

Thyroid Disease Testing

Policy Number: AHS – G2045 – Thyroid Disease Testing	Prior Policy Name and Number, as applicable:
Initial Presentation Date: 03/19/2015 Revision Date: 09/01/2021	
Department Approval: Medical Policy	
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I. Policy Description

Thyroid hormones are necessary for prenatal and postnatal development, as well as metabolic activity in adults (Brent, 2017, 2020).

Thyroid disease includes conditions which cause hypothyroidism, hyperthyroidism, goiter, thyroiditis (which can present as either hypo- or hyperthyroidism) and thyroid tumors (Rugge, Bougatsos, & Chou, 2015).

Thyroid function tests are used in a variety of clinical settings to assess thyroid function, monitor treatment, and screen asymptomatic populations for subclinical or otherwise undiagnosed thyroid dysfunction (Ross, 2019c).

II. Related Policies

Policy Number	Policy Title
AHS-G2035	Prenatal Screening
AHS-G2009	Preventive Screening in Adults
AHS-G2042	Pediatric Preventive Screening

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request

1. Thyroid function testing **MEETS COVERAGE CRITERIA** in the following situations:

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- a. Individuals with symptoms consistent with hypothyroidism (See Policy Guidelines)
 - i. TSH to confirm or rule out primary hypothyroidism.
 - ii. Free T4 as a follow up to abnormal TSH findings
 - iii. Free T4 as a follow up in cases of suspected secondary hypothyroidism when TSH is normal
 - iv. TSH to distinguish between primary and secondary hypothyroidism.
 - v. TSH, free T4 for monitoring individuals being treated for hypothyroidism every 6-12 weeks upon dosage change and annually in stable individuals.
- b. Individuals with symptoms consistent with hyperthyroidism (See Policy Guidelines)
 - i. TSH to confirm or rule out primary hyperthyroidism
 - ii. Free T4 as a follow up to abnormal TSH findings
 - iii. Total or free T3 as a follow up to abnormal FT4 findings or if still concerned with hyperthyroidism
 - iv. Free T4 to distinguish between primary and secondary hyperthyroidism
 - v. TSH and free T4 should be measured for monitoring individuals being treated for hyperthyroidism every 6-12 weeks
 - vi. Monitoring individuals closely after treatment for hyperthyroidism
 - a) Close monitoring first 3 months post treatment
 - b) Annual monitoring after first year even if asymptomatic for risk of relapse or late-onset hypothyroidism
- c. Asymptomatic individuals at high risk for thyroid disease due to:
 - i. A personal or family history of thyroid dysfunction (limited to one time)
 - ii. Personal or family history of type 1 diabetes or other autoimmune disorder (limited to one time)
 - iii. Prescribed drugs that can interfere with thyroid function (annually or when dosage or medication changes). Drugs interfering with thyroid function include, but are not limited to, amiodarone, interferon, iodine, lithium, tyrosine kinase inhibitors, sulfonamides

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- d. Women undergoing evaluation for infertility
- e. Women in pregnancy and postpartum
 - i. Monitoring of pregnant women being treated for hypothyroidism, every 4 weeks
 - ii. Free T₄ or Total T₄ testing for management of thyroid disease during pregnancy (see Note 1)
 - iii. FT₄ measurements in all patients in 1st trimester in the presence of a suppressed serum TSH
 - iv. Measurement of serum total T₃ (TT₃) and *thyrotropin receptor antibodies (TRAb)* for establishing a diagnosis of hyperthyroidism
 - v. TSH testing if there is a thyroid nodule
 - vi. TSH to evaluate hypothyroidism in the first trimester pregnancy and in the postpartum period
 - vii. TSH in euthyroid, but TPO or Tg antibody positive pregnant women
 - viii. Serum TSH in early pregnancy in the following situations:
 - a) History of thyroid dysfunction or prior thyroid surgery
 - b) Age >30 years
 - c) Symptoms of thyroid dysfunction or the presence of goiter
 - d) TPOAb positivity
 - e) Type 1 diabetes or other autoimmune disorders
 - f) History of miscarriage or preterm delivery
 - g) History of head or neck radiation
 - h) Family history of thyroid dysfunction
 - i) Morbid obesity (BMI \geq 40 kg/m²)
 - j) Use of amiodarone or lithium, or recent administration of iodinated radiologic contrast
 - k) Infertility
 - l) Residing in an area of known moderate to severe iodine insufficiency

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- m) TSH, FT₄, and *TPOAb* tests in postpartum depression
- f. Patients with disease or neoplasm of the thyroid or other endocrine glands
- g. Individuals with chronic or acute urticaria.
- h. TSH testing of individuals undergoing immune reconstitution therapy (IRT)
 - i. Individuals with active relapsing remitting multiple sclerosis (MS) undergoing therapy with alemtuzumab (Lemtrada)
 - ii. Individuals with HIV undergoing highly active antiretroviral therapy (HAART)
 - iii. Individuals following allogeneic bone marrow transplantation (BMT) or hematopoietic stem cell transplantation (HSCT)
- i. Individuals suspected of central hypothyroidism
- j. Pediatric individuals diagnosed with short stature.
- 2. Testing for thyroid antibodies **MEETS COVERAGE CRITERIA** for the evaluation of autoimmune thyroiditis.
- 3. Testing for serum thyroglobulin and/or anti-thyroglobulin antibody levels **MEETS COVERAGE CRITERIA** for individuals with thyroid cancer for detection of tumor recurrence, post-surgical evaluation, surveillance and maintenance for differentiated thyroid carcinomas.
- 4. Testing for thyrotropin-releasing hormone (TRH) **MEETS COVERAGE CRITERIA** for the evaluation of the cause of hyperthyroidism or hypothyroidism.
- 5. Testing of reverse T3, T3 uptake and total T4 **DOES NOT MEET COVERAGE CRITERIA** in all situations except for the following:
 - a. Total T4 testing for management of thyroid disease during pregnancy (see Note 1)
- 6. Measurement of total T3 and/or free T3 **DOES NOT MEET COVERAGE CRITERIA** in the assessment of hypothyroidism.
- 7. Measurement of total or free T3 level **DOES NOT MEET COVERAGE CRITERIA** when assessing levothyroxine (T4) dose in hypothyroid patients.
- 8. Testing for thyroid dysfunction in asymptomatic nonpregnant individuals for thyroid disease **DOES NOT MEET COVERAGE CRITERIA** during general exam without abnormal findings.

Note 1: Due to significant changes in Thyroid physiology during pregnancy, measurement of hormone levels should only be performed at labs that have trimester specific normal ranges for

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their assay(s). While FT4 is the preferred test, TT4 may be useful if the TSH and FT4 results are discordant or when trimester specific normal ranges for FT4 are unavailable.

Policy Guidelines

Hypothyroidism signs and symptoms may include:

1. Fatigue
2. Increased sensitivity to cold
3. Constipation
4. Dry skin
5. Unexplained weight gain
6. Puffy face
7. Hoarseness
8. Muscle weakness
9. Elevated blood cholesterol level
10. Muscle aches, tenderness and stiffness
11. Pain, stiffness or swelling in your joints
12. Heavier than normal or irregular menstrual periods
13. Thinning hair
14. Slowed heart rate
15. Depression
16. Impaired memory

Hyperthyroidism signs and symptoms may include:

Hyperthyroidism can mimic other health problems, which may make it difficult for your doctor to diagnose. It can also cause a wide variety of signs and symptoms, including:

1. Sudden weight loss, even when your appetite and the amount and type of food you eat remain the same or even increase
2. Rapid heartbeat (tachycardia) — commonly more than 100 beats a minute — irregular heartbeat (arrhythmia) or pounding of your heart (palpitations)

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3. Increased appetite
4. Nervousness, anxiety and irritability
5. Tremor — usually a fine trembling in your hands and fingers
6. Sweating
7. Changes in menstrual patterns
8. Increased sensitivity to heat
9. Changes in bowel patterns, especially more frequent bowel movements
10. An enlarged thyroid gland (goiter), which may appear as a swelling at the base of your neck
11. Fatigue, muscle weakness
12. Difficulty sleeping
13. Skin thinning
14. Fine, brittle hair

IV. Scientific Background

The thyroid gland regulates metabolic homeostasis through production of thyroid hormones. Thyroid disease is estimated to occur in approximately 20 million Americans, much of which is undiagnosed (Rugge et al., 2015). The thyroid gland is regulated by thyroid stimulating hormone (TSH), which is secreted by the anterior pituitary to stimulate secretion of two hormones, thyroxine (T4) and triiodothyronine (T3). Thyroid function is assessed with one of the following: serum TSH concentration, serum total T4 concentration, serum total T3 concentration, or serum free T4 (or T3) concentration. However, measurement of serum free T4 and T3 tend to have significant issues, such as mathematically adjusting for protein binding abnormalities (Ross, 2019c).

Thyroid hormones must be maintained within a carefully regulated range with adverse clinical consequences at hypothyroid or hyperthyroid extremes. Hypothyroidism has multiple causes, such as the under-secretion of T4 and T3, elevated TSH, or thyroid releasing hormone deficiency. Symptoms include fatigue, chills, weight gain, hair loss, poor concentration, dry skin, and constipation (Ross, 2019a). Another well-documented consequence of hypothyroidism during childhood is that of short stature, serving as presenting feature and is linked to delayed bone age as those treated for hypothyroidism often resume their normal growth potential (Richmond & Rogol, 2021). Thus, newborns with undetected or untreated hypothyroidism will have both mental and physical developmental delay. Hypothyroidism during pregnancy increases the risk for miscarriage, preterm delivery and pre-eclampsia (Alexander et al., 2017). Hyperthyroidism is the oversecretion of T4 and T3 resulting in symptoms such as palpitations, heat intolerance, sweating, weight loss, hyperactivity, and

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fatigue. Because a number of these symptoms are so common and nonspecific, they may be subtle and unrecognized. Both conditions rely on laboratory testing to confirm diagnosis (Ross, 2019a, 2019b).

Current assays for TSH are extremely sensitive at detecting changes in thyroid homeostasis prior to changes in T4 and T3 levels. TSH is most used as an initial test for thyroid function. In general, if the serum TSH is normal, no further testing is needed; however, if serum TSH is high, free T4 is used to determine the degree of hypothyroidism, whereas if serum TSH is low, free T4 and T3 are used to determine the degree of hyperthyroidism. Additionally, if a pituitary or hypothalamic condition is suspected, then both serum TSH and free T4 may be measured, and serum free T4 may be measured if symptoms of hyper- or hypothyroidism are present even if TSH levels are normal (Ross, 2019c). Measurement of free T4 is regarded as a better indicator of thyroid function than total T4 measurement for most situations, as it reflects the amount of available hormone. However, in pregnant individuals, measurement of total T4 is recommended due to significant changes in serum proteins during pregnancy and lack of trimester-specific free T4 reference ranges. Subclinical thyroid dysfunction is defined as an elevated or low TSH test in the setting of normal thyroid hormone levels (Taylor, Razvi, Pearce, & Dayan, 2013). Presently there is considerable controversy as to the appropriate upper limit of normal for serum TSH (currently 0.4-5 mU/L) as well as the cost effectiveness of screening asymptomatic patients (Ross, 2019c).

Thyroiditis may be caused by an autoimmune disorder, an infection, or exposure to certain drugs or toxic chemicals which can be either acute or chronic. The evaluation of possible autoimmune thyroid disorders includes testing for the presence of thyroid antibodies. Several antibodies against thyroid antigens have been described in chronic autoimmune thyroiditis. The antigens include thyroglobulin (Tg), thyroid peroxidase (TPO) and the thyrotropin receptor (TRAb). However, different levels of antibodies correspond to different conditions—for example, nearly all patients with Hashimoto's thyroiditis have high serum concentrations of antibodies to Tg and TPO. Thyrotropin receptor antibodies (TRAb) can be classified as stimulating, blocking, or neutral. Stimulating TRAb cause Graves' disease; however, both blocking and stimulating antibodies can be seen in patients with Graves' disease. Although these antibodies are not typically routinely measured in evaluating thyroid function, measuring them may still be helpful for more specific goals, such as predicting progression of hypothyroidism (Ross, 2019c).

Assessment of the thyroid is particularly important for pregnant individuals. Due to the metabolic changes during pregnancy, the levels of thyroid hormones differ dramatically. For example, thyroxine-binding globulin nearly doubles due to the increased estrogen and TSH is influenced slightly by human chorionic gonadotropin. It is common to find trimester-specific ranges for thyroid hormones that are different from typical reference ranges. Free T4 and TSH are the most typically measured hormones during pregnancy, with total T4 measured if free T4 and TSH measurements do not agree (Ross, 2019d).

The effects of thyroid problems during pregnancy may be dire. Luewan, Chakkabut, and Tongsong (2011) performed a study comparing 180 pregnant women with hyperthyroidism to

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360 controls. The authors found that the mean gestational age and mean birth weight were significantly lower in the study group. The incidence of fetal growth restriction, low birth weight, and preterm weights were 1.3, 1.4, and 1.3 times higher respectively in the study group compared to the control group (Luewan et al., 2011).

The imbalance of thyroid hormones is not only harmful to pregnant individuals, but these effects can also extend to children, producing short stature. Thyroid hormone isoforms and thyroid hormone play an important role in bone development and growth, as defects associated with congenital hypothyroidism include delayed epiphyseal closure and widely spaced cranial sutures (Leung & Brent, 2016). During development, these effects extend to influence chondrocytes and growth plate cartilage in bones. Mediation of the chondrogenesis—the formation of cartilage from condensed mesenchyme tissue—by the endocrine system takes place through the action of hormones including growth hormone, insulin-like growth factor 1 (IGF-1), androgens, glucocorticoids, and thyroid hormone. It is believed that the balance between proliferation and senescence of chondrocytes at the growth plate of bones play a crucial role in both normal and pathologic variations of linear growth, though the pathways are unclear as of date (Leung & Brent, 2016; Richmond & Rogol, 2021).

Tests measuring levels of thyroid-related markers are widely commercially available, often as a panel. Many combinations of thyroid serum markers are available. For example, HealthCheck offers a panel assessing reverse T3, TSH, FT3, and FT4 (HealthCheck, 2020). Health Testing Centers offers thyroid tests which screen for individual thyroid hormones including TSH, FT4, and FT3 (Health_Testing_Centers, 2020). EverlyWell offers a direct-to-consumer home-health panel testing for TSH, T3, T4, and thyroid peroxidase antibodies (EverlyWell, 2020). Other direct-to-consumer home-health panel tests include LetsGetChecked (LetsGetChecked, 2020), Paloma Health (Paloma_Health, 2020), EasyDNA (Easy_DNA, 2020), and TellmeGEN (TellmeGEN, 2020).

Analytical Validity

The current generation of assays measuring serum TSH is a chemiluminometric assay, which have detection limits of about 0.01 mU/L. This amount is sufficiently low enough to distinguish between euthyroidism and hyperthyroidism as well as providing superior sensitivity to the prior generation of assays whose detection limits were approximately 0.1 mU/L (Ross, 2019c; Ross, Ardisson, & Meskell, 1989).

Serum T4 and T3 were typically measured with an immunometric assay, such as RIA. The reference range of T3 is more variable than T4 as the degree of T3 protein binding differs from T4 (99.7% of serum T4 is bound) (Ross, 2019c). A study focusing on validating a new electrochemiluminescent assay for serum TSH, T4, and T3 found their intra-assay coefficient of variation to be under 8% for all three hormones and inter-assay coefficient of variation to be <2.9% for TSH, 2.3% for FT4, and 12.3% for T3. The correlation between this assay and the typical ELISA or RIA assays were all at least $r = .8$ with many correlations near or above .9 (Kazerouni & Amirrasouli, 2012).

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The current immunoassays used to measure T3 do not always agree with other methods. For example, a study by Masika, Zhao, and Soldin (2016) comparing immunoassay methods to LC/MS/MS found that 45% of patients classified as “normal” by immunoassay were classified as “lower than 2.5th percentile” by LC/MS/MS. The authors also noted that in patients not receiving T4, 74% of their results were below the 2.5th percentile by LC/MS/MS whereas only 21% were under that mark by immunoassay. The authors speculate that this discrepancy may be due to deionidase polymorphisms, but overall conclude that because this is a significant method to diagnose thyroid issues, accuracy of T3 measurements should be paramount (Masika et al., 2016).

The measurement of reverse T3 may not be reliable. A study by Burmeister, focusing on total of 246 patients contributing 262 reverse T3 measurements, shows an inverse linear relationship between the log of TSH and reverse T3. However, Burmeister notes that hypothyroidism may cause reverse T3 to appear normal and euthyroidism may cause reverse T3 to appear low. Furthermore, it is possible that symptoms attributed to unusual reverse T3 levels are really caused by hypothyroidism, despite normal TSH levels. Overall, Burmeister concludes that reverse T3 cannot differentiate between hypothyroidism and euthyroidism (Burmeister, 1995; Gomes-Lima & Burman, 2018).

Clinical Validity & Utility

Li et al. (2017) conducted a preliminary study of 6 healthy adult participants and 11 hormone and nonhormone analytes measured by 37 immunoassays and found that ingesting 10 mg/d of biotin for 1 week was associated with potentially clinically important assay interference in some biotinylated assays. These immunoassays use a biotin-streptavidin binding system, so excess biotin may influence the results of these assays using this system. The time at which the biotin was ingested was also a factor in the magnitude of the distortion (Li et al., 2017). Repeating a thyroid test at least two days after biotin discontinuation may be considered (Ross, 2018, 2019c).

Livingston, Birch, Guy, Kane, and Heald (2015) assessed the impact of T3 testing and whether T3 testing provides clinically useful information to patients who are over-treated for hypothyroidism with levothyroxine. Out of 542 patients, 33 were placed in an over-treated group, and 236 were placed in a control group, and the remaining 273 did not fulfill either group. None of the patients in the over-treated group had an increased T3, and the “most discriminant” T3 level was only at 58% sensitivity and 71% specificity. The authors concluded there is no reason to measure T3 in patients with hypothyroidism on levothyroxine therapy (Livingston et al., 2015).

Yazici, Mihmanli, Bozkurt, Ozturk, and Uludag (2016) assessed three predictors of thyroid cancer, thyrotropin (TSH), thyroglobulin (Tg), and their ratio. A study of 242 patients (134 with benign thyroid conditions, 68 with malignancy) was performed. The authors found that preoperative Tg levels were significantly lower in the malignant group (64 ng/mL vs 20 ng/mL) and TSH to Tg ratio was significantly higher in the malignant group due to no major difference in TSH between groups. However, the authors note that a multivariate analysis

revealed only fine-needle aspiration biopsy as a significant factor (Yazici et al., 2016). Autoantibodies may also play a role on diagnosis of cancer. A study by Gholve assessing 301 samples from differentiated thyroid cancer patients (compared to 37 euthyroid controls) found the prevalence of autoantibodies in the cancer patients to be significantly higher than the controls. The authors found the prevalence of the antibodies to be 17.3% by the Immunotech kit and 16.6% by the radioassay whereas the control group was found to be only 5.4% by both methods (Gholve, Kumarasamy, Kulkarni, & Rajan, 2017).

Thyroid antibodies play a role in autoimmune thyroiditis. A study performed by Biktagirova et al. found that 97% of patients with autoimmune thyroiditis had a high antibody to denatured DNA ratio compared to healthy controls. Most of these patients also had a thyroid condition (euthyroidism, hypothyroidism, hyperthyroidism) (Biktagirova et al., 2016). Another study performed by Diana investigated the prevalence of thyroid stimulating hormone receptor (TSHR) blocking antibodies (TBAb) in autoimmune thyroid disease. 1079 patients with autoimmune thyroid disease (AITD) were compared to 302 controls. The authors found that about 10% of patients with AITD were positive for TBAb (82/1079). TBAb also correlated with TSHR binding inhibiting immunoglobulins and negatively with TSHR stimulatory antibodies. The authors concluded that TBAb was a useful and important tool to identify hypothyroidism (Diana et al., 2017).

Kluesner et al. analyzed current thyroid function test ordering practices. The authors examined 38,214 tests (encompassing TSH, FT4, TSH + FT4, FT3, Total T4, and total T3). Overall, TSH alone comprised 52.14% of tests, TSH + FT4 26.72%, FT3 alone 10.63%, FT4 alone 4.26%, and TSH + FT4 + FT3 2.74%. Free thyroid hormone testing amounted to 36% of all tests. The authors estimated the annual cost of free thyroid hormone testing to be \$107,720, with savings of up to \$120,000 (Kluesner et al., 2018).

Jin investigated the prevalence of subclinical hypothyroidism in obese children and its association with thyroid hormone. 1,104 children were included. 27 of 111 (24.3%) obese children were found to have subclinical hypothyroidism, compared to 127 of 993 (12.8%) non-obese children. Body mass index was found to correlate positively with serum concentrations of TSH and correlate negatively with serum concentrations of FT4. Total cholesterol and triglyceride concentration were found to correlate positively with TSH concentrations, with FT4 correlating negatively with total cholesterol. Jin concluded that TSH is correlated with lipid profiles (Jin, 2018).

Korevaar et al. performed a meta-analysis focusing on thyroid function test abnormalities and thyroid autoimmunity with preterm birth. 19 cohorts encompassing 47,045 pregnant women were included. 1,234 of these women had subclinical hypothyroidism. 904 had isolated hypothyroxinemia (“decreased FT4 concentration with normal thyrotropin concentration”). 3,043 were thyroid peroxidase (TPO) antibody positive. 2,357 had preterm birth. Risk of preterm birth was found to be higher for women with subclinical hypothyroidism than euthyroid women (odds ratio = 1.29) as well as higher for women with isolated hypothyroxinemia (odds ratio = 1.46). The authors also found that a one standard deviation increase in maternal serum thyrotropin concentration increased risk of preterm birth by an odds

ratio of 1.04. Finally, TPO antibody positive women were found to have a higher risk of preterm birth compared to TPO antibody negative women by an odds ratio of 1.33 (Korevaar et al., 2019).

In a population-based study by Kiel et al., the use of thyroid hormone measurements in ambulatory care was assessed. Serum TSH, free triiodothyronine (fT3), and free thyroxine (fT4) measurement within 1 year and 3 years prior to the study was reported. A total of 5,552 participants were included in the analysis, with 25% (1,409/5,552) having a diagnosed thyroid disorder or treatment. 30% (1626/5552) received at least one TSH measurement and 6.8% (378/5552) received at least one thyroid ultrasound. In the study, “TSH measurement rates were 1.7 times higher than the highest reported rate (438/1000), fT4 measurement rates were within the reported range (89/1000) and fT3 was measured at a 10- fold higher rate than the highest reported (89/1000).” The study results are in accordance with current guidelines, which recommend measuring TSH levels rather than fT4/fT3 for patients with suspected hypo- and hyperthyroidism and for monitoring purposes. However, the data also suggests that fT4 and fT3 were tested at the same rate, even though fT4 is recommended as sufficient to distinguish between overt and subclinical hypothyroidism. Despite overuse of thyroid hormone testing, there is possible underuse in patients with diagnosed thyroid disorders taking thyroid medication. In the study, 40% did not receive a monitoring TSH test within 1 year, and 16% did not receive a TSH test within 3 years. The authors suggest that “Given the frequency of patients with thyroid disorders, diagnostic and monitoring tests should be used rationally with regard to costs. TSH levels should be monitored regularly in patients on thyroid medication” (Kiel, Ittermann, Völzke, Chenot, & Angelow, 2020).

V. Guidelines and Recommendations

U.S. Preventive Services Task Force (Rugge et al., 2015; USPSTF, 2017)

The USPSTF states that “current evidence is insufficient to assess the balance of benefits and harms of screening for thyroid dysfunction in non-pregnant, asymptomatic adults” (Rugge et al., 2015). In addition, USPSTF recommends against screening for thyroid cancer in asymptomatic adults (USPSTF, 2017).

American College of Obstetricians and Gynecologists (ACOG, 2020)

ACOG published an updated guideline regarding Thyroid Disease in Pregnancy in June 2020. The following recommendations are based on good and consistent scientific evidence (Level A):

- “Universal screening for thyroid disease in pregnancy is not recommended because identification and treatment of maternal subclinical hypothyroidism has not been shown to result in improved pregnancy outcomes and neurocognitive function in offspring.
- If indicated, the first-line screening test to assess thyroid status should be measurement of the TSH level.

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- The TSH level should be monitored in pregnant women being treated for hypothyroidism, and the dose of levothyroxine should be adjusted accordingly with a goal TSH level between the lower limit of the reference range and 2.5 milliunits/L. Thyroid-stimulating hormone typically is evaluated every 4–6 weeks while adjusting medications.
- Pregnant women with overt hypothyroidism should be treated with adequate thyroid hormone replacement to minimize the risk of adverse outcomes.
- The level of free T4 should be monitored in pregnant women being treated for hyperthyroidism, and the dose of antithyroid drug (thioamide) should be adjusted accordingly to achieve a free T4 at the upper end of the normal pregnancy range. Among women who also have T3 thyrotoxicosis, total T3 should be monitored with a goal level at the upper end of normal pregnancy range.
- Pregnant women with overt hyperthyroidism should be treated with antithyroid drugs (thioamides).”

The following recommendation is based on limited or inconsistent scientific evidence (Level B):

- “Either propylthiouracil or methimazole, both thioamides, can be used to treat pregnant women with overt hyperthyroidism. The choice of medication is dependent on trimester of pregnancy, response to prior therapy, and whether the thyrotoxicosis is predominantly T4 or T3.”

The following recommendations are based primarily on consensus and expert opinion (Level C):

- “Indicated testing of thyroid function should be performed in women with a personal or family history of thyroid disease, type 1 diabetes mellitus, or clinical suspicion of thyroid disease.
- Measurements of thyroid function are not recommended in patients with hyperemesis gravidarum unless other signs of overt hyperthyroidism are evident.”

Other miscellaneous, relevant comments from ACOG include:

- “Indicated testing of thyroid function should be performed in women with a personal or family history of thyroid disease, type 1 diabetes mellitus, or clinical suspicion of thyroid disease... In a pregnant woman with a significant goiter or with distinct thyroid nodules, thyroid function studies are appropriate...”
- “In cases of suspected hyperthyroidism, total T3 also is measured...Total T3 is used preferentially over free T3 because assays for estimating free T3 are less robust than those measuring free T4...”
- “Routine testing for antithyroid peroxidase antibodies in women who are euthyroid (eg, no history of thyroid disease and normal thyroid function tests) is not recommended because thyroid hormone replacement for antithyroid peroxidase antibodies alone has not been found to improve pregnancy outcomes... Identification of thyroid antibodies

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including thyroid receptor antibodies and thyroid stimulating immunoglobulin in women with Graves disease may establish those at an increased risk for fetal or neonatal hyperthyroidism.” (ACOG, 2020)

American Thyroid Association (ATA) and American Association of Clinical Endocrinologists (AACE) (Alexander et al., 2017; Garber et al., 2012; Jonklaas et al., 2014; Ross et al., 2016)

The ATA and AACE support TSH testing for individuals with the following conditions: adrenal insufficiency, alopecia, unexplained anemia, unexplained cardiac dysrhythmia, skin texture changes, congestive heart failure, constipation, dementia, type 1 diabetes, dysmenorrhea, hypercholesterolemia, hypertension, mixed hyperlipidemia, malaise and fatigue, unexplained myopathy, prolonged QT interval, vitiligo, or weight gain. The guidelines also recommend assessing serum FT4 instead of total T4 to diagnose hypothyroidism except with pregnant patients.

The ATA and AACE also provide recommendations for thyroid antibody testing including:

- “Anti-thyroid peroxidase antibody (TPOAb) measurements should be considered when evaluating patients with subclinical hypothyroidism.”
- TPOAb measurement should be considered in evaluation of patients with recurrent miscarriage, regardless of fertility.
- “Measurement of TSHRabs should be considered in hypothyroid pregnant patients with history of Graves’ disease if treated with radioactive iodine or thyroidectomy before pregnancy. This should be done either at 20-26 weeks of gestation or during the first trimester and if they are elevated, again at 20-26 weeks of gestation (Garber et al., 2012).”

The guidelines recommend against testing serum T3 or free T3, as well as use of clinical scoring systems to diagnose hypothyroidism. In patients with central hypothyroidism, the guidelines recommend assessing either FT4 or its index and to avoid testing for TSH (Garber et al., 2012).

American Thyroid Association (ATA) (Alexander et al., 2017; Jonklaas et al., 2014; Ross et al., 2016; Stagnaro-Green et al., 2011)

Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum

In 2011, the ATA stated that it does not recommend “universal” TSH or free T4 screening of pregnant women or during the preconception period. It also included the following recommendations:

Thyroid Function Tests in Pregnancy: Trimester-specific reference ranges for TSH, as defined in populations with optimal iodine intake, should be applied. The ATA recommends these

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reference ranges: first trimester, 0.1–2.5 mIU/L; second trimester, 0.2–3.0 mIU/L; third trimester, 0.3–3.0 mIU/L.

The best method to assess serum free thyroxine FT4 during pregnancy is measurement of T4 in the dialysate or ultrafiltrate of serum samples employing LC/MS/MS. If this is not available, clinicians should use the next best method available. However, serum TSH is a more accurate indication of thyroid status in pregnancy than any of these alternative methods. Method-specific and trimester-specific reference ranges of serum FT4 are required.

Thyrotoxicosis in Pregnancy: If the first trimester serum TSH appears low (<0.1 mIU/L), a history and physical examination are indicated. FT4 measurements should be obtained in all patients. Measurement of serum total T3 (TT3) and thyrotropin receptor antibodies (TRAb) may be helpful in establishing a diagnosis of hyperthyroidism. If the patient has a history of Graves' disease, a maternal serum sample of TRAb should be obtained at 20–24 weeks gestation.

Thyroid Nodules and Thyroid Cancer: Treatment of thyroid nodules during pregnancy will depend on risk assessment. However, all women should have the following: a complete history and clinical examination, serum TSH testing, and ultrasound of the neck. Thyroid hormone therapy may be considered in pregnant women who have deferred surgery for well-differentiated thyroid carcinoma until postpartum. The goal of LT4 therapy is a serum TSH level of 0.1–1.5 mIU/L. Furthermore, a preconception TSH goal (determined by risk assessment) should be set in women with differentiated thyroid cancer. This goal should be maintained during pregnancy with monitoring every 4 weeks until 16–20 weeks of gestation followed by once between 26 and 32 weeks of gestation.

Postpartum Thyroiditis (PPT): Women with postpartum depression should have TSH, FT4, and TPOAb tests performed. Women who are symptomatic with hypothyroidism in PPT should either have their TSH level retested in 4–8 weeks or be started on LT4 in certain situations (such as if symptoms are severe). Women who are asymptomatic with hypothyroidism in PPT should have their TSH level retested in 4–8 weeks. Finally, women with a history of PPT should have an annual TSH test to evaluate for permanent hypothyroidism.

Thyroid Function Screening in Pregnancy: There is insufficient evidence regarding universal TSH screening at the first trimester visit. Serum TSH values should be obtained early in pregnancy in the following women at high risk for overt hypothyroidism:

- History of thyroid dysfunction or prior thyroid surgery
- Age >30 years
- Symptoms of thyroid dysfunction or the presence of goiter
- TPOAb positivity
- Type 1 diabetes or other autoimmune disorders

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- History of miscarriage or preterm delivery
- History of head or neck radiation
- Family history of thyroid dysfunction
- Morbid obesity (BMI ≥ 40 kg/m²)
- Use of amiodarone or lithium, or recent administration of iodinated radiologic contrast
- Infertility
- Residing in an area of known moderate to severe iodine insufficiency (Stagnaro-Green et al., 2011)

The ATA published an update in 2017 for thyroid function testing during pregnancy. Recommendations include:

- Total T4 measurement (with a pregnancy-adjusted reference range) is reliable for estimating concentration late in pregnancy. A free thyroxine index can also estimate FT4 well.
- Euthyroid and TPO or Tg antibody positive pregnant women should have serum TSH concentration measured at the start of pregnancy and every 4 weeks through mid-pregnancy.
- All women seeking care for infertility are recommended to have serum TSH levels measured.
- Pregnant women with TSH concentrations >2.5 mU/L should be evaluated for TPO antibodies.
- Women with hypothyroidism or those at risk for hypothyroidism (e.g. patients who are euthyroid but TPO or TGAb positive) should be monitored with a serum TSH measurement every 4 weeks until mid-gestation, and at least once near 30 weeks.
- “When a suppressed serum TSH is detected in the first trimester (TSH less than the reference range), a medical history, physical examination, and measurement of maternal serum FT4 or TT4 concentrations should be performed. Measurement of TRAb and maternal TT3 may prove helpful in clarifying the etiology of thyrotoxicosis”
- In women being treated with antithyroid drugs [ATDs] in pregnancy, FT4/TT4 and TSH should be monitored every 4 weeks.
- “All patients with depression, including postpartum depression, should be screened for thyroid dysfunction.”
- “Evaluation of serum TSH concentration is recommended for all women seeking care for infertility.”
- “If the patient has a past history of GD [Graves Disease] treated with ablation (radioiodine or surgery), a maternal serum determination of TRAb is recommended at initial thyroid function testing during early pregnancy. If maternal TRAb concentration is elevated in early pregnancy, repeat testing should occur at weeks 18–22.

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- “If the patient requires treatment with ATDs for GD through mid-pregnancy, a repeat determination of TRAb is again recommended at weeks 18–22. If elevated TRAb is detected at weeks 18–22 or the mother is taking ATD in the third trimester, a TRAb measurement should again be performed in late pregnancy (weeks 30–34) to evaluate the need for neonatal and postnatal monitoring.”
- “The utility of measuring calcitonin in pregnant women with thyroid nodules is unknown. The task force cannot recommend for or against routine measurement of serum calcitonin in pregnant women with thyroid nodules.”
- “All newborns should be screened for hypothyroidism by blood spot analysis typically 2–5 days after birth.”
- “Following the resolution of the thyrotoxic phase of PPT [postpartum thyroiditis], serum TSH should be measured in approximately 4–8 weeks (or if new symptoms develop) to screen for the hypothyroid phase.”
- “Women with a prior history of PPT should have TSH testing annually to evaluate for the development of permanent hypothyroidism”
- “There is insufficient evidence to recommend for or against universal screening for abnormal TSH concentrations in early pregnancy.
- “There is insufficient evidence to recommend for or against universal screening for abnormal TSH concentrations preconception, with the exception of women planning assisted reproduction or those known to have TPOAb positivity”
- “Universal screening to detect low FT4 concentrations in pregnant women is not recommended.” (Alexander et al., 2017).

The guideline also lists certain populations of pregnant women that should have serum TSH measured “as soon as pregnancy is confirmed” due to presence of risk factors of thyroid disease. These risk factors include “history of thyroid dysfunction, symptoms or signs of thyroid dysfunction, presence of a goiter, and known thyroid antibody positivity... age >30 years, history of diabetes mellitus type 1, or other autoimmune disorders, history of pregnancy loss, preterm delivery or infertility, history of head or neck radiation or prior thyroid surgery, family history of autoimmune thyroid disease or thyroid dysfunction, morbid obesity, use of amiodarone, lithium, or recent administration of iodinated radiologic contrast, two or more prior pregnancies, and residing in area of moderate to severe iodine deficiency.” (Alexander et al., 2017)

ATA, *Task Force on Thyroid Hormone Replacement for Hypothyroidism Treatment* (2014)

The ATA recommended levothyroxine (LT4) as the primary treatment of choice for hypothyroidism due to overall efficacy, low cost, and lack of side effects. The ATA also states that great care should be taken to monitor dose diligently especially in pregnant women, as excessive LT4 can have dangerous side effects (Jonklaas et al., 2014).

ATA, *Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis* (2016)

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The ATA recommends that the cause of the thyrotoxicosis should be determined. Initial diagnostic tests include measurement of TRAb, radioactive iodine uptake, or measurement of thyroidal blood flow on ultrasonography. The guidelines also note that serum TSH is the most accurate and should be the first screening test done, but if thyrotoxicosis is suspected, it is helpful to test FT4 and T3.

The ATA recommends treatment of subclinical hyperthyroidism (persistent TSH <0.1 mU/L) for the high-risk populations such as those with cardiac risk factors or those older than 65. Treatment of asymptomatic and otherwise healthy individuals may be considered. The ATA also recommends testing TRAb in pregnant women with unknown hyperthyroidism. A diagnosis of hyperthyroidism should be made with the serum TSH values and trimester-specific reference ranges for T4 and T3 (Ross et al., 2016).

American Academy of Family Physicians (AAFP, 2012, 2018; Kravets, 2016)

The AAFP has recommended this diagnostic workup for hyperthyroidism: “measuring TSH, free (T4), and total T3 levels to determine the presence and severity of the condition, as well as radioactive iodine uptake and scan of the thyroid to determine the cause.” The level of this evidence is C which is a consensus, disease-oriented evidence, usual practice, expert opinion, or case series (Kravets, 2016). The AAFP also recommends using TSH testing to diagnose primary hypothyroidism (Level C) (AAFP, 2012).

In the case of subclinical thyroid disease, the AAFP recommends that “Physicians should not routinely screen for subclinical thyroid disease” (Donangelo & Suh, 2017). Moreover, the AAFP reaffirms its support for the USPSTF stance on thyroid dysfunction, stating that there is no evidence that population screening is beneficial and that “Screening for thyroid dysfunction in nonpregnant, asymptomatic individuals has uncertain risks and benefits” as there has been a dearth of studies comparing the benefits of harms of screening against no screening (AAFP, 2018; Wilson, Stem, & Bruehlman, 2021).

American Academy of Pediatrics-Section on Endocrinology (AAP, 2017)

The American Academy of Pediatrics recommends against routinely measuring thyroid function or insulin levels in obese children, as well as screening healthy children for thyroid problems (AAP, 2017).

Joint Task Force on Practice Parameters (JTFPP) of the Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology (Bernstein et al., 2014)

The JTFPP within their guidelines concerning the diagnosis and management of acute and chronic urticaria state, “Targeted laboratory testing based on history or physical examination

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findings is appropriate, and limited laboratory testing can be obtained. Limited laboratory testing includes a CBC with differential, sedimentation rate, and/or C-reactive protein, liver enzyme, and thyroid-stimulating hormone (TSH) measurement... Targeted laboratory testing based on history and/or physical examination (eg, obtaining TSH in a patient with weight gain, heat/cold intolerance, and thyromegaly) is recommended (Bernstein et al., 2014).”

American Society for Clinical Pathology (ASCP, 2015, 2020)

The American Society for Clinical Pathology recommends against ordering multiple tests for an initial evaluation for a patient with a suspected thyroid condition. The ASCP recommends starting with TSH and proceeding from that result (ASCP, 2015).

On September 1, 2020, ASCP released a recommendation to avoid TSH screening in annual well-visits for asymptomatic adults, regardless of age, as there is no evidence to support that routine screening improves patient care. ASCP advises TSH screening when patients are considered at-risk or demonstrate subtle or direct signs of thyroid dysfunction upon physical evaluation (ASCP, 2020).

Endocrine Society (Society, 2018a, 2018b) (Last reviewed 2021)

The Endocrine Society recommends against testing for T3 when evaluating levothyroxine (T4) dose in hypothyroid patients, as well as ordering routine ultrasounds for patients without palpable abnormalities of the thyroid . Furthermore, it is recommended that practitioners “Don’t routinely measure 1,25-dihydroxyvitamin D unless the patient has hypercalcemia or decreased kidney function” as they are regulated by parathyroid hormone levels (Society, 2018b).

European Thyroid Association (ETA), *Management of Thyroid Dysfunction following Immune Reconstitution Therapy (IRT)* (Kahaly et al., 2018; Muller et al., 2019)

This guideline discusses IRT in the context of three clinical situations; “alemtuzumab (Lemtrada) treatment for active relapsing remitting multiple sclerosis (MS); (2) after treatment of human immunodeficiency virus (HIV) infected patients with highly active antiretroviral therapy (HAART); (3) following allogeneic bone marrow transplantation (BMT) or hematopoietic stem cell transplantation (HSCT)”

The ETA recommends measuring TSH in all subjects before IRT. If TSH is abnormal, FT4 and FT3 are recommended to be measured.

Routine measurement of TPOAb or TRAb is not recommended before IRT.

TSH measurement is recommended post-IRT, and FT4 may also be routinely measured. If TSH is low (0.10–0.39 mU/L), another test is recommended within 1 month. If TSH is

elevated, a repeat TSH test is recommended, along with FT4. If TSH is “suppressed” (<0.10 mU/L), TSH, FT4, and FT3 are recommended to be tested.

Following alemtuzumab, the ETA recommends “biochemical follow-up” with TSH testing every 3 months. Routine TSH monitoring is not recommended following HAART treatment in HIV patients, although TSH measurement should be performed if thyroid dysfunction is suspected.

Routine measurement of thyroid autoantibodies is not recommended in euthyroid patients during surveillance.

The ETA recommends “routine 3 monthly measuring of thyroid function to be continued for 4 years following the last alemtuzumab treatment” (Muller et al., 2019).

Management of Graves’ Hyperthyroidism (2018)

The ETA notes measurement of TSH-R-stimulating antibody (TSH-R-Ab) as a “sensitive and specific” tool for rapid and accurate differential diagnosis for Graves’ hypothyroidism. Differentiation of TSH-R-Ab is also “helpful and predictive” in Graves’ patients during pregnancy/postpartum, as well as extrathyroidal manifestations.

The ETA also remarks that measurement of TSH-R-Ab levels prior to stopping antithyroid drug treatment (ATD).

For pregnant patients, maternal FT4 and TSH should be measured every 2 weeks after initiation of therapy, every 4 weeks after achieving the target value. All patients with history of autoimmune thyroid disease should have their TSH-R-Ab levels tested at first presentation with pregnancy, and if maternal TSH-R-Ab remains high (>3 times normal cutoff), monitoring the fetus for thyroid dysfunction throughout pregnancy is recommended (Kahaly et al., 2018).

Diagnosis and Management of Central Hypothyroidism

The ETA also published a guideline regarding central hypothyroidism (CeH). Below are the relevant recommendations:

- “We recommend that the diagnosis of CeH should be considered in every subject with low serum concentrations of FT4 and low or normal TSH on a screening examination.
- We recommend that the diagnosis of CeH should be considered in neonates and children with clinical manifestations of congenital hypothyroidism but low or normal neonatal TSH screening.

- We suggest that the diagnosis of CeH should be considered in patients with a low serum concentration of FT4 and slight TSH elevations (< 10 mU/L, or inappropriately lower than expected on the basis of the hypothyroid state).
- We recommend screening for CeH all children with a familial history of CeH and/or failure to thrive, developmental delay, GH deficiency, delayed or precocious puberty, or other hypothalamic-pituitary defects or lesions.
- We recommend that CeH due to *IGSF1* defect should be ruled out in adolescents or adult patients with macroorchidism.
- We recommend screening for CeH all patients with a personal or familial history of hypothalamic-pituitary lesions or diseases, moderate to severe head trauma, stroke, previous cranial irradiation, hemochromatosis or iron overload, in particular when hypothyroid manifestations are present.
- We recommend screening for CeH all patients with hypothyroid manifestations associated with clinical findings pointing to a hypothalamic-pituitary disease (e.g., hyperprolactinemia, acromegalic features, diabetes insipidus, recurrent headaches, visual field defects), newborns with hypotonia and/or prolonged jaundice, and/or signs of congenital hypopituitarism (e.g., micropenis with undescended testes), as well as children with developmental delay.
- We recommend that the onset of CeH should be evaluated in patients with hypothalamic/pituitary disease after the start of treatment with rhGH or estrogen.
- We recommend that the onset of CeH should be evaluated in patients on treatments with ligands of the retinoid X receptor (RXR), ipilimumab (or other checkpoint inhibitors), or mitotane.”

Regarding diagnosis of CeH, the guideline recommends the following:

- “We recommend the combined determination of serum FT4 and TSH in order to evaluate the presence of CeH.
- We recommend that CeH diagnosis should be confirmed by the combined findings of serum FT4 concentrations below the lower limit of the normal range and inappropriately low/normal TSH concentrations on at least two separate determinations, and after exclusion of the conditions reported in Table 3.
- The isolated finding of low FT3 or total T3 concentrations is not indicative of CeH, but rather of nonthyroidal illness or deiodination defects (e.g., *SBP2* gene defect).

- In patients under follow-up for hypothalamic-pituitary disease, FT4 and TSH should be monitored during childhood at least biannually and later on a yearly basis, and we suggest that CeH diagnosis should be considered when serum FT4 falls in the lower quartile of the normal range, in particular when a FT4 decrease > 20% of previous values is seen (provided that the variables are measured by the same assay) despite a low or normal TSH.
- We suggest that the diagnosis of mild CeH (borderline low FT4, with inappropriately low TSH) should be supported by a combination of several other findings summarized in Table 4 (the relative application and importance of these tests and findings may vary in different settings).”

National Institute for Health and Care Excellence (NICE, 2019)

Thyroid Disease: Assessment and Management

NICE states to “consider” thyroid dysfunction tests for adults, children, and “young people” for the following indications:

- “a clinical suspicion of thyroid disease”
- New-onset atrial fibrillation
- Type 1 diabetes or other autoimmune disease
- Depression or unexplained anxiety
- For children and young people, consider tests for abnormal growths or unexplained change in behavior or school performance

NICE states not to test for thyroid dysfunction if a patient only has type 2 diabetes or if the patient has an unrelated acute illness.

If secondary thyroid disease (pituitary disease) is not suspected, NICE states to “consider” measuring TSH. If TSH is “above reference range”, measure FT4 in same sample; if TSH is “below reference range”, measure FT4 and FT3 in same sample.

Measurement of both TSH and FT4 is to be considered for children or young people or if secondary thyroid dysfunction is suspected in adults. If TSH is below the reference range, FT3 should be measured. If symptoms in the above situations worsen, repeat the algorithms.

For adults with TSH levels above the reference range, thyroid peroxidase antibody (TPO-Ab) measurement may be considered. However, this testing should not be repeated. This applies to primary and subclinical hypothyroidism.

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For children and young people, this measurement should be repeated when they become adults.

“For adults who are taking levothyroxine for primary hypothyroidism, consider measuring TSH every 3 months until the level has stabilised (2 similar measurements within the reference range 3 months apart), and then once a year.” For adults with hypothyroidism symptoms after starting levothyroxine, consider measuring FT4 along with TSH.

For children ages 2 and over and young people taking levothyroxine for primary hypothyroidism, consider measuring FT4 and TSH at the following intervals:

“every 6 to 12 weeks until the TSH level has stabilised (2 similar measurements within the reference range 3 months apart), then every 4 to 6 months until after puberty, then once a year.”

For children under 2, consider measuring FT4 and TSH at the following intervals:

“every 4 to 8 weeks until the TSH level has stabilised (2 similar measurements within the reference range 2 months apart), then every 2 to 3 months during the first year of life, and every 3 to 4 months during the second year of life.”

For adults with untreated subclinical hypothyroidism or adults that have stopped treatment, consider measuring TSH and FT4 once a year if they are symptomatic, or once every 2-3 years if they are asymptomatic.

NICE states to consider measuring FT4 and TSH for children 2 and over with untreated subclinical hypothyroidism and TSH <10 mIU/liter at the following intervals: “every 3 to 6 months if they have features suggesting underlying thyroid disease, such as thyroid dysgenesis (an underdeveloped thyroid gland) or raised levels of thyroid autoantibodies, or every 6 to 12 months if they have no features suggesting underlying thyroid disease.”

“Every 1-3 months for children ages 28 days-2 years with untreated subclinical hypothyroidism”. TSH measurements may be stopped in children and young people if TSH has stabilized (defined as “2 similar measurements within the reference range 3 to 6 months apart”) and there are no underlying features suggesting thyroid disease.

Differentiating between thyrotoxicosis with hyperthyroidism and thyrotoxicosis without hyperthyroidism may be performed by measuring TSH receptor antibodies (TRAbs). In children and young people, measuring TPO-Abs and TRAbs may be done to differentiate.

After radioactive iodine treatment, consider measuring FT3, FT4, and TSH every 6 weeks for the first 6 months, until TSH is within reference range.

“For adults, children and young people with TSH in the reference range 6 months after radioactive iodine treatment, consider measuring TSH (with cascading) at 9 months and 12 months after treatment.”

“For adults, children and young people with TSH in the reference range 12 months after radioactive iodine treatment, consider measuring TSH (with cascading) every 6 months unless they develop hypothyroidism”

For patients taking antithyroid drugs for hyperthyroidism, consider measuring TSH, FT4, and FT3 every 6 weeks until TSH is within reference range, then TSH (with cascading) every 3 months until antithyroid drugs are stopped.

“For adults who have stopped antithyroid drugs, consider measuring: TSH (with cascading) within 8 weeks of stopping the drug, then TSH (with cascading) every 3 months for a year, then TSH (with cascading) once a year.”

“For children and young people who have stopped antithyroid drugs, consider measuring: TSH, FT4 and FT3 within 8 weeks of stopping the drug, then TSH, FT4 and FT3 every 3 months for the first year, then TSH (with cascading) every 6 months for the second year, then TSH (with cascading) once a year.”

“Consider measuring TSH every 6 months for adults with untreated subclinical hyperthyroidism. If the TSH level is outside the reference range, consider measuring FT4 and FT3 in the same sample.”

“Consider measuring TSH, FT4 and FT3 every 3 months for children and young people with untreated subclinical hyperthyroidism.”

“Consider stopping TSH measurement for adults, children and young people with untreated subclinical hyperthyroidism if the TSH level stabilises (2 similar measurements within the reference range 3 to 6 months apart)” (NICE, 2019).

Canadian Task Force on Preventive Health Care (CTFPHC, 2019)

The Task Force recommends against screening (measuring levels of thyroid-stimulating hormone (TSH) in patients with no apparent signs and symptoms of thyroid dysfunction) asymptomatic nonpregnant adults aged 18 or older for thyroid dysfunction in primary care settings. This was rated as a “strong” recommendation with low-certainty evidence (CTFPHC, 2019).

Society for Maternal-Fetal Medicine (SMFM, 2019)

The SMFM recommends against screening asymptomatic pregnant women for subclinical hypothyroidism (SMFM, 2019). The SMFM states that “thyroid testing in pregnancy should

be conducted for women “at risk,” including known thyroid disease, symptoms of overt thyroid disease, suspected goiter, autoimmune medical disorders such as Type 1 diabetes mellitus”, but also asserts that “routine thyroid testing of women with hyperemesis gravidarum is not recommended” (Medicine, 2014).

College of Family Physicians of Canada (CFPC, 2020)

The 11th recommendation listed recommends against ordering thyroid function tests for asymptomatic patients. The guideline remarks there is “insufficient evidence” available that screening for thyroid diseases will improve health outcomes (CFPC, 2020).

Canadian Society of Endocrinology and Metabolism (CSEM, 2020)

The CSEM recommends against routine testing for anti-thyroid peroxidase antibodies (anti-TPO). They also recommend against using FT4 or FT3 to screen for hyperthyroidism or to monitor and adjust levothyroxine dose in patients with primary hyperthyroidism, unless that patient has “suspected or known pituitary or hypothalamic disease” (CSEM, 2020).

VI. State and Federal Regulations, as applicable

A search of “thyroid” on the FDA website on August 6, 2021, yielded 107 results. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

VII. Applicable CPT/HCPCS Procedure Codes

Code Number	Code Description
80438	Thyrotropin releasing hormone (trh) stimulation panel; 1 hour This panel must include the following: Thyroid stimulating hormone (TSH) (84443x3)
80439	Thyrotropin releasing hormone (trh) stimulation panel; 2 hours This panel must include the following: Thyroid stimulating hormone (TSH) (84443x4)
83519	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, by radioimmunoassay (eg, RIA)
84432	Thyroglobulin
84436	Thyroxine; total
84437	Thyroxine; requiring elution (eg, neonatal)
84439	Thyroxine; free
84442	Thyroxine binding globulin (TBG)

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84443	Thyroid stimulating hormone (TSH)
84445	Thyroid stimulating immune globulins (TSH)
84479	Thyroid hormone (T3 or T4) uptake or thyroid hormone binding ratio (THBR)
84480	Triiodothyronine T3; total (TT-3)
84481	Triiodothyronine T3; free
84482	Triiodothyronine T3; reverse
86376	Microsomal antibodies (eg, thyroid or liver-kidney), each
86800	Thyroglobulin antibody

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

VIII. Evidence-based Scientific References

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