Thyroid Cascade Testing
## Differential Laboratory Diagnosis of Thyroid Dysfunction

A new test grouping is offered to aid the clinician in obtaining an appropriate diagnosis for common adult thyroid disorders. This panel is based on a cascade algorithm that selects specific assays, based on the results of previously performed tests, which are necessary to arrive at the most appropriate laboratory diagnosis.

The assayed value relative to the reference interval of any test result in the scheme determines which, if any, additional tests are performed. The cascade proceeds, selecting specific tests until the most probable 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 astute clinical skills on the part of the physician with reliable test results supplied by the laboratory. While diagnosis of overt hyperthyroidism or hypothyroidism in patients who present with classical symptoms and diagnostic laboratory results is less of a challenge, those patients not presenting with textbook symptoms are more difficult to diagnose. With the advent of sensitive TSH measurements, accurate free hormone assays, and specific antibody tests, the categorization of thyroid dysfunction has expanded.

In addition, the clinician is faced with many confounding factors to consider in determining whether abnormal thyroid test results are reflective of thyroid disease, drug interference, or nonthyroidal illness. The interpretive comments provided with each thyroid cascade reported 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. The interpretive comments, in the highlighted boxes, have been included under the appropriate heading in this publication. 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. Other biochemical markers, in conjunction with physical, radiological and histological findings, may be better suited for this purpose. Similar thyroid cascades have been successfully implemented in various medical centers[1,2,3] and have been validated for use into late adult life.[4] Recent clinical practice guidelines from the American Thyroid Association now promote the use of TSH as the first test in the screening process.[5] The LabCorp Thyroid Cascade only uses third-generation TSH testing.
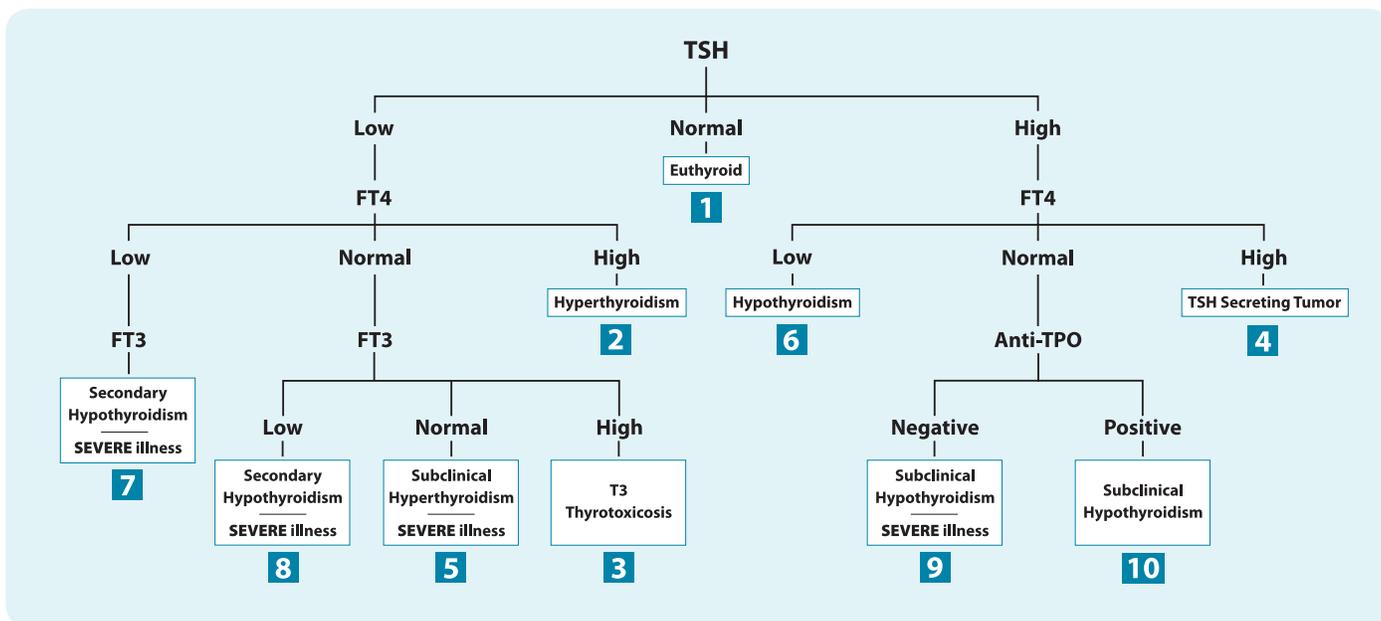
The cascade begins with a third-generation thyroid-stimulating hormone (TSH) test. If the TSH result is normal, a euthyroid status is assumed and testing stops. Under these circumstances, the interpretive comment on the report would read:

> **1** There is no apparent thyroid disorder. Additional testing is not indicated. In rare instances, **Secondary Hypothyroidism** has been reported in some patients with normal TSH values.

Additional testing is only performed if the initial TSH result is abnormally high or low.

Hyperthyroidism

Hyperthyroidism denotes increased secretion of thyroid hormone from the thyroid gland, which leads to a clinical picture of thyrotoxicosis. The most common cause of hyperthyroidism is Graves' disease, which accounts for 60% to 90% of cases. Graves' disease results from the autologous production of antibodies directed against the TSH receptor. These autoantibodies, referred to as thyroid-stimulating immunoglobulin (TSI), cause continual stimulation of the thyroid to produce thyroxine (T_4) and triiodothyronine (T_3).[6] The laboratory hallmarks of hyperthyroidism include suppression of TSH, frequently to levels <0.01 mIU/L, and elevation of free thyroxine (FT_4).

> **2** A low TSH with an elevated FT_4 would be consistent with **Hyperthyroidism** in the appropriate clinical setting.

Greater than 85% of patients will also be positive for antithyroid peroxidase antibodies (anti-TPO).[7] Other causes of hyperthyroidism include transient leak from destructive thyroiditis (Hashimoto's thyroiditis) and excessive iodide intake. Thyrotoxicosis can also result from chronic oral thyroxine overmedication.[8] 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.[8]

> **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.

In rare instance, pituitary adenomas may cause thyrotoxicosis. This would represent an exception to the rule of suppressed TSH values reflecting hyperthyroid states. There are also non-tumorous conditions resulting in inappropriate TSH secretion.[8]

> **4** An elevation of TSH with an elevated FT_4 has been associated with **Inappropriate TSH Syndrome** of tumorous or non-tumorous origin. Clinical correlation would be indicated.

Subclinical Hyperthyroidism

The prevalence of endogenous subclinical hyperthyroidism varies between 0.7% to 6%, depending on the region and age of the population.[6] 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.

> **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 **Nonthyroidal Illness** in severly ill patients.

Very mild Graves' disease and overmedication with levothyroxine can also manifest laboratory findings consistent with subclinical hyperthyroidism.[16] Elderly patients with subclinical hyperthyroidism have been reported to be at increased risk for developing atrial fibrillation.[17]

Hypothyroidism

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 >95% developing anti-TPO[9] and/or antithyroglobulin (anti-TG) antibodies. It is typically found in both atrophic and goitrous forms of Hashimoto's thyroiditis. The TSH level is usually very high (>15.0 mU/L) with depression of FT_4 (<1.0 ng/dL).

> **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.

> **7** A low TSH with a low FT_4 and a normal or low FT_3 has been associated with **Secondary Hypothyroidism** from the disease locus within the pituitary or hypothalamus. Similar values have also been associated with **Nonthyroidal Illness** in severly 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 **Nonthyroidal Illness** in severly ill patients. Clinical correlation would be indicated.

Hypothyroidism can also occur from iatrogenic destruction of the thyroid gland (surgical ablation, radiation, ^{131}I therapy), infiltrative processes (amyloid, lymphocytes, and scleroderma), or from end-stage Graves' disease.[10] In rare cases, genetic mutations of thyroid hormone receptors at the tissue level can produce symptoms of hypothyroidism due to resistance to thyroid hormone.

Congenital hypothyroidism, caused by improper fetal development of the thyroid, may be diagnosed through use of the filter paper spot procedure for neonates to measure thyroxine levels.[9]

Subclinical Hypothyroidism

The term "subclinical hypothyroidism" describes a population of patients who have normal circulating levels of thyroxine but with elevated TSH values.[11]

9	An elevation of TSH and normal FT_4 in the absence of antithyroid peroxidase antibody suggests **Subclinical Hypothyroidism**. Similar values have also been associated with **Nonthyroidal Illness** in severely ill patients.

Frequently, patients with this condition will be positive for anti-TPO.[12] Various symptoms of classical hypothyroidism may be present or completely absent and are not reliable predictors of subclinical hypothyroidism.[13] Studies have indicated that the prevalence of subclinical hypothyroidism varies between 7% and 15% of the population older than age 60[12,13]; but it may be found in younger individuals as well. Manifestations may include dry skin, cold intolerance, easy fatigability, and changes in lipid levels. These symptoms have been shown to improve with thyroid hormone replacement therapy.[12] Those patients diagnosed with subclinical hypothyroidism are at increased risk for developing overt hypothyroidism. This is especially true of patients who are positive for anti-TPO.

10	An elevation of TSH with a normal FT_4 in the presence of antithyroid peroxidase antibody is suggestive of **Subclinical Hypothyroidism**.

Conversion rates for those who have elevated TSH values and detectable antibody vary from 5% to 20% per year.[14,15]

Thyroid Dysfunction Associated with Pregnancy

Human chorionic gonadotropin (hCG) is a weak thyroid stimulator and peaks during the first trimester of pregnancy. This can sometimes result in a slight elevation of FT_4. A slight depression of TSH may also be observed.[18] These levels generally return to normal during the second trimester of a healthy pregnancy.[6] The thyroid stimulatory effect is exaggerated in patients with molar pregnancy, choriocarcinoma, or hyperemesis gravidarum.

Postpartum thyroid dysfunction occurs in 3% to 11% of women in the first year after childbirth.[19] This condition is defined by abnormal TSH and/or FT_4 results without prior history of thyroid disease or drugs known to influence circulating thyroid hormone levels. Postpartum women who are hyperthyroid are likely to become euthyroid without treatment. Those who are hypothyroid follow a more uncertain course with a higher risk of developing chronic thyroiditis.[20] Several investigators have suggested measurement of antithyroid antibodies (anti-TPO and anti-TG) during the first trimester to identify those at increased risk of postpartum thyroiditis.[18]

Nonthyroidal Illness

The "sick euthyroid syndrome" is recognized as a cause of aberrant thyroid indices in a euthyroid state. This syndrome is most frequently observed in the hospitalized patient with nonthyroidal illness (NTI).[16] The absolute level of a third-generation TSH result does not consistently distinguish NTI from true thyroid dysfunction. As high as 13% of patients hospitalized with acute illness may have abnormal thyroid hormone values. In most patients, the abnormalities are transient and return to normal after recovery from the acute illness. Lowering of thyroid hormone, specifically T_3, is an acute response to illness and a valuable calorie-sparing physiologic response, especially in patients with altered nutritional status.[21] It also serves to reduce the destructive protein breakdown that can occur in severe illness.[16] It has been shown that critical illness can involve inhibition of the pituitary-thyroid axis,[22] thus accounting for lowered TSH values in many patients with NTI. Conversely, some patients with NTI will exhibit elevated TSH values.[23] In both circumstances, these patients will demonstrate normal FT_4 results; thus disparate TSH and FT_4 values may suggest a euthyroid state.[24]

The same phenomenon has been reported in patients with acute psychiatric illness such as schizophrenia, major affective disorder, paranoid disorder, and atypical psychosis.[25] TSH is typically elevated along with normal to elevated FT_4 values. Interestingly, thyroid gland treatment targeted to return TSH and FT_4 levels to normal, have been shown to reverse psychiatric symptoms.[26]

Drugs Affecting Thyroid Function

There are a number of 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 shown to affect (1) the secretion of TSH, (2) bioavailability of oral levothyroxine, (3) thyroid hormone-binding proteins, and (4) the metabolism of T_3 and T_4. Dopamine and glucocorticoids diminish TSH secretion. While lithium and iodide preparations usually lower FT_4, amiodarone may either elevate or depress FT_4. Bile acid sequestrants have been reported to diminish the absorption of oral levothyroxine.[27] A number of drugs such as estrogens and androgens are known to affect thyroid hormone-binding proteins but do not alter FT_4 or FT_3. Use of the FT_4 test in this cascade avoids diagnostic problems associated with the fluctuations seen by measuring total T_3 and T_4 under these circumstances.[7]

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 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. Despite these efforts, the biochemical status of the thyroid gland may be misleading. Clinical correlation is extremely important to avoid possible misinterpretation of test results.

Relevant Assays*

Test Name	Test Nº
Thyroid Cascade Profile	**330015**
Thyroid-stimulating Immunoglobulin (TSI)	**140749**

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

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