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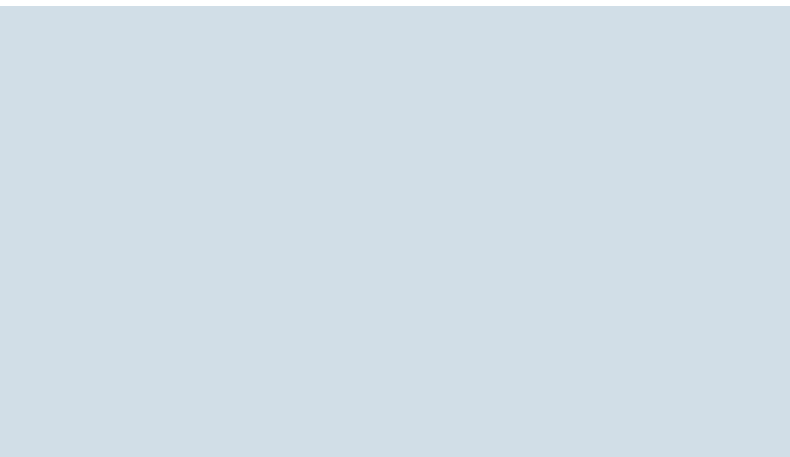
# Laboratory testing: An essential component of thyroid disease diagnosis and management

White Paper

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Answers for life.





### Summary

Thyroid function is essential for optimal health, and disease must be treated. The synthesis of thyroid hormones, which regulate metabolism and gene expression, is complex and tightly regulated. Thyroid disease can be broadly divided into three main categories: hypothyroidism (insufficient thyroid hormones), hyperthyroidism (excess thyroid hormones), and cancer (inappropriate cell growth). Laboratory tests play a crucial role in the diagnosis and effective management of thyroid disease because the signs and symptoms are nonspecific. This paper reviews thyroid hormones, thyroid disease, the utility of laboratory testing in thyroid disease, and three illustrative case studies.

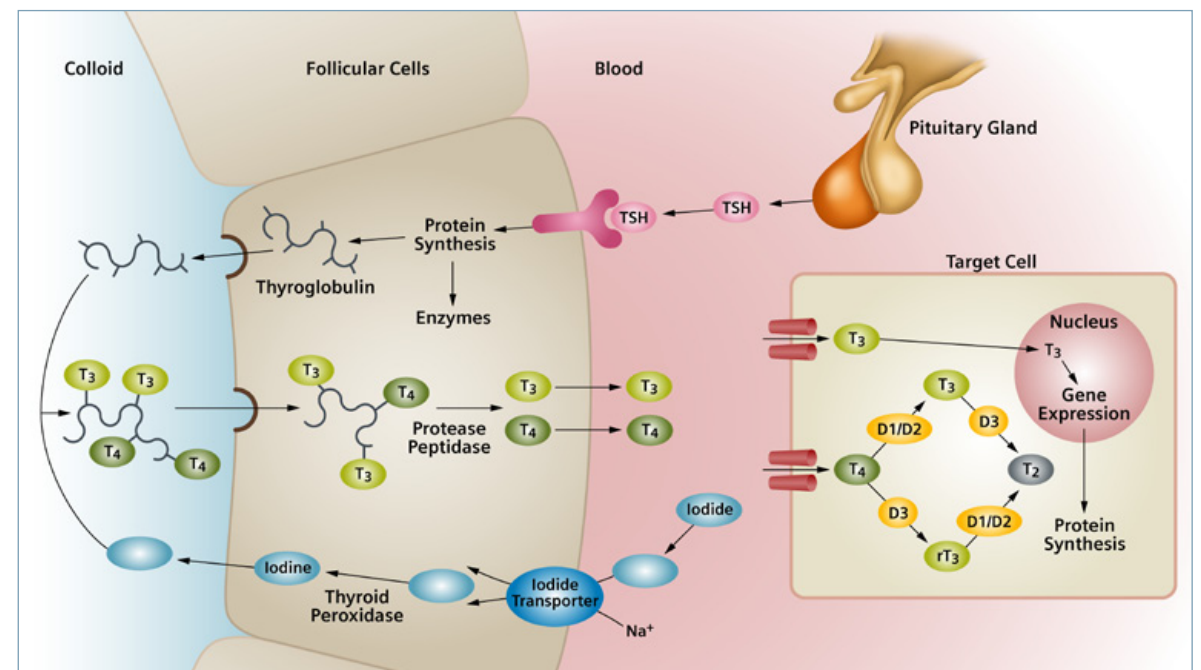


Figure 1. Thyroid hormone synthesis is complex. Deiodinases (D1, D2, and D3) convert  $T_4$  to  $T_3$ ,  $T_3$  to  $T_2$ , and  $T_2$  to  $rT_3$  in target cells outside the thyroid.

### Thyroid hormones are essential to health

The thyroid hormones, thyroxine/tetraiodothyronine ( $T_4$ ) and triiodothyronine ( $T_3$ ), act on virtually every tissue in the body. These hormones bind to nuclear receptors, resulting in alterations in gene expression and protein production. They also regulate metabolism of protein, fats, and carbohydrates, and are essential for normal development of the fetus and newborn.<sup>1</sup> Therefore, disease must be diagnosed and treated.

### Thyroid hormone synthesis is complex

The synthesis of the thyroid hormones requires iodine, which is ingested as iodide. Iodide is concentrated within thyroid follicular cells, where it is converted to organic iodine by thyroid peroxidase (TPO) (Figure 1). Thyroid follicular cells surround a space filled with colloidal material that consists of thyroglobulin.<sup>1</sup> Thyroglobulin (Tg) is a glycoprotein that contains tyrosine residues.

The tyrosine residues that are in contact with the membrane of the follicular cells are iodinated at one or two sites to become monoiodotyrosine and diiodotyrosine, respectively. These iodinated tyrosines are then combined to form the thyroid hormones: either  $T_3$  (monoiodotyrosine + diiodotyrosine) or  $T_4$  (diiodotyrosine + diiodotyrosine).<sup>1</sup> The hormones remain incorporated within Tg until they are cleaved from it within the follicular cell (Figure 1). The free hormones are released into the circulation where they bind to serum proteins: primarily thyroxine-binding globulin (with high affinity and low capacity) that carries about 75 percent of the hormones (Figure 1).<sup>1</sup> The other binding proteins are transthyretin (with low affinity and high capacity for  $T_4$ ) and albumin (with low affinity and high capacity for  $T_4$  and  $T_3$ ). Only 0.3 percent of  $T_3$  is free, and about 0.03 percent of  $T_4$  is free. It is the free hormones that are biologically active: free  $T_3$  is the most active, whereas free  $T_4$  has minimal activity but acts as a reservoir for free  $T_3$ . Most of the conversion of free  $T_4$  to free  $T_3$  (75 percent) occurs outside the thyroid.<sup>1</sup>

Thyroid hormones are tightly regulated

Thyroid-stimulating hormone (TSH), also known as thyrotropin, is secreted by the thyrotropic cells of the pituitary gland. It is controlled by negative feedback: levels of the thyroid hormones (T<sub>3</sub> and T<sub>4</sub>) regulate TSH levels (Figure 2).<sup>1</sup> Increased thyroid hormone levels decrease the synthesis and secretion of TSH, while decreased thyroid hormone levels increase synthesis and secretion of TSH (Figure 2). Thyrotropin-releasing hormone (TRH) increases TSH production. It is believed that the thyroid hormones are also able to modulate TRH release through negative feedback.<sup>1</sup>

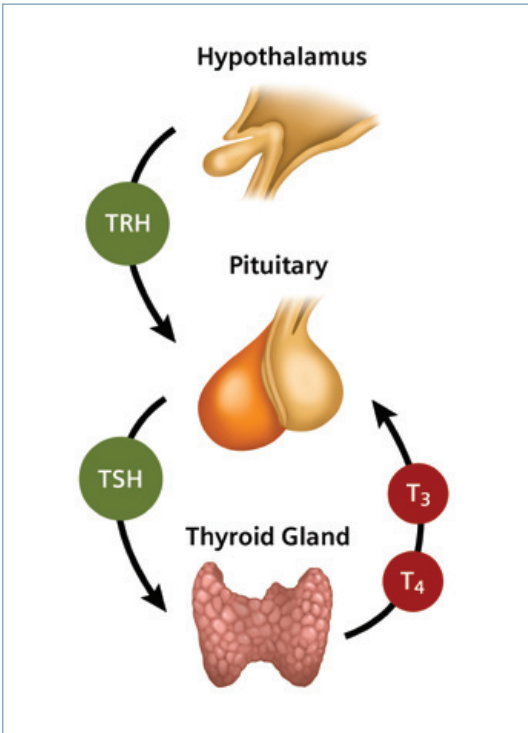


Figure 2. Thyroid hormone regulation by negative feedback.

Thyroid disease can be serious

Hyperthyroidism and hypothyroidism are classified into overt disease and subclinical disease. Overt disease prevalence varies with geography and population: for overt hypothyroidism, the prevalence is 0.3 percent in the U.S., 0.4 percent in the Netherlands, and 6.9 percent among elderly Catalans in Spain;<sup>2-4</sup> for overt hyperthyroidism, the prevalence ranges from 0.2 to 3.6 percent.<sup>2-4</sup> Subclinical disease is characterized by abnormal levels of TSH and normal levels of free T<sub>3</sub> and free T<sub>4</sub>.

Thyroid cancer, however, is rare, and in most cases very treatable. It is common for thyroid cancers to be euthyroid, that is, neither hypothyroid nor hyperthyroid.<sup>1,2,5-8</sup> Thyroid disease requires therapy to maintain thyroid hormones at normal levels.<sup>1,9</sup> Abnormal thyroid function is associated with cardiovascular disease, depression, and in severe cases, death.<sup>1</sup>

Thyroid tests are crucial

The signs and symptoms associated with thyroid disease, both hypo- and hyperthyroidism, are nonspecific; thus, laboratory tests play crucial roles in the diagnosis and management of disease, including monitoring response to therapy (Table 1).<sup>1,9-12</sup> In papillary and follicular thyroid cancers, thyroglobulin is crucial for evaluating treatment response, and in medullary thyroid cancer, calcitonin plays a critical role in diagnosis and monitoring treatment response (Table 1).<sup>5-9,13</sup>

Table 1. Thyroid test description and utility.<sup>5-9,11,13,14-16</sup>

Test	Description and Utility
TSH	Measures thyroid-stimulating hormone, also known as thyrotropin (TSH); it is the primary screening test for thyroid dysfunction (hyperthyroidism and hypothyroidism).
Third-generation TSH	A highly sensitive TSH assay, which is especially helpful in diagnosing and monitoring hyperthyroidism. A third-generation TSH test is defined as having functional sensitivity (20% CV) at a level less than 0.02 µIU/mL.
Free T <sub>4</sub>	Measures free T <sub>4</sub> ; used to evaluate thyroid function; elevations associated with hyperthyroidism, low levels associated with hypothyroidism. Free T <sub>4</sub> is the portion of T <sub>4</sub> not bound to protein and is metabolically active.
Total T <sub>4</sub>	Measures all of T <sub>4</sub> hormone, protein bound and free.
Free T <sub>3</sub>	Measures free T <sub>3</sub> ; used to evaluate thyroid function; elevations associated with hyperthyroidism, low levels associated with hypothyroidism. It is the unbound portion of T <sub>3</sub> and is metabolically active.
Total T <sub>3</sub>	Measures all of T <sub>3</sub> hormone, protein bound and free.
T uptake	Estimates the amount of protein-binding sites for thyroid hormones.
TPOAb/aTPO	Measures antibodies to thyroid peroxidase (TPOAb/aTPO). TPO converts iodide to organic iodine, an important step in thyroid hormone synthesis. It is useful in differentiating Hashimoto's thyroiditis from other hypothyroid conditions.
Thyroglobulin/Tg	Measures thyroglobulin; used in differentiated thyroid cancer to monitor treatment response.
TgAb/aTg (antithyroglobulin antibody)	Measures antibodies to thyroglobulin (TgAb/aTg); useful for evaluating for possible interference in thyroglobulin assays; also useful in both hyper- and hypothyroidism and differentiated thyroid cancer.
TRAb	Measures TSH receptor antibodies, both inhibitory and stimulating immunoglobulins. Used to confirm Graves' disease.
TSI/TSIAb	Measures thyroid-stimulating antibodies (TSI/TSIAb), a subset of thyroid receptor antibodies that are specific to Graves' disease; therefore, a choice assay to confirm Graves' disease.
Thyroxine-binding globulin/TBG	Measures TBG, the major thyroid hormone-binding protein.
Calcitonin	Measures calcitonin, which is produced by the C cells of the thyroid and by medullary thyroid cancer cells; useful as an aid in the diagnosis and management of medullary thyroid cancer.

Diagnosis of Hypothyroidism

Hypothyroidism is the most common thyroid dysfunction in the U.S. and many other countries. It accounts for 80 percent of all thyroid diseases, and affects primarily females. Hypothyroidism, characterized by insufficient amounts of thyroid hormones, can occur due to problems in the thyroid itself (primary disease), pituitary (secondary disease), or hypothalamus (tertiary disease). The recommended screening test for hypothyroidism is a sensitive TSH test; it can be accompanied by or followed by a free T<sub>4</sub> test, and possibly a free T<sub>3</sub> test.<sup>1,3,9-12</sup> The typical profile for primary hypothyroidism is high TSH and low free T<sub>4</sub> levels; free T<sub>3</sub> levels may be normal or low. One of the most common types of primary hypothyroidism is Hashimoto’s disease. It is an autoimmune disease in which the thyroid gland is gradually destroyed by cellular and autoimmune-mediated immune processes. Hashimoto’s is characterized by the presence of anti-TPO antibodies and chronic inflammation of the thyroid gland.<sup>1,3,9-12</sup> Secondary hypothyroidism is typically characterized by low free T<sub>4</sub> levels and low or normal levels of TSH.<sup>1,9,11</sup>

Case study

A 27-year-old female presents with symptoms and signs of fatigue, weight gain, and weakness. She is trying to become pregnant, but her most recent pregnancy test was negative.

Is this patient at risk for thyroid dysfunction? Yes, her symptoms are consistent with hypothyroidism, and she is likely at risk for this disease. Should thyroid testing be performed? Yes, thyroid testing should be considered because she is trying to become pregnant and her symptoms are consistent with hypothyroidism. Hypothyroidism in pregnant women is associated with adverse outcomes that include lasting neurocognitive deficits in their progeny.<sup>10,11,15</sup> The clinician suspects that the patient may have hypothyroidism, probably Hashimoto’s disease. What is the first test that should be run? The guidelines recommend that the first test for the investigation of hypothyroidism is a TSH test.<sup>1,3,9-12</sup> What other tests should be considered? Free T<sub>4</sub>, a free T<sub>3</sub>, an anti-TPO, and anti-thyroglobulin (TgAb) are all reflex tests that would follow an abnormal TSH result. A positive anti-TPO result is consistent with a diagnosis of Hashimoto’s thyroiditis. Patients with this type of hypothyroidism may also have antithyroglobulin antibodies (TgAb) present.<sup>1,3,9-12</sup>

Table 2. Case study test results.

Test	Result
TSH	High
Free T <sub>4</sub>	Low
Anti-TPO	Present
Free T <sub>3</sub>	Normal

Given the test results (Table 2), what is the patient’s likely diagnosis? The likely diagnosis is hypothyroidism due to Hashimoto’s disease. This patient has high TSH and low free T<sub>4</sub> levels, and antibodies to TPO.<sup>1,3,9-12</sup> She will require thyroid hormone supplementation and, if she becomes pregnant, her thyroid function will need to be assessed again and treatment modified as needed to keep her euthyroid and to reduce the risk of adverse pregnancy outcomes.<sup>1,3,9-12</sup> The patient is supplemented with thyroxine and returns after six weeks for follow-up. What tests are most appropriate at this time? The most appropriate tests are a TSH and a free T<sub>4</sub>.<sup>1,3,9-12</sup>

Diagnosis of Hyperthyroidism

Hyperthyroidism is characterized by excess thyroid hormones. Hyperthyroidism can occur due to problems in the thyroid itself (primary disease), pituitary (secondary disease), or hypothalamus (tertiary disease). Among the several types of hyperthyroidism, the most common are Graves’ disease (diffuse toxic goiter), toxic multinodular goiter, and iatrogenic disease (excess supplementation during replacement therapy). The typical profile for primary hyperthyroidism is low TSH and a high free T<sub>4</sub> level. In some cases of hyperthyroidism, the profile is low TSH, normal free T<sub>4</sub>, and high free T<sub>3</sub> levels. A sensitive TSH test is the recommended screening test in patients at risk for hyperthyroidism.<sup>1,3,9-12</sup> The TSH test should be done in conjunction with a free T<sub>4</sub> test and, in select cases, followed by a free T<sub>3</sub> test. In secondary disease, TSH levels may be high or normal with elevated free T<sub>4</sub> levels and/or free T<sub>3</sub> levels.<sup>1,9,11</sup> In addition, the presence of TSI antibodies is indicative of Graves’ disease.<sup>1,3,9-12</sup> The specific presence of thyroid-stimulating antibodies is the key differentiating factor between Graves’ disease and other hyperthyroid conditions. TPO antibodies may also be present in Graves’ disease. If there are thyroid nodules present, then additional studies such as thyroid scans and/or ultrasound may be needed.<sup>1,3,9-12</sup> Patients who have been treated for hyperthyroidism are also at risk for hypothyroidism.<sup>1,3,9-12</sup>

Case study

A 45-year-old female has been experiencing nervousness, irritability, palpitations, and difficulty sleeping for the past three months. She thinks she might be entering menopause because her mother entered menopause around this age. On examination, her thyroid gland is diffusely enlarged, but no distinct nodules are found.

Is this individual at risk for thyroid dysfunction? Yes, her symptoms are consistent with hyperthyroidism, although not specific for hyperthyroidism.<sup>1,3,9-12</sup> Should thyroid testing be performed? Yes, testing should be performed. The clinician suspects that the patient may have hyperthyroidism and possibly Graves’ disease. A sensitive TSH test is the recommended screening test.<sup>1,3,9-12</sup> What other test should be considered? They include free T<sub>4</sub>, free T<sub>3</sub>, TSI, and anti-TPO tests. TSI is strongly associated with Graves’ disease; anti-TPO antibodies are also commonly found in these patients.<sup>1,3,9-12</sup>

Table 3. Case study test results.

Test	Result
TSH	Low
Free T <sub>4</sub>	High
Free T <sub>3</sub>	Normal
TSI	Present

Given these test results (Table 3), what is the likely diagnosis? This patient has low TSH and elevated free T<sub>4</sub> levels. In addition, TSI antibodies were present, and thus the likely diagnosis is Graves’ disease.<sup>1,3, 9-12</sup> After treatment she will require follow-up to ensure that she remains euthyroid. What tests are useful in monitoring her disease? She should be monitored with a sensitive TSH test and a free T<sub>4</sub> test.<sup>1,3, 9-12</sup>



Diagnosis of Thyroid Cancer

There are four types of thyroid cancer: papillary, follicular, medullary, and anaplastic. Except for anaplastic cancer, most thyroid cancers are highly treatable, not highly malignant, and rarely fatal.<sup>1,3, 6-9,12,13</sup> Definitive diagnosis of thyroid cancer is based on biopsy results. Radiological studies and thyroid tests are also important in thyroid cancer care. Treatment for papillary, follicular, and medullary cancer is surgical, which is followed in most cases by radioactive iodine ablation. Patients will typically require lifelong supplementation with thyroxine after treatment. Laboratory tests that are useful in thyroid cancer include thyroglobulin, calcitonin, TSH, and free T<sub>4</sub>.<sup>1,3,6-9,12,13</sup>

Thyroid cancers are rare. Papillary cancer accounts for 70 to 80 percent of thyroid cancers. Follicular cancer accounts for 10 percent of thyroid cancers and is more common among the elderly and in regions of thyroid deficiency. Differentiated thyroid cancers, papillary and follicular cancer, maintain thyroglobulin secretion; thyroglobulin is therefore used to monitor treatment response. In a successfully treated patient who has had a complete thyroidectomy and iodine ablation, thyroglobulin should be undetectable. Detectable levels are indicative of recurrence or incomplete treatment. Medullary carcinoma is composed of the parafollicular/C cells of the thyroid and account for 3 percent of thyroid cancers.<sup>1,3,6,7,9,13</sup> Medullary thyroid cancer cells, like normal C cells of the thyroid, secrete calcitonin. Calcitonin levels are used to aid in the diagnosis and prognosis of medullary cancer (the higher the baseline level, the worse the prognosis) and to monitor treatment response. Anaplastic carcinoma accounts for about 2 percent of thyroid cancers; it is an undifferentiated cancer that is characterized by a rapid, painful enlargement of the thyroid. It is fatal, and no effective therapy exists; about 80 percent of patients die within one year of diagnosis.<sup>1,3,6,7,9,13</sup>

Case study

A 47-year-old man found a painless lump below his Adam’s apple while shaving. For the past few weeks, he has been feeling increasingly fatigued and depressed. He has no other signs or symptoms or medical problems. On physical examination, he has a single distinct nodule originating in the left lobe of his thyroid gland. The clinician suspects that the patient could have hypothyroidism based on his symptoms, and is also concerned about possible thyroid cancer in the single nodule. What are the tests that should be ordered? The tests that should be ordered include TSH, free T<sub>4</sub>, free T<sub>3</sub>, anti-TPO tests, and a biopsy of the nodule.

Table 4. Case study test results.

Test	Result
TSH	Normal
Free T <sub>4</sub>	Normal
Free T <sub>3</sub>	Normal
Ant-TPO	Present

Given the test results, what is this patient’s likely diagnosis? The patient has normal thyroid function, so he is euthyroid: his TSH, free T<sub>4</sub>, and free T<sub>3</sub> levels are all within normal limits. He has TPO antibodies present and is at risk for future hypothyroidism.<sup>1,3,7-9</sup> The biopsy diagnosis is follicular thyroid cancer. He is treated with a total thyroidectomy, iodine ablation, and is supplemented with thyroxine.

Two months after his treatment, he returns for a follow-up visit. What thyroid tests are helpful at this visit? This visit should evaluate whether he is being supplemented adequately by using TSH and free T<sub>4</sub> tests, and whether there is any residual thyroid tissue present by using thyroglobulin and antithyroglobulin tests. Antithyroglobulin antibodies compete with the capture antibodies in thyroglobulin assays and can result in underestimation of thyroglobulin levels.<sup>1,3,7-9</sup> Therefore, running an antithyroglobulin (TgAb/aTg) test along with thyroglobulin (Tg) is critical to ensure thyroglobulin results are accurate.

Table 5. Case study follow-up visit test results.

Test	Result
TSH	Normal
Free T <sub>4</sub>	Normal
Thyroglobulin	Undetectable
Anti-thyroglobulin	Undetectable

Given these test results (Table 5), what is the likely diagnosis? The patient appears to be euthyroid with no biochemical evidence of tumor.



Conclusion

Thyroid hormones control metabolism and gene expression, and thus proper blood levels are critical for optimal health. Thyroid tests are essential for the diagnosis and monitoring of hyperthyroidism and hypothyroidism, in aiding diagnosis and follow-up of patients with medullary cancer, and in the follow-up of patients with differentiated thyroid cancer. Accurate diagnosis and appropriate management of thyroid disease is dependent on the appropriate choice of thyroid laboratory tests and the proper interpretation of their results.

To learn more about Siemens thyroid tests, please contact your local Siemens representative or visit [www.siemens.com/thyroid](http://www.siemens.com/thyroid)

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