MAYO CLINIC LABORATORIES

Test Definition: HTG2

Thyroglobulin, Tumor Marker, Serum

Overview

Useful For

Follow-up of patients with differentiated thyroid cancers after thyroidectomy and radioactive iodine ablation

Highlights

All specimens are screened for the presence of autoantibodies to thyroglobulin.

Method Name

Immunoenzymatic Assay

NY State Available

Yes

Specimen

Specimen Type

Serum Red

Ordering Guidance

For accurate analysis of patients who are known to be thyroglobulin antibody positive, order TGMS / Thyroglobulin Mass Spectrometry, Serum.

Specimen Required

Patient Preparation: For 12 hours before specimen collection, patient **should not** take multivitamins or dietary supplements (eg, hair, skin, and nail supplements) containing biotin (vitamin B7).
Supplies: Sarstedt Aliquot Tube, 5 mL (T914)
Collection Container/Tube:
Preferred: Red top
Acceptable: None (serum gel/SST are **not acceptable**)
Submission Container/Tube: Plastic vial
Specimen Volume: 1 mL
Collection Instructions: Centrifuge and aliquot serum into a plastic vial.

Forms

If not ordering electronically, complete, print, and send 1 of the following forms with the specimen:
-General Request (T239)
-Oncology Test Request (T729)
-Renal Diagnostics Test Request (T830)

Specimen Minimum Volume

0.5 mL

Reject Due To

Gross hemolysis	Reject
Gross lipemia	OK
Gross icterus	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Serum Red	Refrigerated (preferred)	7 days	
	Ambient	7 days	
	Frozen	30 days	

Clinical & Interpretive

Clinical Information

Thyroglobulin (Tg) is a thyroid-specific glycoprotein (approximately 660 kDa) that serves as the source for thyroxine (T4) and triiodothyronine (T3) production within the lumen of thyroid follicles. For T4 and T3 release, Tg is reabsorbed into thyrocytes and proteolytically degraded, liberating T4 and T3 for secretion.

Small amounts of intact Tg are secreted alongside T4 and T3 and are detectable in the serum of healthy individuals with levels roughly paralleling thyroid size (0.5-1.0 ng/mL Tg per gram thyroid tissue, depending on thyroid-stimulating hormone [TSH] level). In situations of disordered thyroid growth (eg, goiter), increased thyroid activity (eg, Graves disease), or glandular destruction (eg, thyroiditis), larger amounts of Tg may be released into the circulation.

Clinically, the main use of serum Tg measurements is in the follow-up of differentiated follicular cell-derived thyroid carcinoma. Because Tg is thyroid-specific, serum Tg concentrations should be undetectable or very low after the thyroid gland is removed during treatment for thyroid cancer.

Current clinical guidelines consider a serum Tg concentrations above 1 ng/mL in an athyrotic individual as suspicious of possible residual or recurrent disease. To improve diagnostic accuracy, it is recommended this measurement be initially obtained after TSH stimulation, either following thyroid hormone withdrawal or after injection of recombinant human TSH. Most patients will have a relatively low risk of recurrence and will thereafter only require unstimulated Tg measurement.

If unstimulated (on thyroxine) serum Tg measurements are less than 0.1 to 0.2 ng/mL, the risk of disease is below 1%. Patients with higher Tg levels who have no demonstrable remnant of thyroid tissue might require additional testing, such as further stimulated Tg measurements, neck ultrasound, or isotope imaging. A stimulated Tg above 2 ng/mL is considered suspicious.

The presence of antithyroglobulin autoantibodies (TgAb), which occur in 15% to 30% of patients with thyroid cancer, could lead to misleading Tg results. In immunometric assays, the presence of TgAb can lead to falsely low results,

whereas it might lead to falsely high results in competitive assays.

Traditionally, there have been no reliable means to obtain accurate Tg measurements in patients with TgAb. However, recently trypsin digestion of serum proteins, which cuts both antibodies and Tg into predictable fragments, has allowed accurate quantification of Tg in samples with antibody interferences through measurement of Tg by mass spectrometry. See TGMS / Thyroglobulin Mass Spectrometry, Serum for accurate analysis of patients who are known to be TgAb positive. If TgAb status is unknown, see HTGR / Thyroglobulin, Tumor Marker Reflex, Serum. When HTGR is ordered, TgAb testing is performed first. If TgAb is negative (<1.8 IU/mL), Tg is assayed by immunoassay (sensitive down to 0.1 ng/mL). If TgAb is positive, Tg is assayed by mass spectrometry (sensitive down to 0.2 ng/mL).

Reference Values

Thyroglobulin Tumor Marker
< or =33 ng/mL

Thyroglobulin Antibody:
<1.8 IU/mL
Reference values apply to all ages.

Interpretation

Current guidelines recommend measurement of thyroglobulin (Tg) with a sensitive immunoassay (limit of quantification <1.0 ng/mL); for measurements of unstimulated Tg, the detection limit should be in the 0.1 to 0.2 ng/mL range.

In all cases, serum thyroglobulin autoantibodies (TgAb) should also be measured, preferably with a method that allows detection of low concentrations of TgAb. If TgAb are detected, the laboratory report should alert the ordering provider to the possibility of falsely low Tg results if using an immunometric assay. If the apparent Tg concentration is below 1.0 ng/mL, the sample should be remeasured by mass spectrometry. This will allow accurate detection of Tg, in the presence of TgAb, down to 0.2 ng/mL (risk of residual/recurrent disease <1%-3%).

Samples from patients with Tg concentrations above 1.0 ng/mL might not require Tg measurement by mass spectrometry because current guidelines suggest further workup might be necessary above this threshold. However, the positive predictive value for residual/recurrent disease is modest when Tg is just above this threshold (3%-25%) in athyrotic patients. Above 10 ng/mL, the risk of residual/recurrent disease is at least 25%, with many studies showing 60% to above 90% risks. In selected patients, therefore, it might also be useful to test TgAb positive samples by mass spectrometry, even if the Tg concentration is above 1.0 ng/mL but not above the 10 ng/mL threshold. These considerations are even more relevant in patients with a known thyroid remnant of a few grams, who may always have serum Tg concentrations of 1.0 to 10 ng/mL, owing to remnant Tg secretion, regardless of the presence or absence of residual/recurrent cancer.

It has been determined that the presence of antithyroglobulin autoantibodies (TgAb) in serum can lead to underestimation of Tg concentration by immunometric methods. When TgAb are present in samples with detectable Tg, the Tg values may be underestimated by up to 60% in immunoassays. In addition, approximately 20% of specimens containing TgAb, which are negative for Tg by immunoassay, tested positive by liquid chromatography tandem mass spectrometry. Therefore, measuring Tg by mass spectrometry is the preferred method in TgAb positive patients.

Thyroglobulin reference intervals are for patients with an intact thyroid and not for patients who have had surgery for thyroid cancer. Tg reference intervals in patients that have undergone thyroidectomy or any treatment for follicular

thyroid cancer are dependent on the residual mass of the thyroid tissue after surgery. Tg results, regardless of concentration, should not be interpreted as absolute evidence for the presence or absence of papillary or follicular thyroid cancer. This result needs to be interpreted in the context of the clinical evaluation.

Cautions

The test is most sensitive for detection of thyroid cancer recurrence when patients are off thyroid replacement long enough to have an elevated thyrotropin (TSH) prior to collecting the specimen. This test also can be used to follow patients with normal TSH; however, thyroglobulin (Tg) values from specimens with high TSH should not be compared with values with normal TSH, because TSH stimulation changes the baseline determinations.

Thyroglobulin autoantibodies (TgAb) may interfere with the measurement of Tg. All specimens are prescreened for TgAb, and a comment appended to the report if they are present. Undetectable levels of Tg should be interpreted with caution if TgAb are present. A Tg antibody result of less than 1.8 IU/mL is unlikely to cause clinically significant Tg assay interference. It is recommended that the Tg result be reviewed for concordance with clinical presentation.

In rare cases, some individuals can develop antibodies to mouse or other animal antibodies (often referred to as human anti-mouse antibodies [HAMA] or heterophile antibodies), which may cause interference in some immunoassays. Caution should be used in interpretation of results, and the laboratory should be alerted if the result does not correlate with the clinical presentation.

Specimens with Tg concentrations greater than 250,000 ng/mL may "hook" and appear to have markedly lower levels.

Thyroglobulin and TgAb values determined by different methodologies might vary significantly and cannot be directly compared with one another. Some patients might be antibody-positive by some methods and antibody-negative by others. Comparing values from different methods might lead to erroneous clinical interpretation.

Clinical Reference

1. Grebe SKG. Diagnosis and management of thyroid carcinoma: a focus on serum thyroglobulin. Exp Rev Endocrinol Metab. 2009;4(1):25-43. doi:10.1586/17446651.4.1.25
2. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167-1214. doi:10.1089/thy.2009.0110
3. Pacini F, Catagana MG, Brilli L, et al. Thyroid cancer. ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21 Suppl 5:v214-9. doi:10.1093/annonc/mdq190
4. National Comprehensive Cancer Network (NCCN) guidelines for treatment of cancer by site: version 4.2024: Thyroid Carcinoma. Accessed January 22, 2025. Available at www.nccn.org/professionals/physician_gls/default.aspx#site
5. Tuttle, RM: Serum thyroglobulin in the management of differentiated thyroid cancer. Updated June 27, 2023. Accessed January 22, 2025. Available at www.uptodate.com/contents/differentiated-thyroid-cancer-role-of-serum-thyroglobulin

Performance

Method Description

The Beckman Coulter Unicel DxI 800 is used for both thyroglobulin tumor marker and thyroglobulin antibody testing.

The Access Thyroglobulin (Tg) assay is a simultaneous 1-step immunoenzymatic (sandwich) assay. A sample is added to a reaction vessel, along with a biotinylated mixture of 4 monoclonal anti-Tg antibodies, streptavidin-coated paramagnetic particles, and monoclonal anti-Tg antibody alkaline phosphatase conjugate. The biotinylated antibodies and the serum Tg bind to the solid phase, while the conjugate antibody reacts with a different antigenic site on the Tg molecule. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos 530 is added to the vessel, and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of Tg in the sample.(Package insert: Access Thyroglobulin. Beckman Coulter Inc; 09/2024)

The Access Thyroglobulin Antibody II assay (TgAb) is a sequential 2-step immunoenzymatic (sandwich) assay. A sample is added to a reaction vessel with paramagnetic particles coated with the thyroglobulin protein. The serum TgAb binds to the thyroglobulin. After incubation in a reaction vessel, materials bound to the solid phase are held in place by a magnetic field, while unbound materials are washed away. The thyroglobulin-alkaline phosphatase conjugate is added and binds to the TgAb. After the second incubation, materials bound to the solid phase are held in place by a magnetic field, while unbound materials are washed away. Then, the chemiluminescent substrate, Lumi-Phos 530 is added to the reaction vessel, and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of thyroglobulin antibody in the sample.(Package insert: Access Thyroglobulin Antibody II. Beckman Coulter Inc; 09/2024)

PDF Report
No

Day(s) Performed
Monday through Saturday

Report Available
1 to 3 days

Specimen Retention Time
6 months

Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Superior Drive

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification
This test has been cleared, approved, or is exempt by the US Food and Drug Administration and is used per

manufacturer's instructions. Performance characteristics were verified by Mayo Clinic in a manner consistent with CLIA requirements.

CPT Code Information

84432
86800

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
HTG2	Thyroglobulin, Tumor Marker	57780-9

Result ID	Test Result Name	Result LOINC® Value
TGAB2	Thyroglobulin Antibody, S	56536-6
HTGN2	Thyroglobulin, Tumor Marker, S	3013-0
HTG2I	Thyroglobulin Interpretation	69053-7