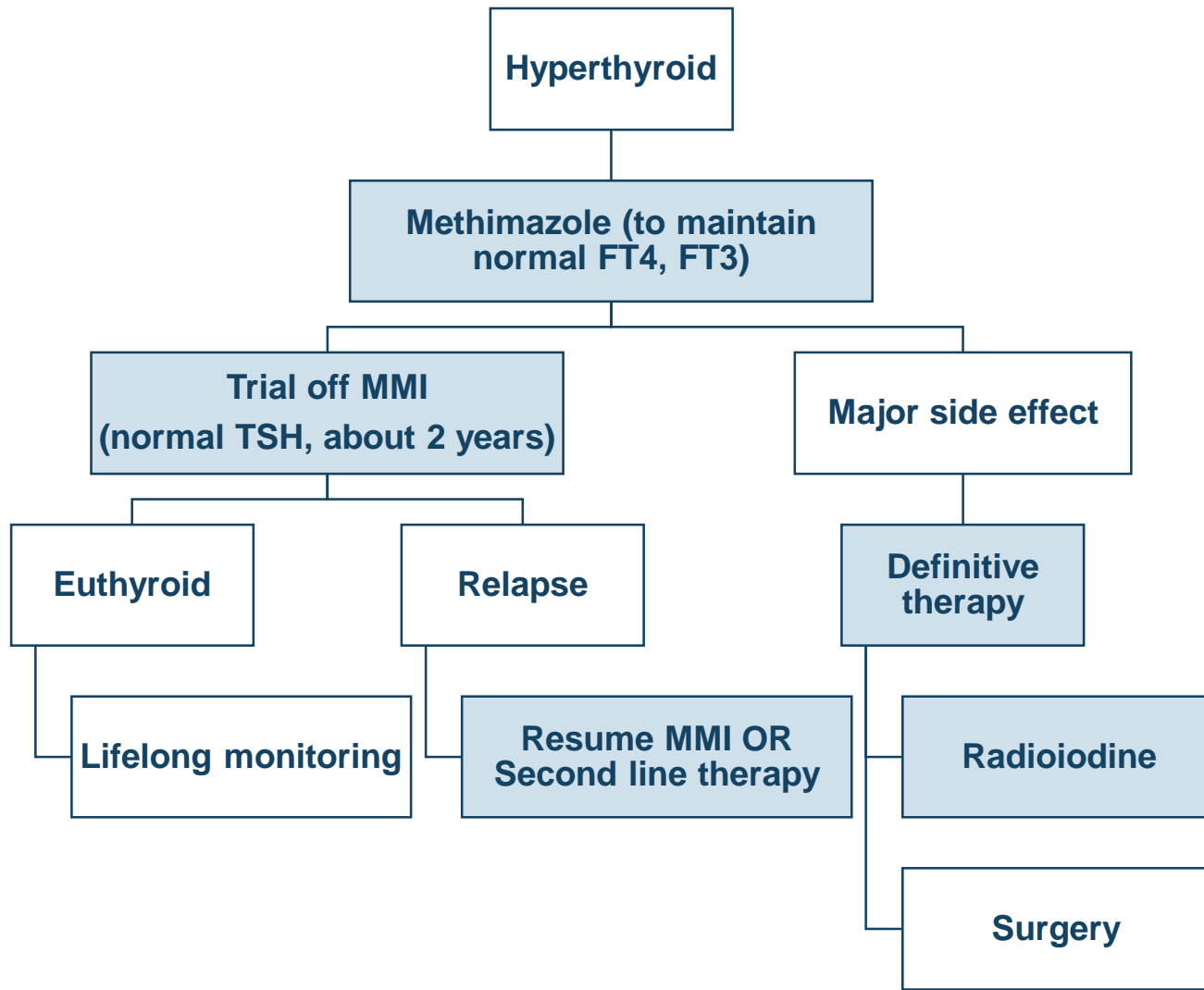
## Question 8

What is the first line treatment for pediatric hyperthyroidism?

- A. Radioiodine
- B. Methimazole
- C. PTU
- D. Surgery



# Management of Graves





## Question 9

You start methimazole. When will you do next bloodwork?

- A. 2 weeks
- B. 1 month
- C. 2 months
- D. 3 months

## Question 9 (no poll)

You start methimazole. When will you do next bloodwork?

- A. 2 weeks
- B. 1 month
- C. 2 months
- D. 3 months

- Typically need monthly labs x 3-4 then q3-4 months
- TSH may be undetectable for many months
- Titrate methimazole to maintain FT4 and FT3 in normal range
- If started propranolol, stop once FT4 is normal (usually 1 month)

# Antithyroid Drugs Side effects

Minor	Major
Skin Rash (4-6%)	Polyarthritits (1-2%)
Arthralgias (1-5%)	Agranulocytosis (0.1-0.2%)
GI Effects (1-5%)	Cholestasis (rare)
Abnormal sense of taste or smell (rare)	ANCA-positive arteritis (rare) (mainly PTU)
Siladenitis (very rare)	Immunoallergic hepatitis (0.1-0.2%) (only PTU)

# Neonatal Graves

- About 1-5% of offspring of women with a history of Graves
- Prenatal:
  - fetal tachycardia, poor fetal growth, goiter, prematurity
- Postnatal:
  - jittery, tachycardia, poor weight gain, staring/ lid retraction, small anterior fontanel, microcephaly
  - Morbidity related to high output cardiac failure, craniosynostosis
- Newborn screening is not helpful to detect neonatal GD
  - Maternal antithyroid drugs
  - Will not detect suppressed TSH

## Question 10

When would you order thyroid function tests in an infant of a mother with PHx of Graves disease?

- A. Birth, day 3-7
- B. Birth, day 3-7 and 2 weeks of age
- C. Birth, day 3-7 then weekly x 1 month
- D. Birth, day 3-7 then q1-2 weeks as long as mother is breastfeeding and taking antithyroid medications

# APPROACH TO THYROID NODULES

# Risk factors for thyroid cancer

- Radiation exposure (particularly at a young age)
- Iodine deficiency
- Several genetic syndrome
- Autoimmune thyroid disease
  
- **Ultrasound features:**
  - hypoechogenicity,
  - irregular margins,
  - increased intranodular blood flow
  - microcalcifications and
  - abnormal cervical lymph nodes increase the likelihood of malignancy

# ACR TI-RADS



COMPOSITION (Choose 1)		ECHOGENICITY (Choose 1)		SHAPE (Choose 1)		MARGIN (Choose 1)		ECHOGENIC FOCI (Choose All That Apply)	
Cystic or almost completely cystic	0 points	Anechoic	0 points	Wider-than-tall	0 points	Smooth	0 points	None or large comet-tail artifacts	0 points
Spongiform	0 points	Hyperechoic or isoechoic	1 point	Taller-than-wide	3 points	Ill-defined	0 points	Macrocalcifications	1 point
Mixed cystic and solid	1 point	Hypoechoic	2 points			Lobulated or irregular	2 points	Peripheral (rim) calcifications	2 points
Solid or almost completely solid	2 points	Very hypoechoic	3 points			Extra-thyroidal extension	3 points	Punctate echogenic foci	3 points

Add Points From All Categories to Determine TI-RADS Level

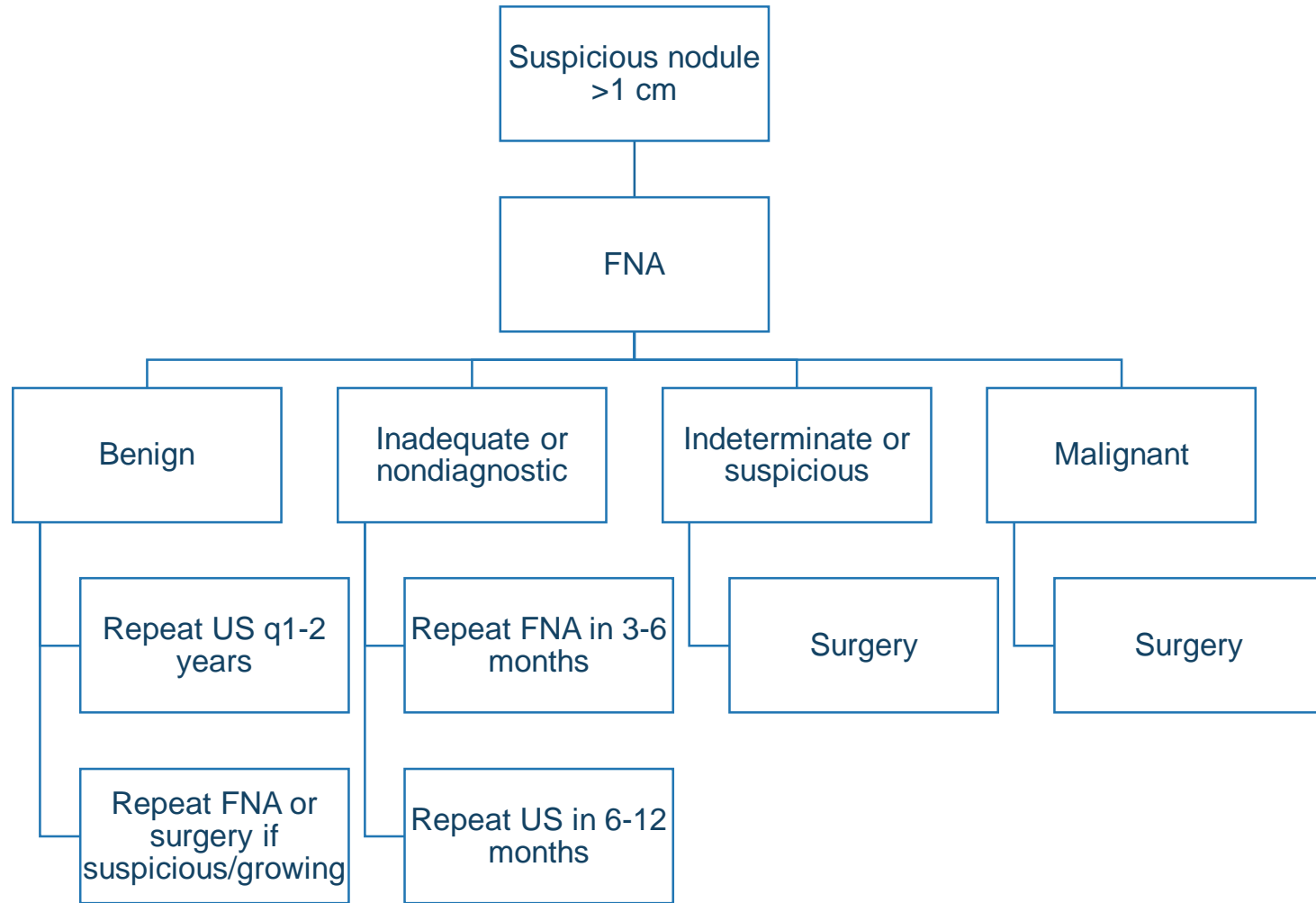


COMPOSITION	ECHOGENICITY	SHAPE	MARGIN	ECHOGENIC FOCI
<p><b>Spongiform:</b> Composed predominantly (&gt;50%) of small cystic spaces. Do not add further points for other categories.</p> <p><b>Mixed cystic and solid:</b> Assign points for predominant solid component.</p> <p>Assign 2 points if composition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

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



# Approach to Pediatric Nodule



# Take home messages

- Thyroid conditions are common
- Reference intervals vary by age and lab
- Goiter is most commonly benign colloid goiter
  - the texture of the gland will give you a clue
  - TSH and TPO are usually the only screening labs needed
  - Ultrasound only if you suspect a nodule (do not routinely ultrasound)
- Hypothyroidism
  - if subclinical and TPO negative, will likely self resolve
  - Outside of infancy, we monitor q6 months or if symptomatic, aiming for TSH WNL
  - Consider re-evaluation after puberty for persistent hypothyroidism
- Congenital hypothyroidism
  - Requires very close monitoring for the first 3 years
  - With normal gland location, consider a trial off treatment at age 3 years

# Take Home Messages

- Hyperthyroidism
  - True hyperthyroidism has an undetectable TSH
  - Typically managed in conjunction with endocrinology with methimazole
  - Radioiodine is a safe option
- Thyroid nodules
  - Colloid cysts are common and usually benign
  - As a general guide, solid nodules require evaluation with FNA if  $> 1$  cm or if calcifications or regional lymphadenopathy