



Thyroid for Primary Care Doctors

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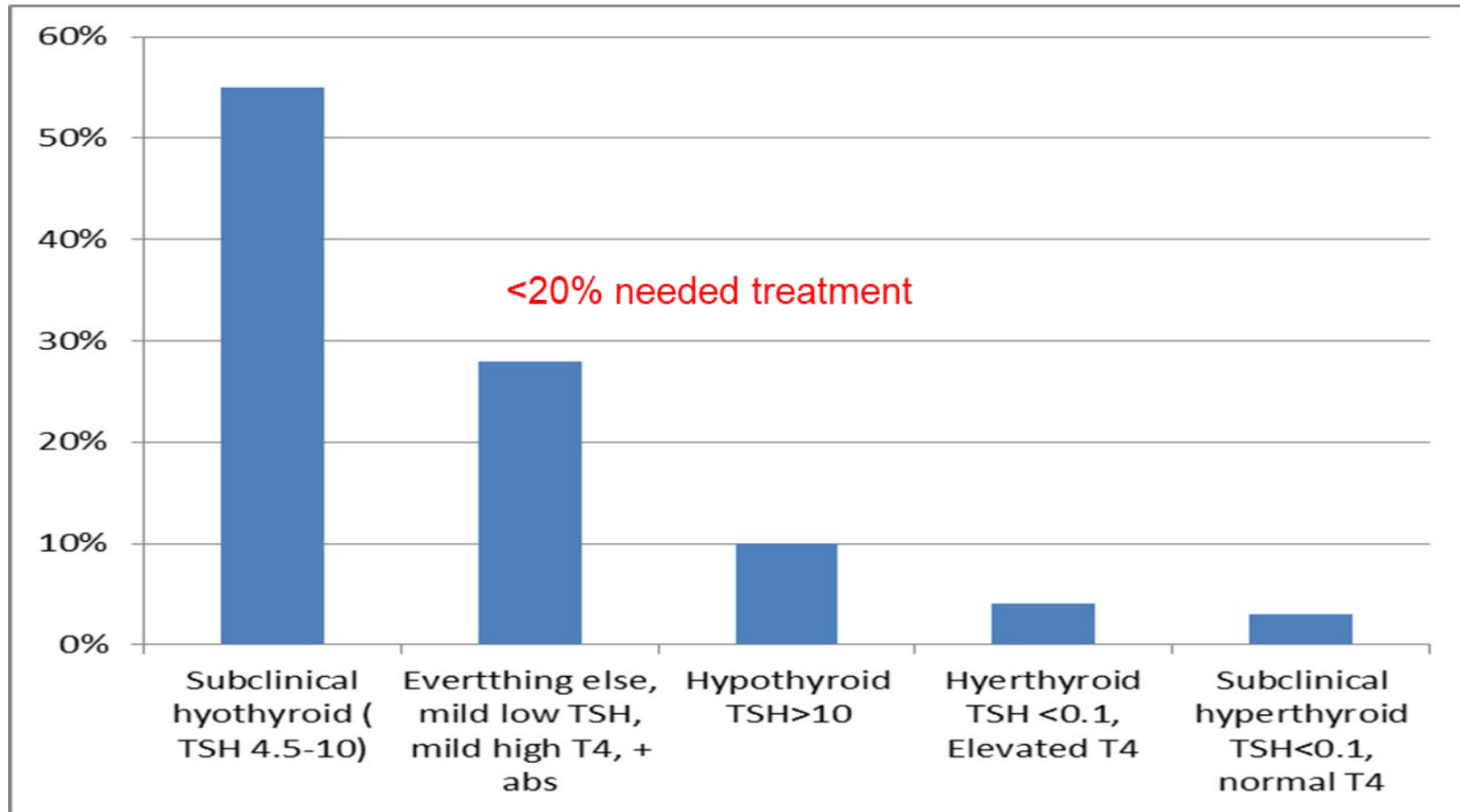
Background

Thyroid tests are commonly ordered in the primary care offices and are the leading cause of referral to endocrinology.

Most thyroid tests end up being normal.

Among those referred to endocrinologist, most do not need treatment.

Distribution of thyroid abnormality amongst 1000 consecutive faxes received from PCP



Objectives

- Review when to order thyroid tests, what to order and how to interpret the results
- Review the 3 common thyroid problems: hypothyroidism, hyperthyroidism and thyroid nodules
- Review who benefits from an endocrine appointment and the process

When to check thyroid levels?

Should all children be screened routinely? No, yield is low and not cost effective.

- Test if you suspect hypothyroidism or hyperthyroidism
- Test if there is thyroid enlargement
- Test if there is suspicion for thyroid nodule

Screening in high-risk children

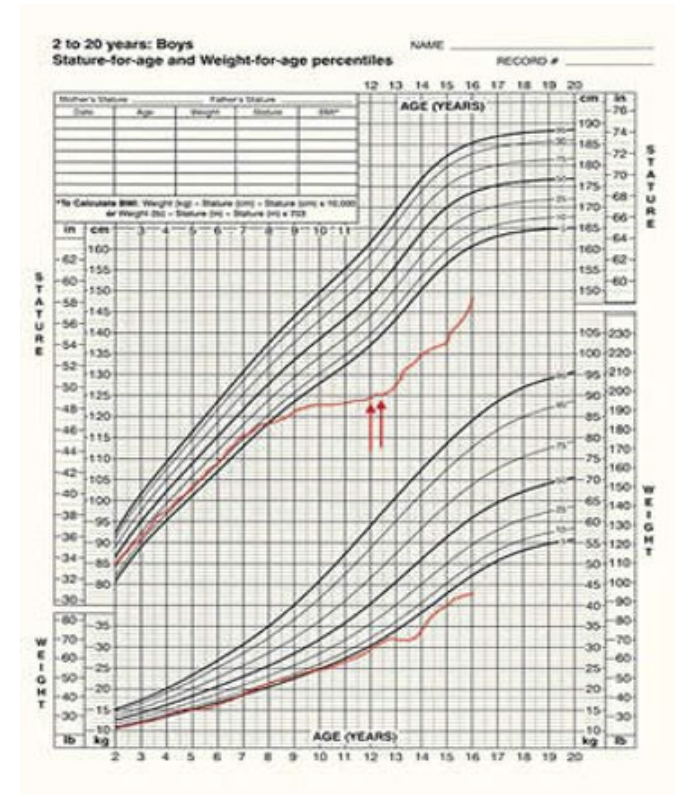
- Newborn: 1:4000 chance for congenital hypothyroidism
- Down syndrome: 4-18% life-time risk, screen at birth, 6 months, 12 months and yearly
- Turner syndrome: every 1-2 years after age 4
- Type 1 diabetes, celiac disease
- Head and neck radiation (oncology patients)
- Medications: Antiepileptics, Lithium, Tyrosine Kinase inhibitors
- FDA recommendation (April 2022): Newborns and children <3 years are at increased risk for hypothyroidism after repeated exposure to Iodinated contrast media

Health supervision for children with Down Syndrome, Pediatrics 2011

Health supervision for children with Turner Syndrome, Pediatrics 2003

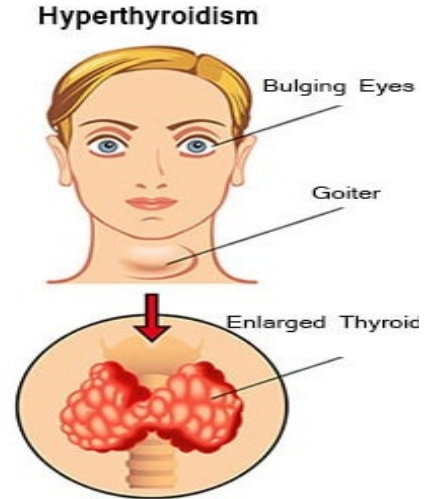
When to suspect hypothyroidism?

- Fatigue
- Constipation
- Cold intolerance
- Pubertal delay
- Menstrual irregularities
- Dry skin
- Goiter+/-
- Poor linear growth with normal weight gain



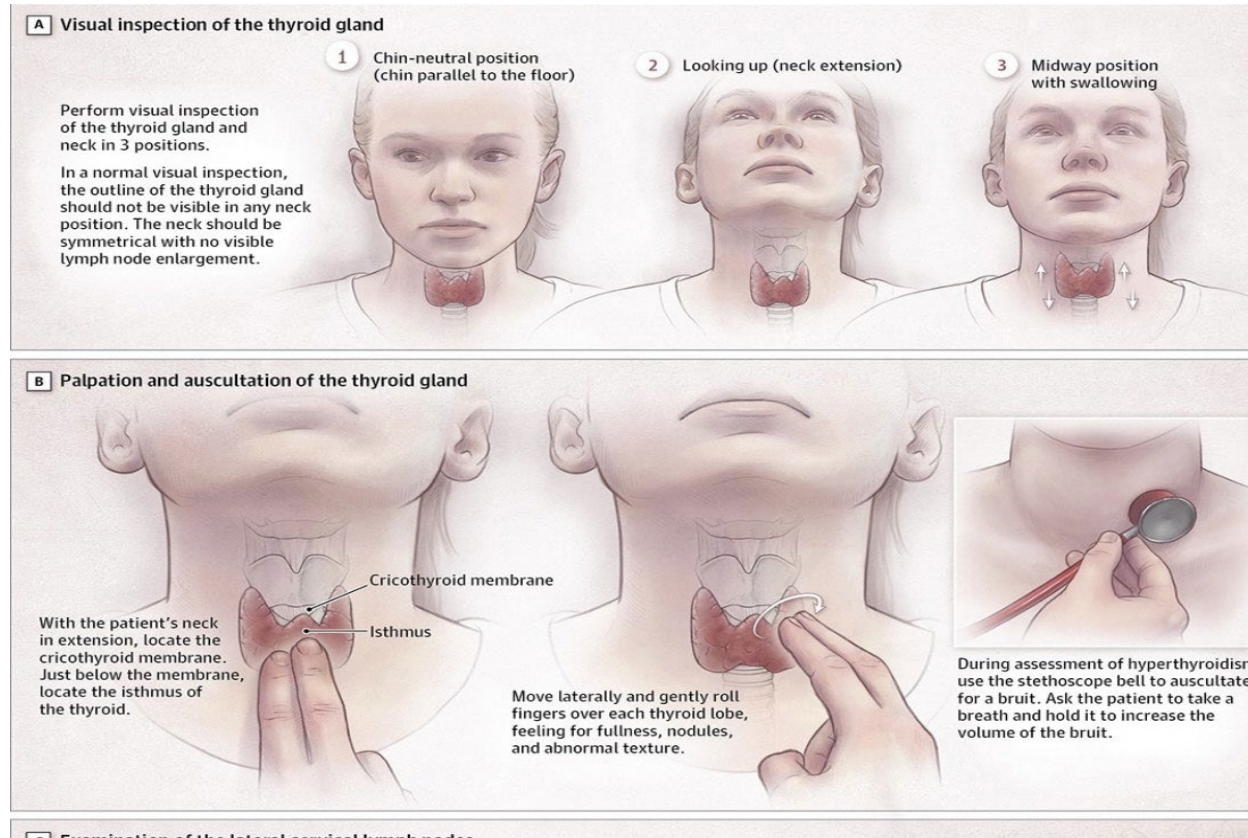
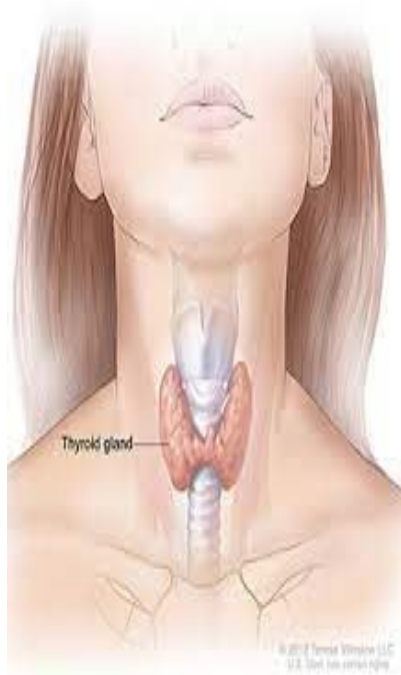
When to suspect hyperthyroidism?

- Unexplained weight loss
- Palpitation
- Heat intolerance
- Hyperactive, behavioral changes
- Poor school performance
- Diarrhea
- Goiter
- Tachycardia, elevated BP
- Tremors
- Exophthalmos



Thyroid exam

Inspection, Palpation and if needed auscultation

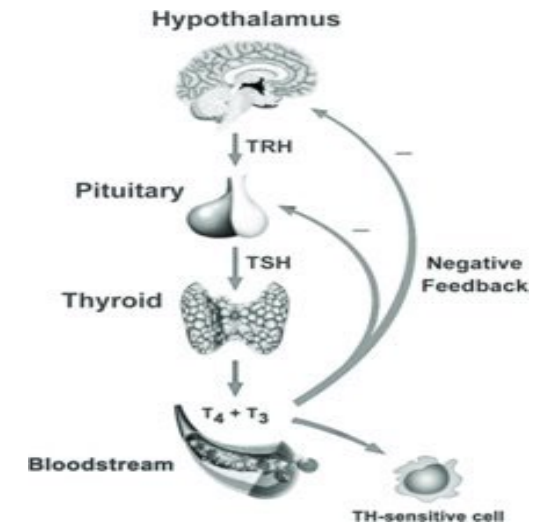


Palpate from behind

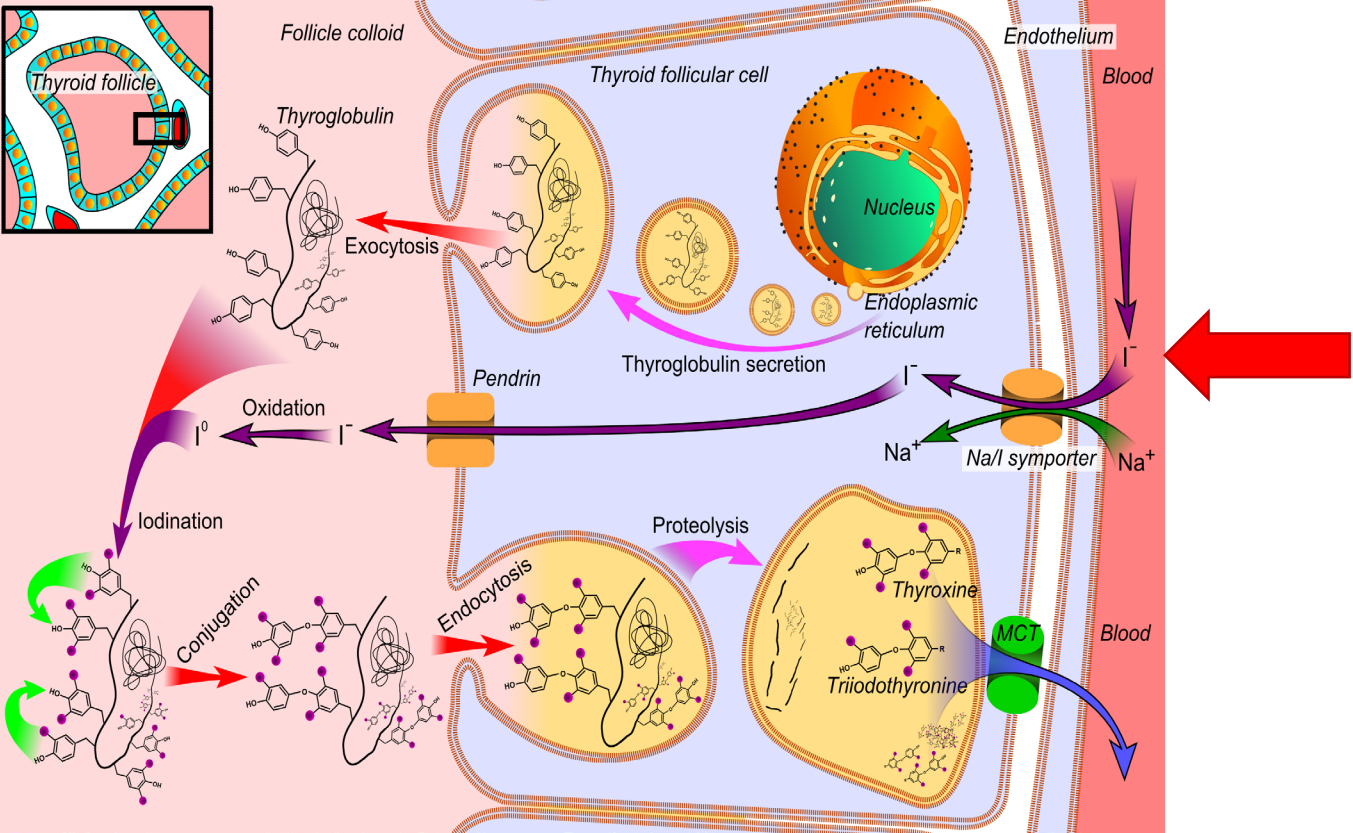


Hypothalamic Pituitary axis and expected change in common disorders

Disorder	TSH (N; 0.5-4.5)	Free T4
Primary Hypothyroidism	>10	Low
Subclinical Hypothyroidism	4.5-10	Normal
Central Hypothyroidism	Normal	Low
Hyperthyroidism	<0.1	High
Subclinical Hyperthyroidism	<0.1	Normal



Thyroid hormone synthesis-Role of Iodine

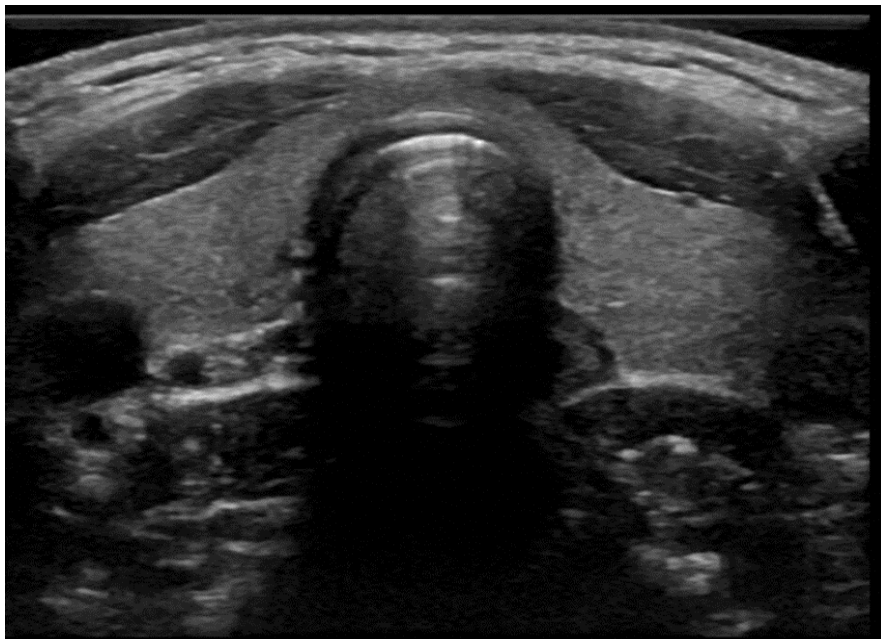


What to order? Utility of different thyroid tests

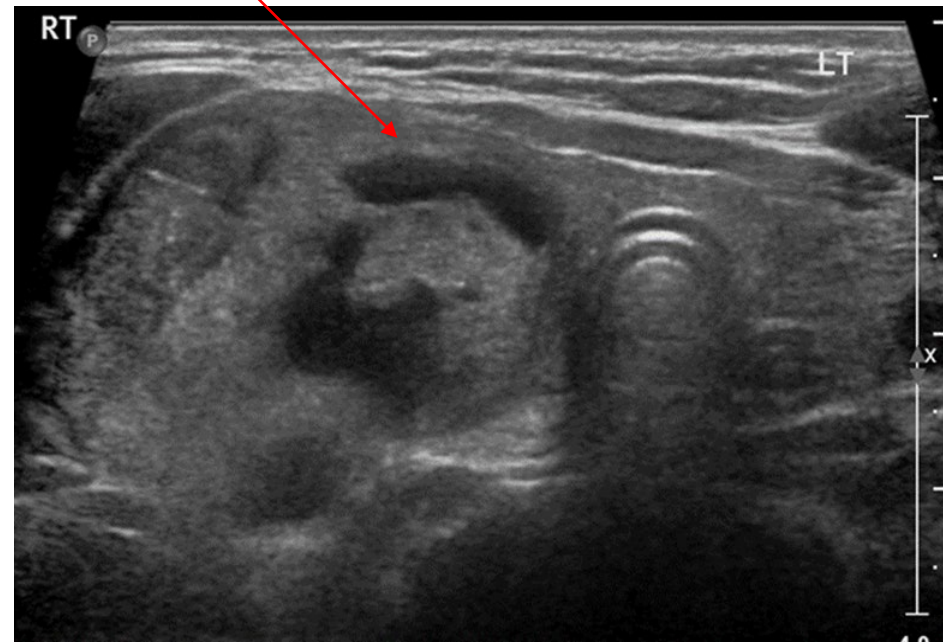
Test	When to order	Comments
TSH	Best screening test	Hypothyroidism and Hyperthyroidism
Free T4 Know the method -Immunoassay -Equilibrium Dialysis (gold standard) -LCMS (CN)	Best screening test with a TSH Higher rate of false low in immunoassay method (quest- free T4 LabCorp- Free T4 direct CN-Free T4 (assay)	Additional benefit of picking up central hypothyroidism due to pituitary problems (congenital, surgery, radiation) where TSH is normal and Free T4 is low
Total T4	Good test	Can be affected by TBG deficiency, medications like OCP
Total T3	Only for hyperthyroidism	
Thyroid peroxidase and anti-thyroglobulin antibody	Thyroid enlargement To further understand the cause of hypothyroidism	Elevation consistent with autoimmunity (Hashimoto)
Thyroid stimulating immunoglobulin (TS)	To understand the cause of hyperthyroidism	Elevation consistent with Graves' disease

Thyroid Ultrasound

Asymmetric thyroid enlargement
Palpable thyroid nodule



Right thyroid nodule



Congenital Hypothyroidism

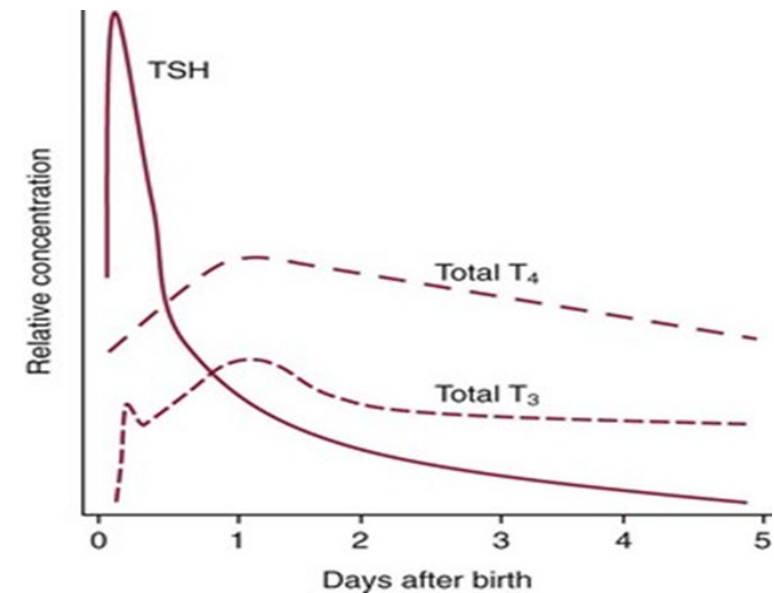
Picked up by newborn screen

Know the screening method in your state

- DC and VA : Both TSH and T4 screened
- MD: Primary T4 screen, lowest 10% get a TSH tested and TSH and T4 reported. Repeat screen in 2 weeks

TSH surge in the first 24 hours

Cause: Thyroid dysgenesis or ectopic gland

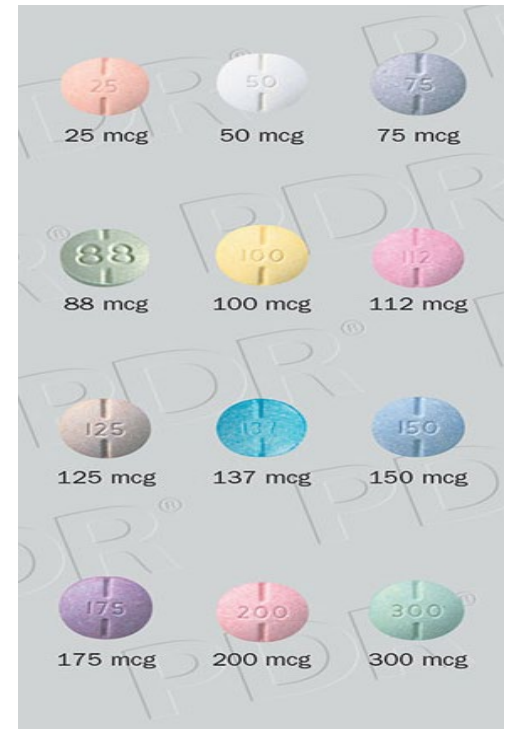


Follow up of abnormal newborn TSH screen

- Confirmatory TSH and Free T4 to be send immediately
- Page endocrinology on call (202-476-5000) and fax report to 202-476-4095 regarding the abnormal screen
- Avoid ED unless on a weekend and no option to get confirmatory labs from a laboratory
- TSH>40, we will start treatment right away
- TSH <40 could wait and repeat in a week and decide
- We don't do scans or additional tests
- Good neurocognitive outcome if L-thyroxine started by 2-3 weeks of age

L-thyroxine therapy

- Available as tablets of various strength
- Crush and dissolve tablet (37.5 mcg) in water, formula or breast milk and give using an oral syringe
- Do not give soy formula, calcium, Iron or antacids at the same time
- Empty stomach preferred as acidic pH aids absorption
- Check TSH and Free T4 in 2 weeks from start of treatment



Acquired hypothyroidism

Autoimmune thyroid disease (Hashimoto), familial
s/p thyroidectomy

s/p radioactive iodine treatment for graves disease

s/p Head and neck radiation treatment

Medications: Lithium, Amiodarone, Anti epileptics, cancer therapy

Treatment with L-thyroxine once a day

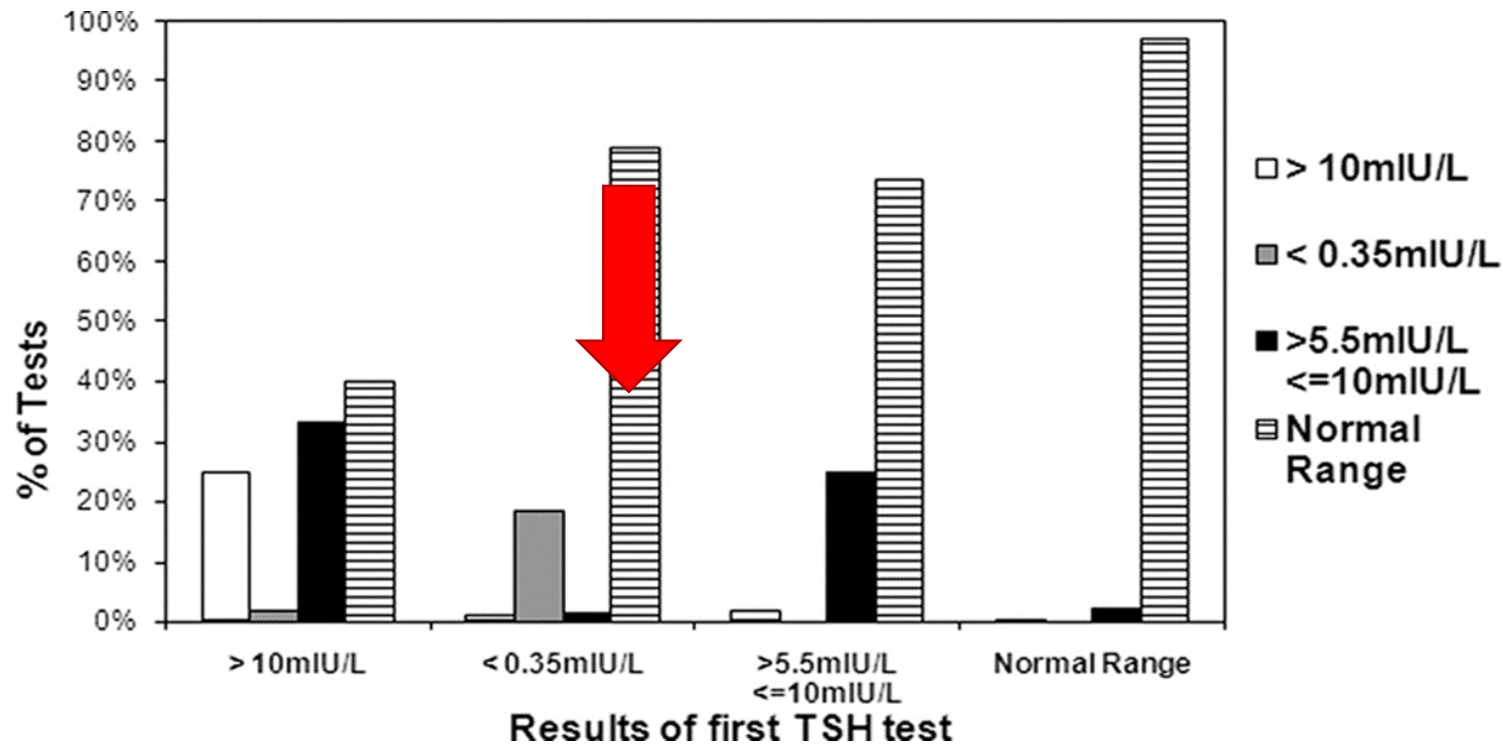


Natural history of subclinical Hypothyroidism (TSH 5-10)

121,052 children in a large pediatric care with TSH results

96.5% normal.

2.9% TSH 5-10 (73% normalized on follow up)



Management of subclinical Hypothyroidism

Mild TSH elevation does not affect growth, BMI or cognitive function
Can be seen in obesity and not a cause of obesity

Repeat TSH, Free T4 and TPO antibody in 4- 6 months.

Subset of patients likely to show persistence/progression are those with
Enlarged thyroid
Positive thyroid antibodies (autoimmunity)
Down syndrome, Turner syndrome
FH of thyroid disease
TSH>7.5

Bottom Line: Refer pts with thyroid enlargement, positive antibody, Down syndrome, or persistent TSH elevation on repeat testing

Impact of weight loss and TSH normalization

	Decrease in BMI-SDS >0.5			Decrease in BMI-SDS 0.2-0.5			No weight loss		
N	23			21			20		
Gender	61% girls			52% girls			45% girls		
	Baseline	Six month later	p	Baseline	Six mths later	p	Baseline	Six mths later	p
BMI z-score	2.9 ± 1.3	2.0 ± 1	0.007	2.8 ± 0.5	2.5 ± 0.6	0.3	2.7 ± 0.5	2.7 ± 0.6	0.4
TSH (μUI/ml)	5.1 ± 1	3.6 ± 1.1	0.0001	5.2 ± 0.9	4.6 ± 2.6	0.3	5.27 ± 1.3	4.6 ± 2.6	0,4

Thyroid function derangement and childhood obesity: an Italian experience
 Anna Grandone,¹ Nicola Santoro,¹ Filomena Coppola,¹ Paolo Calabrò,² Laura Perrone,¹ and Emanuele Miraglia del Giudice

BMC Endocr Disord. 2010; 10: 8.

Etiology of Hyperthyroidism

- Graves disease (autoimmune)
- Hashitoxicosis (transient hyperthyroidism)
- Toxic nodule (Hyperfunctioning nodule)
- Subacute thyroiditis (viral), fever, tender gland
- Bacterial suppurative thyroiditis, fever, toxic looking
- TSH receptor mutations (McCune Albright syndrome)

Treatment of Graves disease

Medical treatment with Methimazole 5-20 mg a day

May start beta blockers

Prolonged treatment for 6-8 years to see if remission is achieved

Permanent treatment are thyroidectomy and Radioactive iodine inducing hypothyroidism

Side effect of Methimazole: rash, Idiosyncratic neutropenia and hepatitis

- If patients on methimazole come with fever and sore throat, send CBC
- If they develop jaundice or vague abdomen symptoms, send LFT

Case

During morning rounds in the newborn nursery, you note a 1-day old F infant with rapid heart rate and poor feeding (HR 180-200). You learn that mom has hypothyroidism. What next?

1. Find out etiology for hypothyroidism- Mom had graves disease and received radioactive iodine 2 years ago
2. Send TSH, T4, Free T4 immediately
3. That evening you get the following labs; TSH <0.001 , T4 24 mcg/dl consistent with Neonatal Graves
4. Page endocrinology (202-476-5000)
5. We will help start Methimazole and Propranolol

Transplacental transfer of TSH receptor antibody and resolved in about 2 months. If mom taking methimazole, presentation can be delayed.

Management of neonate at risk for neonatal graves

Check Maternal TSH receptor antibody (TRAb) in 2nd/3rd trimester or in Cord blood and if negative, no risk.

If unknown or positive TRAb and symptomatic, immediately send TSH, Free T4, TRAb from the neonate and page endocrine.

If unknown antibody status and asymptomatic, page endocrine and follow this pathway and update results as available. Do not discharge until we have at least one set of results

- Day 1 Physicals and TRAb
- Day 3-5 Physicals, TSH, Free T4
- Day 10-14 TSH, Free T4 to capture delayed hyperthyroidism
- 4 weeks and 8 weeks PCP follow up

Management of Neonates Born to Mothers With Graves' Disease,
NEJM, 2016

Evaluation for thyroid nodule

All patient with suspected thyroid nodule should get a TSH screen and an Ultrasound.

All patients should be referred to endocrinology with thyroid sonogram on a CD and a copy of thyroid labs for an expedited appointment in the multidisciplinary THYNC clinic (Thyroid nodule and cancer clinic) by faxing reports to 202-476-4095 and if urgent can page on call endocrine provider or email me directly at pvaidyan@childrensnational.org.

After review of the sonogram, suitable patients are offered fine needle aspiration cytology and molecular genetic analysis. We are a high-volume thyroidectomy center.

Further care of thyroid cancer patient is individualized and coordinated by endocrinology and the multidisciplinary team.

What could be going on?

15 y/o F with congenital hypothyroidism on a stable dose of 100 mcg of L-thyroxine for several years. A routine TSH came back low at 0.11 and Free T4 high at 1.9 and dose reduced to 88 mcg/day. Mom called 3 months later worried that the test is still abnormal, and that the child was not feeling well. PCP had done labs and her TSH was low again at 0.1 and Free T4 again high at 2 ng/dl.

Biotin Treatment Mimicking Graves' Disease (2016)

Table 1. Characteristics of Six Children with Biotin-Induced Laboratory Indications of Autoimmune Hyperthyroidism.*

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Sex	Female	Female	Male	Male	Male	Male
Age	9 yr	2 yr	2 yr	5 mo	1 mo	1 mo
Primary disease	BTBGD	BTBGD	BTBGD	Infantile mitochondrial disease	Neonatal mitochondrial disease	Neonatal mitochondrial disease
Biotin dose (mg/kg/day)	10	14	15	2	7	8
Concomitant medication	Thiamine	Thiamine, methimazole, cholecalciferol, levetiracetam, chloral hydrate	Thiamine, methimazole, oxcarbazepine	Thiamine, sodium phenylbutyrate, propranolol, nystatin, cholecalciferol	CoQ10, thiamine, cholecalciferol, carnitine, riboflavin, bisoprolol, aspirin, furosemide	CoQ10, thiamine, methimazole, cholecalciferol, carnitine, riboflavin
Laboratory results						
During biotin treatment						
Thyrotropin (μ IU/ml)	0.05	0.02	0.04	0.02	0.08	0.03
Free T ₄ (ng/dl)	6.24	>7.77	>7.77	>7.77	>7.77	>7.77
Anti-thyrotropin receptor antibodies (IU/liter)	38.6	>40.0	>40.0	>40.0	>40.0	>40.0
Total T ₃ (ng/dl)	>6.5	ND	>6.5	>6.5	>6.5	ND
1–7 Days after discontinuation of biotin						
Thyrotropin (μ IU/ml)	1.80	3.75	6.07	2.20	8.12	2.87
Free T ₄ (ng/dl)	1.58	1.70	1.16	1.13	1.84	1.91
Anti-thyrotropin receptor antibodies (IU/liter)	<0.3	ND	0.7	1.0	0.4	<0.3
Total T ₃ (ng/dl)	2.0	ND	1.8	ND	1.8	2.3
Antithyroid medication	No	Methimazole treatment for 14 mo with up to 1.9 mg/kg/day [†]	Methimazole treatment for 3.5 mo with up to 0.9 mg/kg/day [‡]	No	No	Methimazole treatment for 2 wk

* Serum biotin levels were highly elevated in all children during therapy (>3000 ng per liter). Levels of free thyroxine (T₄), total triiodothyronine (T₃), and thyrotropin were normalized within 24 to 48 hours after the discontinuation of biotin in all patients, whereas normalization of levels of anti-thyrotropin receptor antibodies took up to several days in some patients. Normal ranges are as follows: thyrotropin, 0.85 to 6.46 μ IU per milliliter; free T₄, 0.94 to 1.71 ng per deciliter; anti-thyrotropin receptor antibodies, less than 1.7 IU per liter; and total T₃, 0.8 to 2.6 ng per deciliter. BTBGD denotes biotin-thiamine-responsive basal ganglia disease, CoQ10 coenzyme Q10, and ND not determined.

[†] After the discontinuation of biotin, mild hypothyroidism became evident, with spontaneous recovery after the discontinuation of methimazole. Possible long-term complications due to transient hypothyroidism are unclear in this patient.

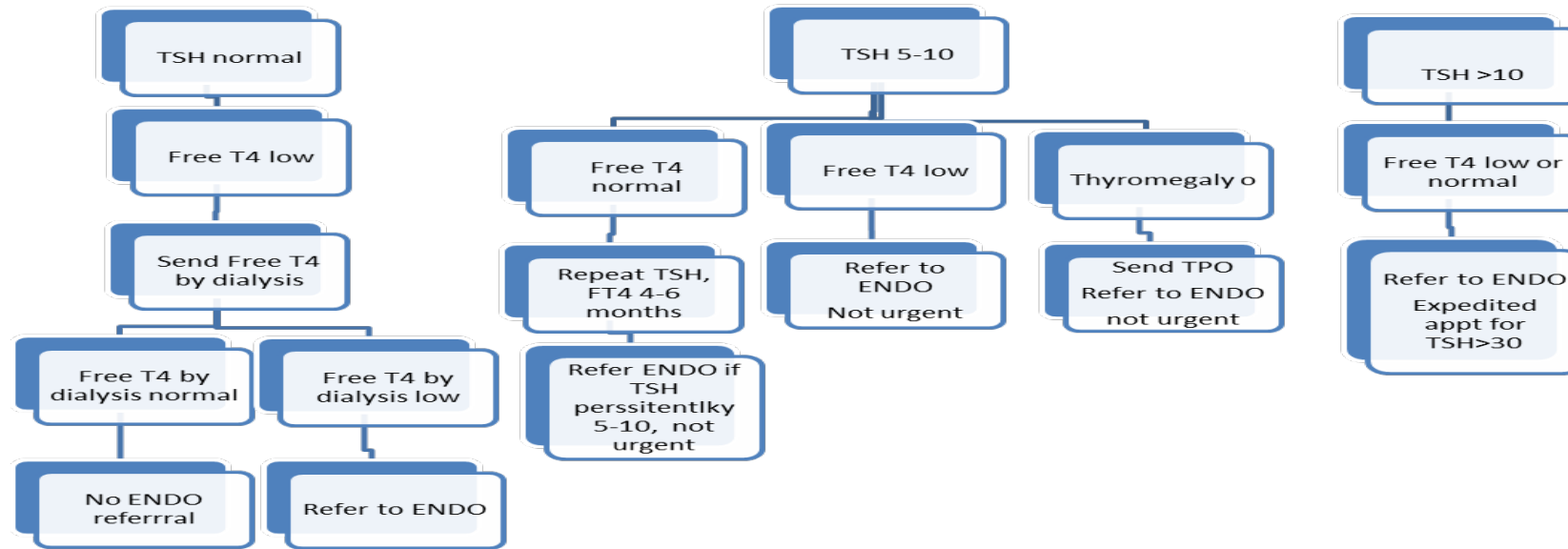
[‡] Methimazole treatment intermittently normalized laboratory values during biotin treatment. After the discontinuation of biotin and methimazole, all values normalized completely. There was no evidence of long-term complications due to transient hypothyroidism.

ATA recommends stopping high dose Biotin for 2 days before test

Interpretation of thyroid tests

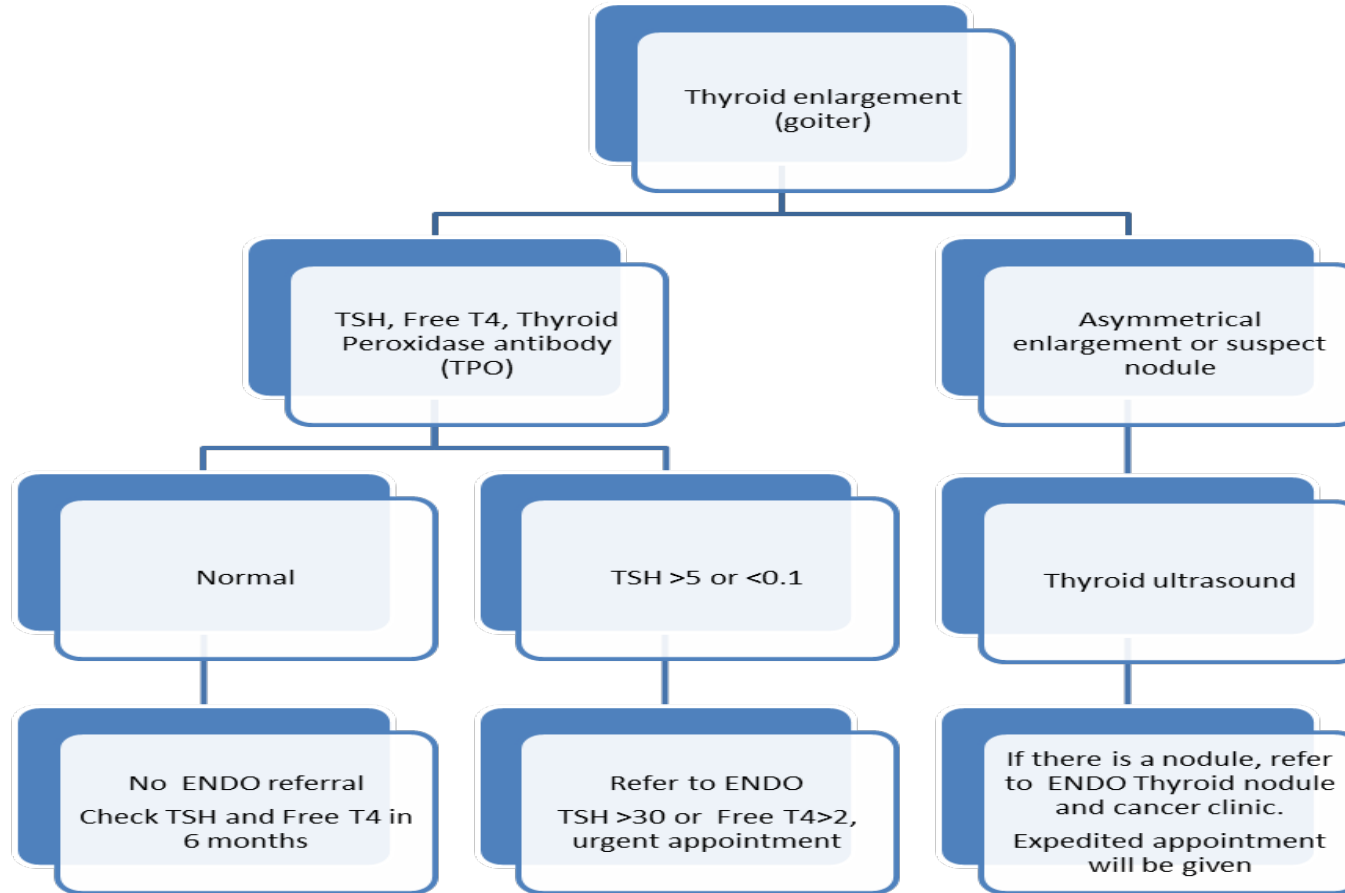
TSH (0.5-4.5)	Free T4 (0.9-1.6)	Total T4 (4.5-10)	Total T3 (80-200)	Diagnosis
50	0.8			Primary Hypothyroidism likely autoimmune, refer
6.2	1.4			Subclinical hypothyroidism. Recheck in 6 months with antibodies, Refer if persistent, Down syndrome, +ve antibody, goiter
4	0.56			Central Hypothyroidism but check the Free T4 assay to be sure, refer
<0.1	4		450	Hyperthyroidism, refer
3.1		3.2		TBG deficiency is possible in otherwise well child, XL, check Free T4 and if normal, no need to refer
2.4		12		Check if on OCP, can cause TBG excess
0.46	1.5		150	Not worrisome
2.2	1.1		213	Not worrisome
1.4	1.2			TPO antibody positive, can check TSH in 6 months

TSH flow chart



Fax lab results to 202-476-4095 with contact information for the family. The family will be contacted directly to set up an appointment. If an expedited appointment is required beyond our triage flow chart, do not hesitate to contact our on-call doctor at 202-476-2121.

Thyroid enlargement flow chart



Thank You!

