

## Thyroid Disease Testing

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### I. Policy Description

Thyroid hormones are necessary for both prenatal and postnatal development, as well as metabolic activity in adults.<sup>1</sup>

Thyroid disease includes conditions which cause hypothyroidism, hyperthyroidism, goiter, thyroiditis (which can present as either hypo- or hyperthyroidism), and thyroid tumors.<sup>2</sup>

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.<sup>3</sup>

Terms such as male and female are used when necessary to refer to sex assigned at birth.

### II. 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:
  - a) For individuals with signs and symptoms consistent with hypothyroidism (see Note 1):
    - i) Thyroid stimulating hormone (TSH) testing to confirm or rule out primary hypothyroidism.
    - ii) Free T4 (fT4) testing as a follow up to abnormal TSH finding.
    - iii) TSH and fT4 testing in cases of suspected secondary hypothyroidism.
  - iv) For individuals being treated for primary hypothyroidism, monitoring with TSH and fT4 testing every 6 weeks upon dosage change and annually in stable individuals.
  - v) For individuals being treated for secondary hypothyroidism, monitoring with fT4 testing every 6 weeks upon dosage change and annually in stable individuals.
  - b) For individuals with signs and symptoms consistent with hyperthyroidism (see Note 2):
    - i) TSH testing to confirm or rule out overt hyperthyroidism.
    - ii) fT4 testing as a follow up to abnormal TSH findings.
    - iii) Total T3 (TT3) or free T3 (fT3) testing to confirm a diagnosis of hyperthyroidism.

- iv) fT4 testing to distinguish between overt and subclinical hyperthyroidism.
- v) Monitoring individuals after treatment for hyperthyroidism:
  - (a) In patients being treated for hyperthyroidism, repeat testing of TSH and fT4 should occur every 8 weeks.
  - (b) Annual monitoring after first year even if asymptomatic for risk of relapse or late-onset hypothyroidism.
- c) For asymptomatic individuals who have been prescribed drugs that can interfere with thyroid function and thus who are at an increased risk for thyroid disease, TSH testing at the following intervals:
  - i) Annually.
  - ii) When dosage or medication changes.
  - iii) If symptoms consistent with thyroid dysfunction develop.
- d) TSH testing for individuals capable of becoming pregnant who have experienced two or more pregnancy losses.
- e) TSH testing for individuals with a thyroid nodule.
- f) One-time TSH screening:
  - i) For asymptomatic individuals at high risk for thyroid disease due to:
    - (a) Personal or family history of thyroid dysfunction.
    - (b) Personal or family history of type 1 diabetes or other autoimmune disease.
  - ii) For individuals with disease or neoplasm of the thyroid or other endocrine glands.
  - iii) For individuals with chronic or acute urticaria.
  - iv) For pediatric individuals diagnosed with short stature.
  - v) For pediatric individuals with a clinical finding of failure-to-thrive.
- g) TSH testing once every 3 months, with reflex fT4 and fT3 when TSH is abnormal, for 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).
- h) For individuals with hypothalamic-pituitary disease, monitoring of TSH and fT4:
  - i) Biannually for individuals less than 18 years of age.
  - ii) Annually for individuals 18 years of age or older.
- i) Annual screening of TSH and fT4 for individuals diagnosed with primary mitochondrial disease.

- 2) For individuals who are pregnant or who are postpartum and who have symptoms of thyroid dysfunction (see Note 1 and Note 2), TSH and fT4 testing (once every 4 weeks) **MEETS COVERAGE CRITERIA** (see Note 3).
  - 3) For individuals who are pregnant or who are postpartum and who have been diagnosed with hyperthyroidism, total T4 (TT4), antithyroglobulin antibody (Tg-Ab), thyrotropin receptor antibodies (TRAb), and antithyroid peroxidase antibody (TPOAb) **MEETS COVERAGE CRITERIA** (see Note 3).
  - 4) For individuals with hypothyroidism or hyperthyroidism, testing once every three years for thyroid antibodies (i.e., Tg-Ab, TPOAb, TRAb, thyroid-stimulating immunoglobulins [TSI]) **MEETS COVERAGE CRITERIA**.
  - 5) For individuals with thyroid cancer, testing for serum thyroglobulin and/or Tg-Ab levels for the detection of tumor recurrence, post-surgical evaluation, surveillance, and maintenance for differentiated thyroid carcinomas **MEETS COVERAGE CRITERIA**.
  - 6) For the evaluation of the cause of hyperthyroidism or hypothyroidism, testing for thyrotropin-releasing hormone (TRH) or thyroxine-binding globulin (TBG) **DOES NOT MEET COVERAGE CRITERIA**.
  - 7) For all other situations not mentioned above, testing of reverse T3, T3 uptake, and TT4 **DOES NOT MEET COVERAGE CRITERIA**.
  - 8) For the assessment of hypothyroidism, measurement of TT3 and/or fT3 **DOES NOT MEET COVERAGE CRITERIA**.
  - 9) To assess levothyroxine dose in hypothyroid patients, measurement of total or fT3 level **DOES NOT MEET COVERAGE CRITERIA**.
  - 10) For asymptomatic nonpregnant individuals, testing for thyroid dysfunction during a general exam without abnormal findings **DOES NOT MEET COVERAGE CRITERIA**.
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## NOTES:

**Note 1:** Signs and symptoms of hypothyroidism include:

- Fatigue
- Increased sensitivity to cold
- Constipation
- Dry skin
- Unexplained weight gain
- Puffy face
- Hoarseness
- Muscle weakness
- Elevated blood cholesterol level
- Muscle aches, tenderness, and stiffness

- Pain, stiffness or swelling in your joints
- Heavier than normal or irregular menstrual periods
- Thinning hair
- Slowed heart rate
- Depression
- Impaired memory

**Note 2:** Hyperthyroidism can mimic other health problems, which may make it difficult for doctors to diagnose. It can also cause a wide variety of signs and symptoms, including:

- Sudden weight loss, even when your appetite and the amount and type of food you eat remain the same or even increase
- Rapid heartbeat (tachycardia) — commonly more than 100 beats a minute — irregular heartbeat (arrhythmia) or pounding of your heart (palpitations)
- Increased appetite
- Nervousness, anxiety, and irritability
- Tremor — usually a fine trembling in your hands and fingers
- Sweating
- Changes in menstrual patterns
- Increased sensitivity to heat
- Changes in bowel patterns, especially more frequent bowel movements
- An enlarged thyroid gland (goiter), which may appear as a swelling at the base of your neck
- Fatigue, muscle weakness
- Difficulty sleeping
- Skin thinning
- Fine, brittle hair

**Note 3:** 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 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.

### III. Table of Terminology

Term	Definition
AAAAI	Academy of Allergy, Asthma & Immunology
AACE	American Association of Clinical Endocrinologists
AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
AAAAI	American College of Allergy, Asthma & Immunology
ACOG	American College of Obstetricians and Gynecologists
AITD	Autoimmune thyroid disease
AJGP	Australian Journal of General Practice
ALPS	Autoimmune lymphoproliferative syndrome

Anti-TPO	Antithyroid peroxidase antibodies
ASCP	American Society for Clinical Pathology
ATA	American Thyroid Association
ATD	Antithyroid drug treatment
ATDs	Antithyroid drugs
BMI	Body mass index
BMT	Bone marrow transplantation
CeH	Central hypothyroidism
CFPC	College of Family Physicians of Canada
CLIA '88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid Services
CSEM	Canadian Society of Endocrinology and Metabolism
CTFPHC	Canadian Task Force on Preventive Health Care
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
ES	Endocrine Society
ETA	European Thyroid Association
ft3/FT3	Free triiodothyronine
ft4/FT4	Free thyroxine
GD	Graves' Disease
HAART	Highly active antiretroviral therapy
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HSCT	Hematopoietic stem cell transplantation
IBM	Inclusion body myositis
IGF-1	Insulin-like growth factor 1
<i>IGSF1</i>	<i>Immunoglobulin superfamily member 1</i>
IRT	Immune reconstitution therapy
JCAAI	Joint Council of Allergy, Asthma & Immunology
JTFPP	Joint Task Force on Practice Parameters
LC	Liquid chromatography
LDL	Low-density lipoprotein
LDTs	Laboratory-developed tests
LT4	Levothyroxine
MMS	Mitochondrial Medicine Society
MR	Mendelian randomization
MS	Multiple sclerosis
NICE	National Institute for Health and Care Excellence
NSAID	Non-steroidal anti-inflammatories
ADEM	Acute disseminated encephalitis and encephalomyelitis

PPT	Postpartum thyroiditis
QT interval	The interval from the beginning of the QRS complex to the end of the T wave on an electrocardiogram
rhGH	Recombinant human growth hormone
RIA	Radioimmunoassay
RXR	Retinoid X receptor
<i>SBP2</i>	<i>Selenocysteine (Sec) insertion sequence-binding protein 2</i>
SLE	Systemic lupus erythematosus
SMFM	Society for Maternal-Fetal Medicine
T3	Triiodothyronine
T4	Thyroxine
TBG	Thyroxine-binding globulin
TC	Total cholesterol
Tg	Thyroglobulin
TG-Ab	Antithyroglobulin antibodies
THBR	Thyroid hormone binding ratio
TNs	Thyroid nodules
TPO	Thyroid peroxidase
TPOAb	Thyroid peroxidase antibody
TRAb	Thyrotropin receptor antibodies
TRAbs	T receptor antibodies
TRH	Thyrotropin-releasing hormone
TSH	Thyroid stimulating hormone
TSHR	Thyroid stimulating hormone receptor
TSH-R-Ab	TSH-R-stimulating antibody
TSHRabs	Thyrotropin receptor autoantibodies
TSI	Thyroid stimulating immunoglobulins
TT3	Total T3
TT4	Total T4
USPSTF	United States Preventive Services Task Force

#### IV. Scientific Background

Metabolic homeostasis is regulated by the thyroid gland through production of thyroid hormones. Thyroid disease is estimated to occur in approximately 30 million Americans, much of which is undiagnosed.<sup>4</sup> The thyroid gland is regulated by TSH or thyrotropin. TSH is secreted by the anterior pituitary and stimulates thyroid gland to secrete two hormones, thyroxine (T4) and triiodothyronine (T3), and TSH secretion is stimulated by TRH, which is distributed throughout the hypothalamus with traces found in the central nervous system and in the pituitary gland, gastrointestinal tract, pancreatic islets, and reproductive tract. Both TSH and TRH levels are controlled through a negative feedback loop by T4 and T3. Thyroid hormone production is also regulated by the extrathyroidal conversion of T4 to T3, allowing for rapid changes in tissue thyroid hormone availability.<sup>3,5</sup>

More than 99.95 percent of T4 and 99.5 percent of T3 in serum are bound to several serum proteins, including TBG, transthyretin (TTR, formerly called thyroxine-binding prealbumin [TBPA]), albumin, and lipoproteins. Since nearly all the T4 and T3 found in serum is bound, changes in serum concentration of binding proteins, namely TBG, influence the total serum T4 and T3 concentrations and the fractional metabolism of T4 and T3.<sup>5</sup>

Thyroid function is best assessed by measuring TSH (assuming steady state conditions and the absence of pituitary or hypothalamic disease). However, direct measurement of all TSH and all other serum thyroid hormone levels serum total T3 and total T4, serum free T3 (fT3) and free T4 (fT4) is still important, as it may be difficult in some patients to be certain about the state of pituitary and hypothalamic function.<sup>3</sup>

Thyroid hormones must be maintained within a carefully regulated range, as levels outside this range (both hypo- or hyperthyroid) can result in adverse clinical consequences. Hypothyroidism diagnosis depends heavily on laboratory tests because of the lack of specificity of the typical clinical manifestations. Primary hypothyroidism is characterized by high TSH and low fT4 concentrations. Subclinical hypothyroidism is defined biochemically as a patient having elevated TSH but a normal fT4 concentration and secondary (central) hypothyroidism is characterized by a patient having low serum T4 concentration but a normal serum TSH concentration. Symptoms include fatigue and weakness, cold intolerance, weight gain, cognitive dysfunction, dyspnea on exertion, hair loss, hoarseness, dry skin, edema, decreased hearing, myalgia and paresthesia, depression, menorrhagia, arthralgia, or pubertal delay.<sup>6</sup> 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.<sup>7</sup> 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.<sup>8</sup>

Overt hyperthyroidism refers to patients with elevated levels of fT4, fT3, or both, and subnormal TSH levels, while subclinical hyperthyroidism is defined as patients having normal T4 and T3 in the presence of subnormal TSH levels. Hyperthyroid symptoms are nonspecific, but can include tachycardia, heat intolerance, sweating, tremor, dyspnea on exertion, and weight loss. Because a number of these symptoms are so common and nonspecific, they may be subtle and unrecognized. Both hypothyroidism and hyperthyroidism conditions rely on laboratory testing to confirm diagnosis.<sup>6,9</sup>

Current assays for TSH are extremely sensitive at detecting changes in thyroid homeostasis prior to changes in T4 and T3 levels. Thus, TSH assessment is the most often used initial test for thyroid function. In general, if serum TSH is normal, no further testing is needed; however, if serum TSH is high, fT4 is used to determine the degree of hypothyroidism. In contrast, if serum TSH is low, fT4 and fT3 are used to determine the degree of hyperthyroidism. If a pituitary or hypothalamic condition is suspected, both serum TSH and fT4 may be measured, and serum fT4 may be measured if symptoms of hyper- or hypothyroidism are present in a patient with normal TSH levels.<sup>3</sup> Measurement of fT4 is regarded as a better indicator of thyroid function than total T4 measurement for most situations, as it reflects the amount of available hormone. Presently, there is considerable controversy as to the appropriate upper limit of normal for serum TSH, with most labs using upper limits of approximately 4.5 to 5.0 mU/L (current “normal” range 0.4-5

mU/L) and there are debates on the cost effectiveness of screening asymptomatic patients. In addition, research has shown an age-related shift toward higher TSH concentrations in older patients.<sup>3</sup>

While thyroid nodules are prevalent and found in up to 50% of all individuals, with most being benign, some TNs can be malignant. Several clinical features and patient history factors can increase the risk of malignancy in thyroid nodules. A hard nodule, evidence of local invasion such as fixation to adjacent structures or vocal cord palsy, cervical lymphadenopathy, or rapid nodule growth are all indicators of a higher risk of thyroid cancer. Additionally, a prior hemithyroidectomy with discovery of thyroid cancer, a history of thyroid cancer, or a family history of thyroid cancer or thyroid cancer syndromes in first-degree relatives can also elevate the risk. Evaluation of these nodules is crucial to rule out malignancy and identify those individuals requiring surgical intervention. One important laboratory test for the differentiation between a benign or malignant TN is assessment of TSH levels. In individuals with a TN, serum TSH levels that either exceed the normal range or are near the upper limit of the range are concerning, as this corresponds to an increased risk of malignancy.<sup>10-12</sup>

In patients with low TSH levels, a radionuclide thyroid scan is indicated to determine whether the nodule is hyperfunctioning (autonomously producing thyroid hormone) or if the entire thyroid gland is overactive, as seen in conditions like toxic multinodular goiter. If the nodule is "hot" (hyperfunctioning), the risk of malignancy is extremely low, and further workup may not be necessary. Conversely, if the nodule is "cold" (nonfunctioning), further evaluation, including fine-needle aspiration biopsy, is warranted to assess for potential malignancy. Additionally, a subnormal TSH level increases suspicion for a hyperfunctioning nodule, and only in this circumstance should a thyroid uptake scan be ordered. If the nodule is "hot," the patient can be managed by their endocrinologist without further workup, as there is less than a 1% risk of malignancy.<sup>13,14</sup>

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. There are a few forms of thyroiditis, including Hashimoto's, painless, postpartum, subacute, drug-induced, radiation, and acute or infectious thyroiditis, each with its own symptoms and progression.

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, including thyroglobulin (Tg), thyroid peroxidase (TPO), thyroid stimulating immunoglobulins, and the thyrotropin receptor. High levels of these antibodies are commonly found in patients with autoimmune thyroid conditions, such as Hashimoto's thyroiditis, where nearly all patients show elevated levels of antibodies to Tg and TPO. There are three main forms of thyroiditis considered autoimmune: Hashimoto's thyroiditis, painless thyroiditis, and postpartum thyroiditis. Hashimoto's typically leads to hypothyroidism and is usually permanent. Painless and postpartum thyroiditis follow a similar pattern, starting with a thyrotoxic phase followed by hypothyroidism, though postpartum thyroiditis occurs after childbirth, while painless thyroiditis can affect both men and women who are not postpartum. Symptoms during the thyrotoxic phase may include anxiety, insomnia, palpitations, fatigue, weight loss, and irritability, lasting 1–3 months. The hypothyroid phase follows 1–3 months later

and can last 9–12 months, presenting with fatigue, weight gain, constipation, dry skin, depression, and poor exercise tolerance. Most cases (~80%) resolve within 12–18 months.<sup>3,9,15</sup>

Subacute thyroiditis follows a similar course to painless and postpartum thyroiditis but is often accompanied by thyroid pain, which typically occurs during the thyrotoxic phase (1–3 months). However, not all patients with thyroid pain experience thyrotoxicosis. Most individuals (~95%) recover within 12–18 months, with rare recurrences. Drug-induced and radiation thyroiditis can cause both thyrotoxicosis and hypothyroidism, though the thyrotoxic phase is usually brief. In drug-induced cases, hypothyroidism often resolves after discontinuing the medication, while radiation-induced hypothyroidism is usually permanent. Finally, acute or infectious thyroiditis may lead to thyroid pain, systemic illness, painless thyroid enlargement, and hypothyroidism, but symptoms typically resolve once the infection is treated.<sup>15</sup>

Assessment of the thyroid is particularly important for pregnant individuals. Due to the metabolic changes during pregnancy, the levels of thyroid hormones differ dramatically. In pregnant individuals, total T4 and total T3 are higher than in nonpregnant individuals, TBG nearly doubles due to the increased estrogen, and in the first trimester, TSH concentrations are reduced due to high serum human chorionic gonadotropin (hCG) levels. Thyroid physiology changes during pregnancy, therefore trimester-specific ranges for TSH and fT4 should be utilized. Unfortunately, not all commercial laboratories provide these reference ranges. As such, when trimester-specific reference ranges for fT4 are not available and fT4 levels appear discordant with TSH, total T4 measurements may be superior to fT4.<sup>16</sup>

The effects of thyroid problems during pregnancy may be dire. Luewan, et al. (2011) performed a study comparing 180 pregnant individuals with hyperthyroidism to 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.<sup>17</sup>

An imbalance of thyroid hormones is not only harmful to pregnant individuals, but it can also negatively impact children, producing short stature. Thyroid hormone isoforms and thyroid hormones play an important role in bone development and growth, as defects associated with congenital hypothyroidism include delayed epiphyseal closure and widely spaced cranial sutures.<sup>18</sup> 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 plays a crucial role in both normal and pathologic variations of linear growth, though the pathways are unclear as of date.<sup>7,18</sup>

Tests measuring levels of thyroid-related markers are widely available commercially, often as a panel. Many combinations of thyroid serum markers are available. For example, Testing.com offers thyroid tests which screen for individual thyroid hormones including TSH, fT4, and fT3.<sup>19</sup> EverlyWell offers a direct-to-consumer home-health panel testing for TSH, T3, T4, and thyroid peroxidase antibodies.<sup>20</sup> Other direct-to-consumer home-health panel tests include

LetsGetChecked,<sup>21</sup> Paloma Health,<sup>22</sup> myLABBOX Thyroid Health Screening,<sup>23</sup> and TellmeGEN.<sup>24</sup>

Common variable immunodeficiency (CVID) is one of the more common antibody deficiency disorders. In one large series of primary immunodeficiency (PID) in children diagnosed over a 10-year period, CVID made up 17 of 189 total PID cases and 20 percent of the 87 cases of antibody deficiency. Most patients with CVID present after puberty, and the disorder is usually diagnosed in the second or third decade of life. However, about 25 percent of all CVID patients present in childhood or adolescence and there is an earlier peak of diagnosis occurring around eight years of age. A diagnosis of CVID before six years of age should be considered preliminary because of immunologic immaturity and the persistence of transient hypogammaglobulinemia of infancy in some children. In addition, the possible presence of a monogenic defect that causes a CVID-like disorder should be considered in children who present at a very young age. Children with failure-to-thrive should be evaluated for thyroid function and growth hormone deficiency. Growth hormone replacement therapy should be offered if deficiency is identified.<sup>25</sup>

### ***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.<sup>3</sup>

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  $r = 0.8$  with many correlations near or above 0.9.<sup>26</sup>

Serum T4 and T3 are typically measured by automated competitive binding chemiluminometric assays. Older competitive binding radioimmunoassays are still available for serum total T4. Serum total T4 and total T3 measure both bound and unbound (free) T4 and T3, respectively. A large percentage of serum T4 is bound (99.97%) to TBG, transthyretin (also called TBPA [thyroxine-binding prealbumin]), and albumin. Serum T3 is less tightly bound to TBG and TBPA but more tightly bound to albumin than T4. Normal reference ranges do vary among laboratories; however, a typical reference range for total T4 is 4.6-11.2 mcg/dL (60-145 nmol/L) and for total T3, while more variable across laboratories even than total T4, a typical reference range is ~75-195 ng/dL (~1.1-3 nmol/L).<sup>3</sup>

The current immunoassays used to measure T3 do not always agree with other methods. For example, a study by Masika, et al. (2016) compared immunoassay methods to LC/MS/MS and found that 45% of patients classified as “normal” by immunoassay were classified as “lower than 2.5<sup>th</sup> percentile” by LC/MS/MS. The authors also noted that in patients not receiving T4, 74% of their results were below the 2.5<sup>th</sup> percentile by LC/MS/MS whereas only 21% were under that mark by immunoassay. The authors speculate that this discrepancy may be due to deiodinase polymorphisms but overall conclude that because this is a significant method to diagnose thyroid issues, accuracy of T3 measurements should be paramount.<sup>27</sup>

The measurement of reverse T3 may not be reliable. A study by Burmeister, focused on a total of 246 patients contributing 262 reverse T3 measurements, showed 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 caused by hypothyroidism, despite normal TSH levels. Overall, Burmeister concludes that reverse T3 cannot differentiate between hypothyroidism and euthyroidism.<sup>28,29</sup>

### ***Clinical Utility & Validity***

Koike, et al. (2001) aimed to identify key ultrasound features that predict malignancy in thyroid nodules. The study focused on five ultrasound characteristics: margin, shape, echo structure, echogenicity, and calcification. The authors found that these features were statistically significant in identifying thyroid cancer. Specifically, irregular margins, a taller-than-wide shape, hypoechogenicity, the presence of microcalcifications, and a solid echo structure were all associated with a higher likelihood of malignancy. These results emphasize the importance of ultrasound in assessing the risk of thyroid cancer, though the study also highlighted that these features alone cannot definitively confirm malignancy. A fine-needle aspiration biopsy remains essential for an accurate diagnosis.<sup>30</sup>

Li, et al. (2017) conducted a preliminary study to investigate how certain dietary supplements could affect clinical assays. They examined six healthy adult participants and 11 hormone and nonhormone analytes measured by 37 immunoassays and found that ingesting 10 mg/d of biotin for one week was associated with a potentially clinically important interference with some biotinylated assays. These immunoassays use a biotin-streptavidin binding system, so excess biotin may influence the results of assays using this system. The time at which the biotin was ingested was also a factor in the magnitude of the distortion.<sup>31</sup> Repeating a thyroid test at least two days after biotin discontinuation may be considered.<sup>3</sup>

Livingston, et al. (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, 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.<sup>32</sup>

Yazici, et al. (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 that the TSH to Tg ratio was significantly higher in the malignant group, as there was no major difference in TSH between groups despite the Tg changes. However, the authors note that only fine-needle aspiration biopsy was a significant factor.<sup>33</sup> Autoantibodies may also play a role in the 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 in patients with cancer, whereas the control group was found to be only 5.4% by both methods.<sup>34</sup>

Thyroid antibodies play a role in autoimmune thyroiditis. A study performed by Biktagirova, et al. (2016) 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).<sup>35</sup> Another study performed by Diana investigated the prevalence of thyroid stimulating hormone receptor (TSHR) blocking antibodies (TBAb) in autoimmune thyroid disease. In total, 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 positively 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.<sup>36</sup>

Kluesner, et al. (2018) 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.<sup>37</sup>

Jin (2018) investigated the prevalence of subclinical hypothyroidism in obese children and its association with thyroid hormone. The study included 1,104 children and 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 positively correlate with serum concentrations of TSH and negatively correlate with serum concentrations of fT4. Total cholesterol and triglyceride concentration were found to positively correlate with TSH concentrations, with fT4 negatively correlating with total cholesterol. Jin concluded that TSH is correlated with lipid profiles.<sup>38</sup>

In a 2018 study, Muraresku, et al. (2018) reviewed mitochondrial disease and recent advances in clinical diagnosis, management, therapeutic development, and preventive strategies. They noted that routine screening of individuals with mitochondrial diseases is imperative. Screening should include examining the “multitude of symptoms known for diabetes mellitus, adrenal insufficiency, thyroid hormone insufficiency, hearing loss, cardiac arrhythmias, and other disease related symptoms, with appropriate multi-specialist management provided.” They also noted that “primary mitochondrial disease encompasses an impressive range of inherited energy deficiency disorders having highly variable molecular etiologies as well as clinical onset, severity, progression, and response to therapies of multi-system manifestations.”<sup>39</sup>

Sarkar (2012) examined literature surrounding recurrent pregnancy loss in patients with thyroid dysfunction. Disturbances in thyroid function and thyroid hormone levels are common in women during their reproductive years and that dysfunction can interfere with reproductive physiology, can reduce the likelihood of pregnancy, and can adversely affect pregnancy outcome. They note that “universal screening for thyroid hormone abnormalities should be conducted in [individuals] with fetal loss or menstrual disturbances. Practitioners providing health care for women should be alert to thyroid disorders as an underlying etiology for recurrent pregnancy loss.” However,

universal screening for thyroid hormone abnormalities is not routinely recommended at present. In individuals capable of pregnancy and of reproductive age, hypothyroidism can be reversed by thyroxine therapy and this can improve fertility and help individuals avoid needing to use assisted reproduction technologies.<sup>40</sup>

Korevaar, et al. (2019) performed a meta-analysis focusing on thyroid function test abnormalities and thyroid autoimmunity with preterm birth. They assessed 19 cohorts encompassing 47,045 pregnant individuals and found that 1,234 of these individuals had subclinical hypothyroidism, 904 had isolated hypothyroxinemia (“decreased fT4 concentration with normal thyrotropin concentration”), 3,043 were thyroid peroxidase (TPO) antibody positive, and 2,357 had preterm birth. Risk of preterm birth was found to be higher for individuals with subclinical hypothyroidism than with euthyroidism (odds ratio = 1.29), as well as higher for individuals 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 individuals were found to have a higher risk of preterm birth compared to TPO antibody negative individuals by an odds ratio of 1.33.<sup>41</sup>

In a population-based study by Kiel, et al. (2020) the use of thyroid hormone measurements in ambulatory care was assessed. Measurement of serum TSH, fT3, and fT4 within the one to three 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. Of these, 30% (1,626/5,552) received at least one TSH measurement and 6.8% (378/5,552) 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 both for patients with suspected hypo- and hyperthyroidism as well as 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 who are taking thyroid medication. In the study, 40% did not receive a monitoring TSH test within one year, and 16% did not receive a TSH test within three 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.”<sup>42</sup>

In 2021, Degrandi, et al. (2021) examined the prevalence of thyroid autoimmunity in children with developmental dyslexia. Serum TSH, fT3, and fT4 were measured and thyroid autoimmunity was evaluated by measuring TPOAbs and antithyroglobulin antibodies (TG-Abs). The authors also performed thyroid ultrasonography in the subjects with developmental dyslexia. The study enrolled 51 subjects with developmental dyslexia (M : F = 39 : 12, mean age  $12.4 \pm 9$  years) and 34 controls (M : F = 24 : 10, mean age  $10.8 \pm 4$  years) and found a significant increase in TPOAb positivity in subjects as compared to controls (60.8% vs 2.9%,  $p < 0.001$ ) but no significant change in Tg-Ab positivity (16% vs 5.8%). Additionally, in the subjects with developmental dyslexia who received ultrasonography (49 of 51 subjects), 60% of them had a thyroiditis pattern. Overall, this study showed a high prevalence of thyroid autoimmunity in children with developmental dyslexia and while further research is needed to confirm these initial

findings, these results may change the approach to developmental dyslexia and eventually lead to a systematic determination of thyroid autoimmunity in affected children.<sup>43</sup>

Wang, et al. (2021) examined the association between thyroid function and serum lipid metabolism, utilizing a genetic analysis termed Mendelian randomization (MR). While thyroid dysfunction is known to be associated with cardiovascular disease, the role of thyroid function in lipid metabolism is still partly unknown. “The MR approach uses a genetic variant as the instrumental variable in epidemiological studies to mimic a randomized controlled trial” and for this study, the authors performed a two-sample MR to assess the causal association, using summary statistics from the Atrial Fibrillation Genetics Consortium (n = 537,409) and the Global Lipids Genetics Consortium (n = 188,577). TSH, fT3 and fT4 levels, the fT3:fT4 ratio, and the concentration of TPOAb were all used to get a clinical measurement of thyroid function. Serum lipid metabolism traits included total cholesterol (TC) and triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels. To assess the association between thyroid function and serum lipid metabolism, the MR estimate and MR inverse variance-weighted method were used. The authors found that increased TSH levels were significantly associated with higher TC and LDL levels, as was the fT3:fT4 ratio. However, they observed no significant differences between genetically predicted fT4 and TPOAb and serum lipids. They concluded that their results suggest an association between thyroid function and serum lipid metabolism, “highlighting the importance of the pituitary-thyroid-cardiac axis in dyslipidemia susceptibility.”<sup>44</sup>

Tolosa, et al. (2022) performed a systematic review and meta-analyses of data collected from pregnant patients (excluding pre-existing thyroid disease and multifetal pregnancies) to analyze the primary outcomes of gestational hypertension and pre-eclampsia; data was taken from cohort studies that included maternal concentrations of TSH, FT4, and TPO antibodies as well as data regarding maternal gestational hypertension, pre-eclampsia, or both. The study comprised 46,528 pregnant individuals, of which 39,826 individuals had enough data to be classified by thyroid function status. Individuals who had subclinical hypothyroidism made up 3.2% of the cohort (1,275 individuals). After analyses, a total of 933 individuals had isolated hypothyroxinemia, 619 had subclinical hyperthyroidism, and 337 had overt hyperthyroidism. The authors concluded that “compared with euthyroidism, subclinical hypothyroidism was associated with a higher risk of pre-eclampsia...In a continuous analysis, both a higher and a lower TSH concentration were associated with a higher risk of pre-eclampsia.”<sup>45</sup>

## **V. Guidelines and Recommendations**

### **United States Preventive Services Task Force (USPSTF)**

The USPSTF states that “current evidence is insufficient to assess the balance of benefits and harms of screening for thyroid dysfunction in nonpregnant, asymptomatic adults.”<sup>42</sup> As such, USPSTF recommends against screening for thyroid cancer in asymptomatic adults.<sup>46</sup>

### **American College of Obstetricians and Gynecologists (ACOG)**

The 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.
- The TSH level should be monitored in pregnant [individuals] 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 [individuals] 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 [individuals] 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 [individuals] 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 [individuals] 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 including

thyroid receptor antibodies and thyroid stimulating immunoglobulin in women with Graves [sic] disease may establish those at an increased risk for fetal or neonatal hyperthyroidism.”<sup>47</sup>

### **American Thyroid Association (ATA) and American Association of Clinical Endocrinologists (AACE)**

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:

- “Antithyroid 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 [Thyrotropin receptor autoantibodies] 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.”<sup>48</sup>

The guidelines recommend against testing serum T3 or fT3, 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.<sup>48</sup>

### **American Thyroid Association (ATA)**

#### *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 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 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 levothyroxine (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 four 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 four to eight 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 four to eight 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
- History of miscarriage or preterm delivery
- History of head or neck radiation
- Family history of thyroid dysfunction
- Morbid obesity ( $\text{BMI} \geq 40 \text{ kg/m}^2$ )
- Use of amiodarone or lithium, or recent administration of iodinated radiologic contrast
- Infertility
- Residing in an area of known moderate to severe iodine insufficiency<sup>49</sup>

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

- "The accuracy of serum FT4 measurement by the indirect analog immunoassays is influenced by pregnancy and also varies significantly by manufacturer. If measured in pregnant women, assay method-specific and trimester-specific pregnancy reference ranges should be applied.

- In lieu of measuring FT4, TT4 measurement (with a pregnancy-adjusted reference range) is a highly reliable means of estimating hormone concentration during the last part of pregnancy. Accurate estimation of the FT4 concentrations can also be done by calculating a FT4 index.
- 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 Tg-Ab 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.
- 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, 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.”<sup>8</sup>

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.”<sup>8</sup>

The ATA recommends that “the appropriate management of abnormal maternal thyroid tests attributable to gestational transient thyrotoxicosis and/or hyperemesis gravidarum includes supportive therapy, management of dehydration, and hospitalization if needed. Antithyroid drugs are not recommended, though  $\beta$ -blockers may be considered. In women being treated with antithyroid drugs in pregnancy, FT4/TT4 and thyroid hormone secretion should be monitored approximately every 4 weeks. Antithyroid medication during pregnancy should be administered at the lowest effective dose of MMI or PTU, targeting maternal serum FT4/TT4 at the upper limit or moderately above the reference range. A combination regimen of LT4 and antithyroid drugs should not be used in pregnancy, except in the rare situation of isolated fetal hyperthyroidism.”<sup>8</sup>

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

The ATA recommended 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.<sup>50</sup>

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

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.<sup>51</sup>

### **American Academy of Family Physicians (AAFP)**

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.<sup>52</sup> The AAFP also recommends using TSH testing to diagnose primary hypothyroidism (Level C).<sup>53</sup>

In the case of subclinical thyroid disease, the AAFP recommends that “Physicians should not routinely screen for subclinical thyroid disease.”<sup>54</sup> 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.<sup>55,56</sup>

In 2020, AAFP recommended the following for the evaluation and management of thyroid nodules:

- “Thyroid ultrasonography with a survey of the cervical lymph nodes should be performed in all patients with thyroid nodules.
- The serum thyroid stimulating hormone level should be measured during the initial evaluation of a thyroid nodule. If it is low, a radionuclide thyroid uptake scan should be performed.
- Fine-needle aspiration is recommended for thyroid nodules 1 cm or larger that have a suspicious pattern on ultrasonography.
- Before molecular testing is performed, patients should be counseled about the potential benefits and limitations of the test.”<sup>13</sup>

The American Family Physician recommends “the term failure-to-thrive should be used as a clinical finding and not as a diagnosis. Recognition depends on reliable and valid measurements over time; therefore, serial measurements of weight and height must be accurately obtained and charted on an appropriate reference scale. No standard set of laboratory tests is recommended for failure-to-thrive. A thorough history and physical examination may be all that is indicated to initiate treatment. If used, reasonable initial laboratory testing includes complete blood count, urinalysis, electrolyte measurement, thyroid tests, and testing for celiac disease. Specific testing for cystic fibrosis, food allergies, human immunodeficiency virus infection, or tuberculosis may be indicated depending on the presentation. Additional testing should be specific for a suspected diagnosis based on history and physical examination findings.”<sup>57</sup>

### **American Society for Reproductive Medicine (ASRM)**

The 2024 guideline on subclinical hypothyroidism in the infertile female population states the following recommendations:

- “Universal screening of thyroid function during pregnancy is not recommended (strength of evidence: B; strength of recommendation: moderate).
- Screening of thyroid function during pregnancy with a serum thyrotropin level is recommended in patients at increased risk of overt hypothyroidism (strength of evidence: B; strength of recommendation: moderate).
- There is insufficient evidence to counsel women that SCH is associated with infertility (strength of evidence: C; strength of recommendation: weak).
- It is not recommended to screen for TAI in asymptomatic women with infertility or pregnancy. Targeted screening may be considered in women with a history of RPL (strength of evidence C; strength of recommendation weak).
- Universal screening of thyroid function during pregnancy is not recommended (strength of evidence: B; strength of recommendation: moderate).
- Screening of thyroid function during pregnancy with a serum thyrotropin level is recommended for patients at increased risk. (strength of evidence: B; strength of recommendation: moderate).
- Thyroid-stimulating hormone and T4 levels should be tested in patients with signs or symptoms of hypothyroidism (including irregular menstrual cycles) rather than in all patients with infertility (strength of evidence: B; strength of recommendation: moderate).”<sup>58</sup>

In conclusion, the ASRM states: “Most of the evidence advocating for screening and treatment of SCH in women with infertility or pregnancy is based on low-quality observational data and one clinical trial, which should be withdrawn because of significant concerns over data integrity. On the basis of current evidence, it is not recommended to screen or treat for asymptomatic SCH in women with infertility or pregnancy.”<sup>58</sup>

### **Australian Journal of General Practice (AJGP)**

According to the AJGP, “Thyroid stimulating hormone (TSH) should be checked:

- when screening for thyroid hormone excess or deficiency on the basis of symptoms or risk factors
- when goiter or thyroid nodules are identified
- when monitoring uncomplicated thyroxine replacement therapy, with a minimum interval of 4–6 weeks following a dose change to allow achievement of a steady state, and annually when stable
- prior to, and early in the first trimester of, pregnancy in women treated with levothyroxine or those with risk factors for thyroid dysfunction.”<sup>59</sup>

Moreover, “An elevated TSH level should be investigated in the following ways:

- If TSH is high, check TSH with free T4 (FT4)
  - elevated TSH with FT4 below the reference range diagnoses primary hypothyroidism.

- elevated TSH with FT4 within the reference range diagnoses mild or subclinical hypothyroidism.
- A mildly raised TSH will often resolve without treatment; therefore, thyroid function tests should generally be repeated at least once after 1–3 months before further investigation or treatment.
- Thyroid ultrasonography and thyroid scintigraphy should not be performed for uncomplicated hypothyroidism without a palpable nodule.”<sup>59</sup>

The AJGP also outlines when a suppressed TSH level be investigated:

- “if TSH is low, check FT4 and FT3
  - FT4 and/or FT3 above the reference range diagnoses primary hyperthyroidism
  - a mildly low TSH (0.1–0.5 mIU/L) with normal free thyroid hormones suggests mild or subclinical hyperthyroidism, non-thyroidal illness or interference from other medications
- positive TSH receptor antibodies (TRAb; or thyroid stimulating immunoglobulins [TSI]) support a diagnosis of Graves’ disease
- thyroid scintigraphy should be performed to distinguish between Graves’ disease, toxic nodules and thyroiditis if the TRAb test is negative or there is diagnostic uncertainty
- thyroid ultrasonography is generally unhelpful in determining the cause of hyperthyroidism.”

“It is important to:

- check TSH, FT4 and FT3 to evaluate thyroid function in settings where TSH alone may be unreliable, such as
  - suspected pituitary or hypothalamic disease
  - suspected assay interference
  - rapidly changing thyroid function
- check FT4 (not TSH) to monitor and adjust levothyroxine replacement in patients with central hypothyroidism due to pituitary or hypothalamic disease
- note that measurement of reverse T3 is not recommended for the investigation of thyroid dysfunction.”<sup>59</sup>

The AJGP recommends that “couples with two of more pregnancy losses should have thyroid antibody and function testing performed. Abnormal results should be managed by a specialized clinic. There is evidence that suggests hypothyroidism and even subclinical hypothyroidism is associated with recurrent pregnancy loss. All guidelines recommend testing for thyroid stimulating hormone (TSH) levels, but there is contention about what is considered a ‘normal’ TSH. Current guidelines suggest treating all women with overt hypothyroidism, considering treatment of subclinical hypothyroidism, and not treating euthyroid patients with recurrent pregnancy loss who test positive for thyroid antibodies.”<sup>60</sup>

**Joint Task Force on Practice Parameters (JTFPP) of the Academy of Allergy, Asthma & Immunology (AAAAI); the American Academy of Allergy, Asthma & Immunology (AAAAI); and the Joint Council of Allergy, Asthma & Immunology (JCAAI)**

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 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.”<sup>61</sup>

### **American Society for Clinical Pathology (ASCP)**

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. Any diagnosis made by the physician should be confirmed with free thyroxine (T4) testing. They also recommend avoiding 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.<sup>62</sup>

### **Endocrine Society (ES)**

The Endocrine Society recommends against testing for total or free T3 when evaluating LT4 dose in hypothyroid patients. They also recommend against ordering routine ultrasounds for patients without palpable abnormalities of the thyroid. While routine thyroid ultrasounds should not be ordered without palpable abnormalities, thyroid vascularity assessments may be performed by color flow Doppler in patients who show overt hyperthyroidism evidenced by elevated free T4 and T3 and lower TSH values; color flow Doppler (a noninvasive ultrasound test) may help diagnose Graves’ hyperthyroidism and toxic nodular goiter from destructive thyroiditis.<sup>63</sup>

### **European Thyroid Association (ETA)**

#### *Management of Thyroid Dysfunction following Immune Reconstitution Therapy (IRT)*

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 HIV infected patients with HAART; (3) following allogeneic BMT or HSCT.”<sup>64</sup>

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 one 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 three 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 three monthly measuring of thyroid function to be continued for 4 years following the last alemtuzumab treatment.”<sup>64</sup>

### *Thyroid Disorders Prior to and during Assisted Reproduction*

The ETA recommends women of subfertile couples (“subfertile” is defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse) should be screened routinely for the presence of thyroid disorders. The ETA notes that severe thyroid dysfunction is linked to menstrual disorders as well as subfertility. In a meta-analysis that included mostly women with TSH levels above 4.0 mIU/L, treatment with levothyroxine was effective at increasing live birth rates.<sup>65</sup>

### *Management of Graves’ Hyperthyroidism*

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 two weeks after initiation of therapy, every four 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 (> three times normal cutoff), monitoring the fetus for thyroid dysfunction throughout pregnancy is recommended.<sup>66</sup>

In 2022, the ETA published guidelines for the management of GD in pediatric patients. Hyperthyroidism caused by GD is relatively rare in children and treatment options for pediatric patients are the same as those available to adults (ATD, radioactive iodine (RAI), or thyroid surgery). However, the risks and benefits of each modality are different in pediatric patients than they are in adult patients. The ETA recommends that “clinicians should be alert that GD may present with behavioral changes or declining academic performance in children. Measurement of serum TSH receptor antibodies is recommended for all pediatric patients with hyperthyroidism. Management recommendations include the first-line use of a prolonged course of methimazole/carbimazole ATD treatment (three years or more), a preference for dose titration instead of block and replace ATD, and to avoid propylthiouracil use. Where definitive treatment is required either total thyroidectomy or RAI is recommended, aiming for complete thyroid ablation with a personalized RAI activity. We recommend avoiding RAI in children under 10

years of age but favor surgery in patients with large goiter. Pediatric endocrinologists should be involved in all cases.”<sup>67</sup>

### *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 *immunoglobulin superfamily member 1 (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 recombinant human growth hormone (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 non-thyroidal illness or deiodination defects (e.g., *selenocysteine (Sec) insertion sequence-binding protein 2 (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)."

In their 2023 clinical practice guidelines for thyroid nodule management, the ETA recommends that:

- "Initial evaluation should include personal and family history, physical evaluation, thyroid function testing, and neck US assessment (*Ungraded good practice statement. Agreement: 9/9 (100%); round: 1*)
- Consider the use of a disease-specific patient-reported outcome measure for evaluation of symptomatology (*Strength of recommendation: 1; quality of evidence: 0000. Agreement: 8/9 (88.9%); round: 1*)."<sup>68</sup>

## **National Institute for Health and Care Excellence (NICE)**

### *Thyroid Disease: Assessment and Management*

The 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

The 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.

In a 2023 update, the NICE offered some additional guidance on testing when thyroid dysfunction is suspected, namely to

“1.2.8 Consider measuring thyroid stimulating hormone (TSH) alone for adults when secondary thyroid dysfunction (pituitary disease) is not suspected. Then:

- if the TSH is above the reference range, measure free thyroxine (FT4) in the same sample
- if the TSH is below the reference range, measure FT4 and free triiodothyronine (FT3) in the same sample.

1.2.9 Consider measuring both TSH and FT4 for:

- adults when secondary thyroid dysfunction (pituitary disease) is suspected
- children and young people.

If the TSH is below the reference range, measure FT3 in the same sample.

1.2.10 Consider repeating the tests for thyroid dysfunction in recommendations 1.2.8 or 1.2.9 if symptoms worsen or new symptoms develop (but no sooner than 6 weeks from the most recent test).

1.2.11 Ask adults, children and young people with suspected thyroid dysfunction about their biotin intake because a high consumption of biotin from dietary supplements may lead to falsely high or low test results.”<sup>69</sup>

For adults with TSH levels above the reference range, TPOAb measurement may be considered. However, this testing should not be repeated. This applies to primary and subclinical hypothyroidism.

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 stabilized (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 two and over and young people taking levothyroxine for primary hypothyroidism, consider measuring fT4 and TSH “every 6 to 12 weeks until the TSH level has stabilized (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 two, consider measuring fT4 and TSH “every 4 to 8 weeks until the TSH level has stabilized (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 two to three years if they are asymptomatic.

The NICE states to consider measuring fT4 and TSH for children two 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.”

Furthermore, “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 TPOAbs and TRABs may be done to differentiate.

After radioactive iodine treatment, consider measuring fT3, fT4, and TSH every six weeks for the first six 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 six weeks until TSH is within reference range, then TSH (with cascading) every three 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 stabilizes (2 similar measurements within the reference range 3 to 6 months apart).”<sup>69</sup>

## Society for Maternal-Fetal Medicine (SMFM)

The SMFM recommends against screening asymptomatic pregnant individuals for subclinical hypothyroidism.<sup>70</sup>

## Mitochondrial Medicine Society (MMS)

In 2017, the MMS created a working group to provide consensus-based recommendations for optimal management and care for patients with primary mitochondrial disease. From the guidelines, “initial triage stratification of critically ill mitochondrial patients should include a systemic assessment of all body systems since the disease is multisystemic and patients may develop new organ system involvement during an acute decompensation” and thyroid dysfunction can occur in patients with mitochondrial disease, as “both hypothyroidism and, to a far lesser extent, hyperthyroidism have been reported in patients with primary mitochondrial diseases.” In addition to routine intensive care management that might be undertaken for a critically ill patient, they recommend that “thyroid and adrenal function should be assessed in patients at times of critical illness and reassessed during a prolonged intensive care unit stay. Hypo- and hyperglycemia can occur and regular blood glucose monitoring is needed.” They also state that “an annual hemoglobin A1c (HgbA1c), thyroid stimulating hormone, free thyroxine level (FT4), vitamin D, and screening for hypoparathyroidism (serum calcium, magnesium, phosphate, parathyroid hormone, vitamin D (25-OHD and 1,25-OHD); urine: creatinine, calcium, and phosphate) can be considered in individuals with mitochondrial diseases. In those with mtDNA deletions, which are more strongly associated with secondary endocrinopathies, annual screening is recommended.”<sup>71</sup>

## VI. Applicable State and Federal Regulations

### Food and Drug Administration (FDA)

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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

## VII. Applicable CPT/HCPCS Procedure Codes

Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all inclusive and is subject to updates. In addition, codes listed are not a guarantee of payment.

CPT	Code Description
80438	Thyrotropin-releasing hormone (TRH) stimulation panel; 1 hour This panel must include the following: Thyroid stimulating hormone (TSH) (84443 x 3)
80439	Thyrotropin-releasing hormone (TRH) stimulation panel; 2 hour This panel must include the following: Thyroid stimulating hormone (TSH) (84443 x 4)
83519	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, by radioimmunoassay (eg, RIA)

CPT	Code Description
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
84432	Thyroglobulin
84436	Thyroxine; total
84439	Thyroxine; free
84442	Thyroxine-binding globulin (TBG)
84443	Thyroid stimulating hormone (TSH)
84445	Thyroid stimulating immune globulins (TSI)
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

Current Procedural Terminology<sup>®</sup> American Medical Association. All Rights reserved.

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## IX. Revision History

Revision Date	Summary of Changes
01/01/2022	Initial Effective Date
07/19/2022	Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following modifications to the CC: CC1a: added “In” for clarity CC1ai: added “Thyroid stimulating hormone” to define the initialism CC1aii: added “(fT4)” for consistency CC1aiii: added “TSH and” due to BCBSM suggestion, but also supported by our description of secondary hypothyroidism and NICE guidelines, that TSH should be measured.

	<p>CC1aiv: deleted due to redundancy with the above CC CC1av: reworded for clarity</p> <p>CC1b reorganized and edited for clarity: CC1biv: Changed “primary and secondary” to “overt and subclinical” hyperthyroidism. Now reads:</p> <p>b) In individuals with symptoms consistent with hyperthyroidism (See Policy Guidelines):</p> <p>i) TSH to confirm or rule out overt hyperthyroidism</p> <p>ii) fT4 as a follow up to abnormal TSH findings</p> <p>iii) Total or free T3 (fT3) as a follow up to abnormal fT4 findings or if still concerned with hyperthyroidism</p> <p>iv) fT4 to distinguish between overt and subclinical hyperthyroidism</p> <p>v) Monitoring individuals closely after treatment for hyperthyroidism</p> <p>(a) In patients being treated for hyperthyroidism, repeat testing of TSH and fT4 should occur every 6-12 weeks</p> <p>(b) Annual monitoring after first year even if asymptomatic for risk of relapse or late-onset hypothyroidism</p> <p>CC1ci and CC1cii: removed “(limited to one time)”</p> <p>CC1ciii: added “or if symptoms consistent with thyroid dysfunction develop”; “including, but not limited to”; “and immune checkpoint inhibitors” in response to suggestion by BCBSM and literature support (e.g., <a href="https://pubmed.ncbi.nlm.nih.gov/33875857/">https://pubmed.ncbi.nlm.nih.gov/33875857/</a>)</p> <p>CC1eiv: removed italics from “thyrotropin receptor antibodies (TRAb)”</p> <p>CC1eviii: deleted “(k) infertility” due to redundancy with the CC above</p> <p>CC4 changed from MCC to DNMCC based on clinical guidance: “Testing for thyrotropin-releasing hormone (TRH) DOES NOT MEET COVERAGE CRITERIA for the evaluation of the cause of hyperthyroidism or hypothyroidism.”</p> <p>CC8: addition of “(Note 1)” to end of CC as a reference Note 1: uncapitalized “FT4” 3 times</p> <p>(80438 &amp; 80439) GA MCD are covered codes</p> <p>Removal of related policies: M2108, M2078, M2066, M2109</p> <p>Revised code disclaimer statement</p>
04/04/2023	<p>Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria:</p> <p>CC1.d. edited to add thyroid screening for individuals who have experienced two or more pregnancy losses. Previously read: “Women undergoing evaluation for infertility” Now reads: “For individuals capable of becoming pregnant who:</p> <p>i) Are undergoing evaluation for infertility.</p> <p>ii) Have experienced two or more pregnancy losses.</p> <p>Addition of CC1.j. “For individuals diagnosed with primary mitochondrial disease, annual screening of TSH and fT4.”</p>

	<p>Addition of CC1.i. “For pediatric individuals with a clinical finding of failure-to-thrive.”</p> <p>All CC edited for clarity and consistency.</p> <p>Coding Enhancement: Removed CPT codes 84437 and 84442.</p> <p>Committee approved 04/04/2023</p>
06/12/2023	<p>Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria: CC1 edited for clarity and consistency. “Policy Guidelines” section replaced with Note 1 (signs of hypothyroidism) and Note 2 (signs of hyperthyroidism), former Note 1 on testing in pregnancy becomes Note 3.</p> <p>CC1.a.iv. frequency for hypothyroidism follow up changed from “6-12” to “every 6 weeks”. Now reads: “iv) For individuals being treated for hypothyroidism, monitoring with TSH and fT4 testing every 6 weeks upon dosage change and annually in stable individuals.”</p> <p>CC1b.v.a., frequency for hyperthyroidism follow up changed from “6-12” to “every 8 weeks”. Now reads: “(a) In patients being treated for hyperthyroidism, repeat testing of TSH and fT4 should occur every 8 weeks.”</p> <p>Former CC1.e. pertaining to thyroid testing has been replaced with new CC2 and CC3: “2) For individuals who are pregnant or who are postpartum and who have symptoms of thyroid dysfunction (see Note 1 and Note 2), TSH and fT4 testing (once every 4 weeks) MEETS COVERAGE CRITERIA (see Note 3).</p> <p>3) For individuals who are pregnant or who are postpartum and who have been diagnosed with hyperthyroidism, total T4 (TT4), antithyroglobulin antibody (Tg-Ab), thyrotropin receptor antibodies (TRAb), and anti-thyroid peroxidase antibody (TPOAb) MEETS COVERAGE CRITERIA (see Note 3).”</p> <p>Thyroid antibody testing expanded beyond autoimmune thyroiditis, now allowing testing in hypothyroidism or hyperthyroidism, with testing restricted to once every 3 years. Former CC2, now CC4 reads: “4) For individuals with hypothyroidism or hyperthyroidism, testing for thyroid antibodies (once every three years) MEETS COVERAGE CRITERIA.”</p> <p>**TBG added as not covered under any circumstances. Former CC4, now CC6 now reads: “6) For the evaluation of the cause of hyperthyroidism or hypothyroidism, testing for thyrotropin-releasing hormone (TRH) or thyroxine-binding globulin (TBG) DOES NOT MEET COVERAGE CRITERIA.”</p> <p>Added CPT 84442</p> <p>Committee approved: 06/12/2023</p>
10/21/2024	<p>Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria:</p> <p>CC1 edited to address appropriate type of thyroid function testing for all subcriteria (previously only broken down in CC1a and b).</p>

	<p>Central hypothyroidism and secondary hypothyroidism are the same, for clarity, wrapped former CC1h into CC1a, added appropriate fT4 monitoring for those diagnosed with secondary hypothyroidism. New CC1.a.v. now reads “v) For individuals being treated for secondary hypothyroidism, monitoring with fT4 testing every 6 weeks upon dosage change and annually in stable individuals.”</p> <p>Former CC1.c.iii. is now CC1.c. Edited for clarity, added that TSH is the appropriate screening test. Now reads: “c) For asymptomatic individuals who have been prescribed drugs that can interfere with thyroid function and thus who are at an increased risk for thyroid disease, TSH testing at the following intervals:</p> <ul style="list-style-type: none"> <li>i) Annually.</li> <li>ii) When dosage or medication changes.</li> <li>iii) If symptoms consistent with thyroid dysfunction develop.”</li> </ul> <p>TSH is the appropriate marker for CC1.d.</p> <p>New CC1.e. to address all the reasons (former CCs 1.c.i., 1.c.ii., CC1.e., CC1.f., CC1.j, CC1.k) for one time TSH screening: “e) One-time TSH screening:</p> <ul style="list-style-type: none"> <li>i) For asymptomatic individuals at high risk for thyroid disease due to: <ul style="list-style-type: none"> <li>(a) Personal or family history of thyroid dysfunction.</li> <li>(b) Personal or family history of type 1 diabetes or other autoimmune disease.</li> </ul> </li> <li>ii) For individuals with disease or neoplasm of the thyroid or other endocrine glands.</li> <li>iii) For individuals with chronic or acute urticaria.</li> <li>iv) For pediatric individuals diagnosed with short stature.</li> <li>v) For pediatric individuals with a clinical finding of failure-to-thrive.”</li> </ul> <p>Formerly CC1.g., now CC1.f., added TSH with reflex fT4 and fT3 when initial result is abnormal, as appropriate marker testing</p> <p>New CC1.g., “g) For individuals with hypothalamic-pituitary disease, monitoring of TSH and fT4:</p> <ul style="list-style-type: none"> <li>i) Biannually for individuals less than 18 years of age.</li> <li>ii) Annually for individuals 18 years of age or older.”</li> </ul> <p>Former CC1.i., now CC1.h., edited for clarity and consistency.</p> <p>Added CPT code 83520</p> <p>Committee approved: 10/21/2024</p>
05/21/2025	<p>Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria:</p> <p>Removed “are undergoing evaluation for infertility” from CC1.d. Adjusted language of CC1.d. following that update, now reads: “d) TSH testing for individuals capable of becoming pregnant who have experienced two or more pregnancy losses.”</p>

	<p>Added CC1.e.: “e) TSH testing for individuals with a thyroid nodule.”</p> <p>Reformatted CC4 and added specific thyroid antibodies. Now reads: “4) For individuals with hypothyroidism or hyperthyroidism, testing once every three years for thyroid antibodies (i.e., Tg-Ab, TPOAb, TRAB, thyroid-stimulating immunoglobulins [TSI]) MEETS COVERAGE CRITERIA.”</p> <p>Committee approved: 05/21/2025</p>
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