Thyroid Cascade Testing

Differential Laboratory Diagnosis of Thyroid Dysfunction

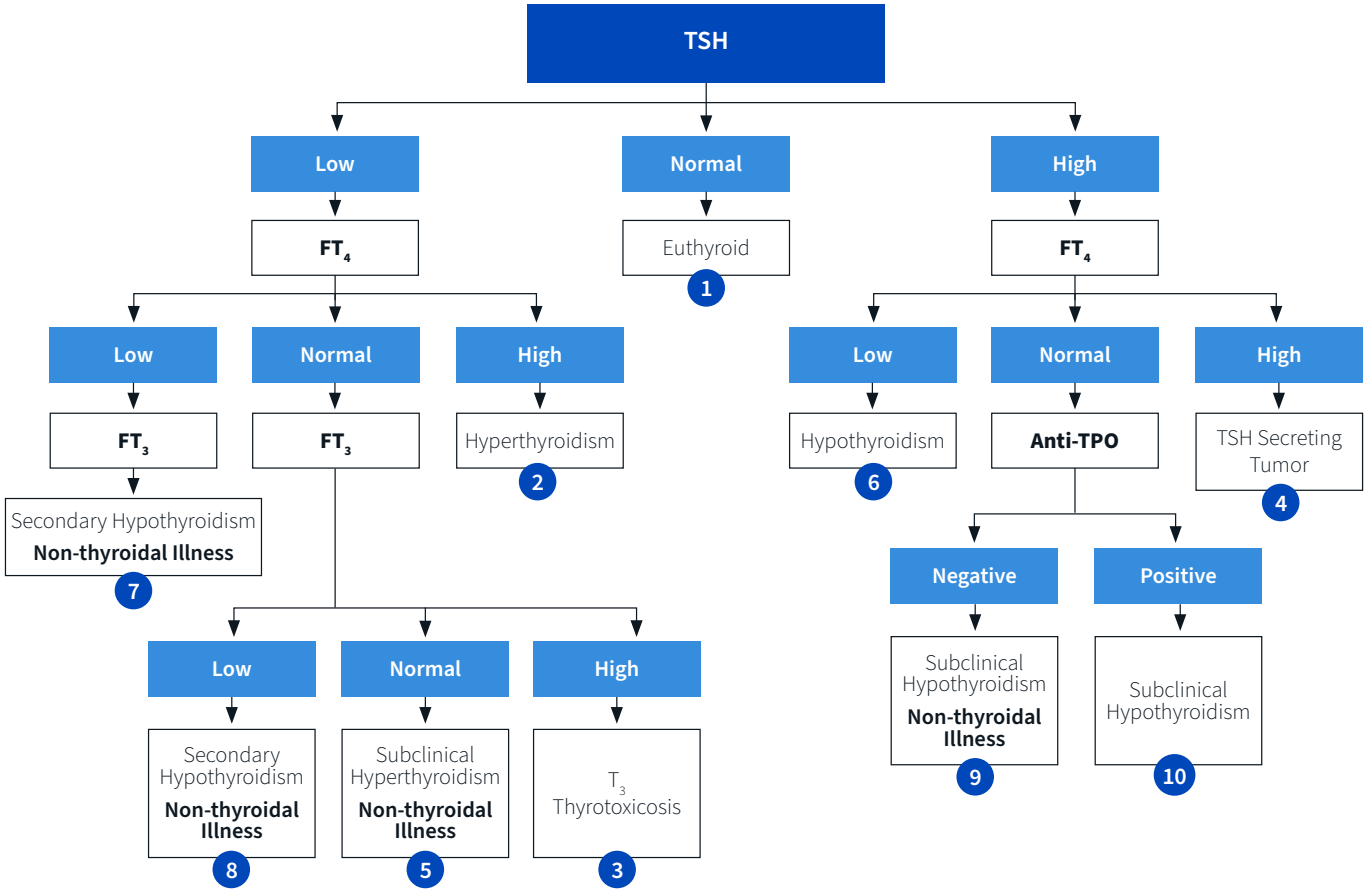
This panel employs a cascading algorithm of thyroid tests, proceeding from those that are more clinically sensitive and automatically reflexing to those that are more clinically specific, to aid the clinician in obtaining an appropriate laboratory diagnosis for common adult thyroid disorders.

The assayed test result relative to the reference interval in the scheme determines which, if any, additional tests are performed. The cascade proceeds, selecting specific tests until the most probable laboratory diagnosis can be made. The algorithm and the associated tests are shown in the illustration below. The numbers within the algorithm refer to the interpretive comments provided on the final report as referenced in this article.

Arriving at the correct diagnosis for thyroid disease is not trivial; it requires a combination of clinical deduction along with laboratory and/or imaging test results. With the advent of sensitive thyroid-stimulating hormone (TSH) measurements, accurate free hormone assays and specific antibody tests, the categorization of thyroid dysfunction can be unveiled.

In addition, the clinician is faced with many confounding factors to consider in determining whether abnormal thyroid test results are reflective of primary thyroid disease, secondary thyroid disease, drug interference or non-thyroidal illness syndrome (NTIS). The interpretive comments, in the highlight boxes provided with each reported thyroid cascade, have been written with these caveats in mind and are designed to alert the physician to other conditions that may influence the final test result. As with any laboratory result, clinical correlation is indicated.

The thyroid cascade panel was designed as a diagnostic tool to aid in the initial diagnosis of common adult thyroid disorders. This panel is not intended for use in pediatric patients or in monitoring patients receiving treatment for thyroid disease with either ablative or suppressive therapy. It would also not be appropriate to use this panel to diagnose primary thyroid neoplasm. Clinical practice guidelines from the American Thyroid Association promote the use of TSH as the first test in the screening process.[1] Labcorp's Thyroid Cascade Profile [330015] only uses the latest generation ultrasensitive TSH testing.



Euthyroid

The cascade begins with the TSH test. Additional testing is only performed if the initial TSH result is abnormally high or low. If the TSH result is normal, a euthyroid status is assumed and testing stops. Under these circumstances, the interpretive comment on the report would read:

1. There is no apparent thyroid disorder. Additional testing is not indicated; however Secondary Hypothyroidism has been reported in some patients with normal TSH values.

Hyperthyroidism

Hyperthyroidism denotes increased secretion of thyroid hormone from the thyroid gland, which leads to a clinical picture of thyrotoxicosis. The laboratory hallmarks of hyperthyroidism include suppression of TSH, frequently to levels less than 0.01 µIU/mL, and elevation of free thyroxine (FT_4), triiodothyronine (T_3) or both. The most common cause of hyperthyroidism is Graves' Disease, and results from the autologous production of thyrotropin receptor antibodies (TRAb) or thyroid stimulating immunoglobulins (TSI) directed against the TSH receptor that cause continual stimulation of the thyroid to produce thyroxine (T_4) and triiodothyronine (T_3)accounts for 80% of all cases of hyperthyroidism.[2,3] The presence of TRAb antibodies is highly suggestive of Graves' Disease and has a specificity of 99%.[1]

2. A low TSH with an elevated FT_4 would be consistent with Hyperthyroidism in the appropriate clinical setting. If Graves' Disease is suspected, consider thyrotropin receptor antibody (TRAb) testing.

   In patients with early Graves' disease and those with solitary or multinodular toxic goiters, the FT_4 may be within the normal reference interval, but the FT_3 may be elevated. This condition is known as T_3 thyrotoxicosis.[1]

3. A low TSH with a normal FT_4 and an elevated FT_3 would be suggestive of T_3 Thyrotoxicosis in the appropriate clinical setting. If Graves' Disease is suspected, consider thyrotropin receptor antibody (TRAb) testing.

   Instances do occur where the TSH may be within reference interval or slightly elevated along with an elevated FT_4. These test results may be indicative of several conditions such as thyroxin replacement therapy, various drugs, non-thyroidal illness including psychiatric disorders, pituitary adenomas and thyroid transport disorders.[2]

4. A normal or elevated TSH with an elevated FT_4 has been associated with TSH secreting pituitary adenomas, thyroid replacement therapy and resistance, familial dysalbuminemic hyperthyoxinemia, various drugs and non-thyroidal illness. Clinical correlation would be indicated.

Subclinical Hyperthyroidism

This condition, characterized by low TSH values with normal amounts of circulating thyroid hormone, is most commonly caused by nodular goiter, especially in the elderly.[4] A low TSH with a normal FT_4 and a normal FT_3 have been associated with subclinical hyperthyroidism. Similar values have also been associated with NTIS in severely ill patients.

5. A low TSH with a normal FT_4 and a normal FT_3 have been associated with Subclinical Hyperthyroidism. Similar values have also been associated with non-thyroidal Illness in severely ill patients.

   Very mild Graves' disease and overmedication with levothyroxine can also manifest laboratory findings consistent with subclinical hyperthyroidism, as well as with malabsorption of levothyroxine, with various drugs (amiodarone) and TSH resistance.[2]

Hypothyroidism

In the U.S., hypothyroidism is most caused by chronic autoimmune thyroiditis (Hashimoto's thyroiditis), resulting in thyroid failure, and is five to 10 times more common in women than in men. Hypothyroidism most commonly results from primary gland failure, which accounts for 90% to 95% of all cases. Many of these patients show evidence of an autoimmune origin of thyroid failure, with greater than 75% developing anti-thyroid peroxidase antibodies (anti-TPO) and/or antithyroglobulin (anti-Tg) antibodies. The TSH level is usually very high (greater than 10.0 µU/mL) with depression of FT_4. Patients who are suspected to have autoimmune thyroiditis, and who are seronegative for ant-TPO or anti-Tg antibodies may be also tested for the presence of TRAb antibodies, which may be present in early Graves' Disease.[5]

6. An elevation of TSH with a low FT_4 is suggestive of Primary Hypothyroidism in the appropriate clinical setting.

   Hypothyroidism may also occur secondary to pituitary failure (secondary hypothyroidism) or as a result of hypothalamic (tertiary) suppression of thyrotropin-releasing hormone (TRH). These causes of hypothyroidism can typically be distinguished from autoimmune disease by the presence of low TSH and a resultant low FT_4.[6]

7. A low TSH with a low FT_4 and a normal or low FT3 has been associated with secondary hypothyroidism from the disease locus within the pituitary or hypothalamus. Similar values have also been associated with non-thyroidal Illness in severely ill patients. Clinical correlation would be indicated.

OR

8. A low TSH with a normal FT_4 and a low FT_3 have been associated with secondary hypothyroidism from the disease locus within the pituitary or hypothalamus. Similar values have also been associated with non-thyroidal Illness in severely ill patients. Clinical correlation would be indicated.

   Hypothyroidism can also occur from iatrogenic destruction of the thyroid gland (surgical ablation, radiation, I-131 therapy), infiltrative processes (amyloid, lymphocytes, and scleroderma), from end-stage Graves' disease or from congenital hypothyroidism caused by improper fetal development of the thyroid.[5]

Subclinical Hypothyroidism

The term "subclinical hypothyroidism" describes a population of patients who have normal circulating levels of thyroxine but with elevated TSH values.[5] The prevalence of subclinical hypothyroidism in the United States varies from 4%-8.5% and increases with age to around 20% in women above age 60.[8]

9 An elevation of TSH and normal FT_4 in the absence of anti-thyroid antibodies suggests subclinical hypothyroidism. Similar values have also been associated with non-thyroidal Illness in severely ill patients.

Eighty-five percent of subclinical hypothyroid patients positive for anti-TPO antibodies, which is predictive of an increased risk for developing overt hypothyroidism and converts at a rate of approximately 4.6% per year.[5]

10 An elevation of TSH with a normal FT_4 in the presence of antithyroid peroxidase antibody (anti-TPO) or without a positive anti-TPO is suggestive of subclinical hypothyroidism.

Thyroid Dysfunction Associated with Pregnancy

Thyroid dysfunction affects about 15% of all pregnancies, and although hyperthyroidism can occur, hypothyroidism is more common with both conditions contributing to an increased risk of adverse outcomes. Normal pregnancy is associated with increased renal excretion of iodine, which increases T_4 and thyroid binding globulin (TBG) production, as well as having a stimulatory effect by human chorionic gonadotropin (hCG) on the thyroid gland. Aberrant production of TSH and T4 remain so until delivery.[9,10] For these reasons the reference intervals are altered throughout the gestational period and are trimester dependent. The following reference intervals have been adopted by Labcorp following the American Thyroid Association guidance and may be ordered separately Thyroid-stimulating Hormone (TSH) in Pregnancy [004593].

TSH Reference Intervals in Pregnancy (µIU/mL)

First Trimester	0.100–4.000
Second Trimester	0.200–4.000
Third Trimester	0.300–4.000
Non-Pregnant Adult	0.450–4.500

Postpartum thyroid dysfunction occurs in approximately 5% of women within the first year after childbirth who were euthyroid prior to pregnancy and presents as an inflammatory autoimmune condition. Typically, it begins with a transient thyrotoxicosis, which may develop into a mild form of Graves' disease, followed by transient hypothyroidism, usually with the presence of anti-TPO antibodies. In most cases, the thyroid dysfunction resolves spontaneously by the end of the first year following delivery returning to a euthyroid state.[10]

Nonthyroidal Illness Syndrome (NTIS)

NTIS is recognized as a cause of aberrant thyroid indices in a euthyroid state during severe illness This syndrome is most frequently observed in the hospitalized patient with up to 13% having abnormal thyroid hormone values. NTIS usually presents with markedly low T_4 and T_3 hormones in the absence of an elevated TSH pointing to the hypothalamus-pituitary-thyroid axis dysfunction.[11] Recent reports indicate the NTIS is highly prevalent in critically ill patients and may be associated with mortality in the ICU.[12]

Similar phenomena in thyroid dysfunction, especially hypothyroidism has been reported in patients with acute psychiatric illness such as schizophrenia, major affective disorder, paranoid disorder and atypical psychosis.[13,14]

Drugs Affecting Thyroid Function

There are many drugs that can complicate the biochemical picture in attempting to assess thyroid status. These drugs can confound the clinician attempting to discern the thyroid status of patients undergoing initial differential diagnosis for thyroid disease and of patients being treated for existing thyroid disease. Drugs have been reported to affect hypothalamic-pituitary-thyroid axis, thyroid hormone synthesis or release, enhance thyroid autoimmunity, thyroid damage, thyroid binding proteins, thyroid hormone activation or metabolism, absorption of thyroid hormone preparations and drugs that affect thyroid hormone testing. The list of causal drugs and their effects is extensive.[15,16]

Summary

The clinician must be vigilant for confounding factors that can make the assessment of thyroid status ambiguous. While the thyroid hormone assays offered by Labcorp can provide analytically reliable results, there are numerous conditions that can alter the homeostatic mechanisms of hormone secretion. The comments, which are provided as part of the cascade panel results, are designed to suggest when such influences may be present with the *proviso* that they correlate with the clinical presentation.

Relevant Assays*

Test Name	Test No.
Thyroid Cascade Profile	**330015**
Thyroid-stimulating Immunoglobulin (TSI)	**140749**
Thyroid Peroxidase (TPO) Antibodies	**006676**
Thyroid-stimulating Hormone in Pregnancy	**004593**
Thyrotropin Receptor Antibody, Serum	**010314**

*For the most current information regarding test options, including specimen requirements and CPT codes, please consult the online Test Menu at **Labcorp.com**.

References

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Visit the online test menu at **Labcorp.com** for additional test options and full test information, including CPT codes and specimen collection instructions.

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