MAYO CLINIC LABORATORIES

Test Definition: HTGR

Thyroglobulin, Tumor Marker Reflex, Serum

Overview

Useful For

Reporting of accurate thyroglobulin results, depending on the antithyroglobulin antibodies status of the patient

Accurate measurement of serum thyroglobulin in patients with known or suspected antithyroglobulin autoantibodies or possible heterophile antibodies

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
HTGT	Thyroglobulin, Tumor Marker, IA, S	No	No
TGMS	Thyroglobulin, Mass Spec., S	Yes	No

Testing Algorithm

This test begins with the analysis of thyroglobulin antibody by immunoassay. If the thyroglobulin antibody result is negative (<1.8 IU/mL), then thyroglobulin testing will be performed by immunoassay.

If the thyroglobulin antibody result is positive (> or =1.8 IU/mL), then thyroglobulin testing will be performed by mass spectrometry.

Method Name

HTGT: Immunoenzymatic Assay
TGMS: Tryptic Protein Fragmentation, purified with Immunocapture, Analysis by Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) (This service is performed pursuant to an agreement with SISCAPA Assay Technologies Inc. covering US Patent 7,632,686)

NY State Available

Yes

Specimen

Specimen Type

Serum Red

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: 2 mL
Collection Instructions: Centrifuge and aliquot serum into a plastic vial.

Forms
If not ordering electronically, complete, print, and send an Oncology Test Request (T729) with the specimen.

Specimen Minimum Volume
1.25 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	72 hours	
	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 thyrotropin [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 concentration 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 thereafter will 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 additional stimulated Tg measurements, neck ultrasound, or isotope imaging. A stimulated Tg above 2 ng/mL is considered suspicious.

The presence of anti-thyroglobulin 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 measurement, 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-specific tryptic peptides by mass spectrometry.

Reference Values

THYROGLOBULIN ANTIBODY
<1.8 IU/mL

THYROGLOBULIN, TUMOR MARKER
< or =33 ng/mL

Interpretation

Current guidelines recommend measurement of thyroglobulin (Tg) using a sensitive immunoassay (limit of quantification less than 1 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 anti-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 the apparent Tg concentration is below 1.0 ng/mL, the sample should be remeasured by liquid chromatography tandem mass spectrometry (LC-MS/MS). This will allow confident 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 work-up may 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, 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 has not yet passed 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 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, some specimens containing TgAb, which are negative for Tg by immunoassay, tested positive by LC-MS/MS. Therefore, measuring of Tg by LC-MS/MS is the preferred method in TgAb positive patients.

Thyroglobulin by Immunoassay and Mass Spectrometry:
Thyroglobulin (Tg) 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

Thyroglobulin by Mass Spectrometry:
Rare normal amino acid sequence variations within thyroglobulin (Tg) can cause a false-low result in the Tg mass spectrometry assay if they happen to be present in the Tg proteotypic peptides that are used for Tg quantification. While the exact prevalence of such changes is unknown, the validation data on large sample numbers indicate that this affects less than 1% of samples. In the heterozygote state, the result would be an apparent reduction in Tg concentration by about 50%, while the homozygous state (<0.01%) is predicted to result in total loss of signal. Therefore, if the results of the mass spectrometry measurement are much lower than those obtained previously (within 3-6 months) with an immunometric immunoassay, this possibility should be considered. In this event, alert Mayo Clinic Laboratories as soon as possible, and an attempt will be made to resolve the discrepancy.

Thyroglobulin by Immunoassay:
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 can also be used to follow patients with normal TSH; however, 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.

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

Tg 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.

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.

Supportive Data

Clinical Reference

1. Grebe SKG. Diagnosis and management of thyroid carcinoma: A focus on serum thyroglobulin. Expert 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, Haugen BR, 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, Pentheroudakis G; on behalf of the ESMO Guidelines Working Group: 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. Haddad RI, Bischoff L, Applewhite M, et al. NCCN Guidelines Insights: Thyroid Carcinoma, Version 1.2025. J Natl Compr Canc Netw. 2025;23(7):e250033. doi:10.6004/jnccn.2025.0033
5. Tuttle RM. Differentiated thyroid cancer: Role of serum thyroglobulin. In: Cooper DS, Ross DS, Mulder JE, eds. Updated June 27, 2023. Accessed October 3, 2024. Available at: www.uptodate.com/contents/differentiated-thyroid-cancer-role-of-serum-thyroglobulin

Performance

Method Description

Thyroglobulin Antibody:
The Access Thyroglobulin Antibody II assay (TgAb) is a sequential 2-step immunoenzymatic (sandwich) assay performed on a Beckman Coulter Unicel DxI 800 system. 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)

Thyroglobulin, Tumor Marker, Immunoassay:
Thyroglobulin by immunoassay is performed using a Beckman Coulter Unicel DxI 800 system. 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)

Thyroglobulin, Mass Spectrometry:
Serum is subjected to salt fractionation. The fractionated serum is then reduced, alkylated, and digested with trypsin. Tryptic fragments are further purified by immunocapture with antibodies specific to the individual fragments. Finally, these fragments are analyzed by liquid chromatography tandem mass spectrometry.(Unpublished Mayo method)

PDF Report
No

Day(s) Performed
Monday through Saturday

Report Available
1 to 6 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
86800
84432 (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
HTGR	Thyroglobulin Reflex to MS or IA	56536-6

Result ID	Test Result Name	Result LOINC® Value
TGABR	Thyroglobulin Antibody, S	56536-6