TSI Literature Compendium:

Third party articles comparing the diagnostic value of the IMMULITE 2000 TSI assay (a bridge assay) to TRAb assays

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The role of autoantibody detection in Graves' disease diagnosis

Introduction

Graves' disease (GD) is the most common type of hyperthyroidism and can cause profound metabolic disruption. It is an autoimmune disorder in which stimulating autoantibodies (TSAbs) targeting the TSH receptor (TSHR) induce production of excess T3 and T4, despite low or absent TSH.[1,2] Diagnosis can often be made on the basis of hormonal testing and clinical presentation alone, however when GD is suspected but not supported by thyroid hormone results, or when confirmation is needed, testing for TSAbs can play a crucial role in confirming the diagnosis since they are highly specific for GD.[2,3] The absence of TSAbs can also help to differentiate between GD and other pathologies causing thyrotoxicosis (such as multinodular toxic goiter or thyroid hormone—secreting adenomas) when clinical presentation and other biomarkers do not provide sufficient information.[2,4]

Currently, two types of tests are used to detect TSAbs: bioassays and immunoassays. Bioassays expose specially modified cells in culture to patient serum.[5-7] In TSAb bioassays, the cells contain membrane-bound TSHRs and undergo a metabolic reaction that causes them to luminesce when the receptors are triggered by TSAbs. TRAb assays are immunoassays that use a labeled ligand to detect TSHR antibodies.[7] Commercial TRAb assays use a competitive format in which either labeled anti-TSHR antibodies or labeled TSH compete with antibodies in the patient's serum sample for TSHR bound to some form of substrate.[7] Three generations of TRAb immunoassays have been developed over the past several decades. Generational differences are defined by the type of substrate and the type of ligand.[7]

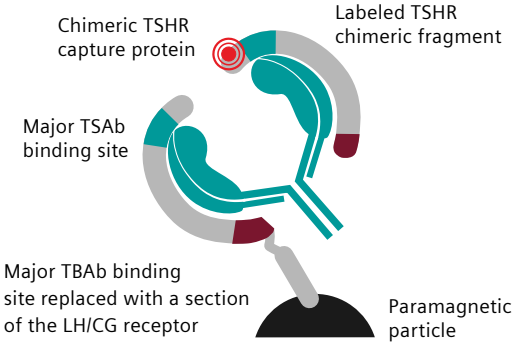
For any assay, good clinical sensitivity is necessary for accurate and early diagnosis, while good specificity is necessary for differentiating between GD and other diseases. The sensitivity of commercial TRAb assays has increased with successive generations, but performance between assays and generations can be highly variable.[7,8] While most demonstrate good clinical specificity and can differentiate between patients with and without GD, they are not specific for TSAbs and can detect TSHR blocking autoantibodies (TBAbs) as well. Although TBAbs are more likely to be associated with Hashimoto's thyroiditis (HT—a type of hypothyroidism), several case studies have reported increasing TBAb concentrations in GD patients while undergoing therapy.[9,10] In some patients, rising TBAbs can eventually predominate and cause a hypothyroid shift. Conversely, some patients diagnosed initially with HT eventually developed TSAbs and GD, leading investigators to suggest that GD and HT could be different aspects of a single, evolving disease.[6,9,10]

TBAbs bind to the same TSHR as TSAbs.[11] Because both autoantibody types can be present simultaneously, it is difficult to know for certain if a positive TRAb result is due to elevated TSAbs, TBAbs, or both species.[7] In some cases, TRAb assays can yield false-positive results if TSAbs are absent or low and TBAbs are present. Despite their high specificity for TSAbs, bioassays can generate false negative results if the TBAb activity is greater than the TSAb activity. TBAbs can potentially bind to TSHR sites and effectively block TSAbs from binding and triggering the metabolic events needed to generate a signal.[12] A high TSH level in the sample can also interfere with TSAb bioassays and cause false-positive results.[13]

The Siemens Healthineers IMMULITE® 2000 TSI assay is an immunoassay that uses an innovative bridge format. It is designed to reduce TBAb detection with the objective of more specifically detecting TSAbs. It does this by using genetically engineered chimeric TSH receptors to capture and label TSAbs (Figure 1). X-ray crystallographic evidence suggests that the TSAb binding sites are located near the N-terminal region of TSHR while many of the amino acids needed to bind TBAbs are located in the area of the binding pocket closer to the hinge region of the protein.[11,14] The chimeric capture receptor used in the IMMULITE 2000 TSI assay is composed of the N-terminal portion of human TSHR containing the TSAb binding sites spliced to an amino acid sequence from the rat LH/CG hormone receptor. This format results in an assay whose clinical sensitivity and specificity are at least as good as—and in some cases superior to—commercial TRAb assays and bioassays.

Several published studies evaluating and confirming the high analytical performance and diagnostic accuracy of the IMMULITE 2000 TSI assay are presented in this compendium. Each article is presented as a brief abstract followed by Siemens Healthineers' interpretation of the significance of each work and the authors' own conclusions. We hope that these synopses encourage you to read each article in its entirety for a more complete understanding of these highly relevant works in the field.

Figure 1. The bridge format of the IMMULITE 2000 TSI assay. Artist's rendition. Drawing is highly simplified and not to scale. Not intended to depict actual structure, molecular shape or all binding epitopes.



Glossary of terms

GD: Graves' Disease; an autoimmune disease that causes hyperthyroidism and is marked by some combination of tachycardia, fatigue, muscle weakness, heat intolerance, sleep disturbance, weight loss despite increased appetite and caloric consumption, ocular changes, visual disturbances, nervousness, irritability, depression, and mood swings.

TSH: Thyroid stimulating hormone; hormone released from the pituitary that stimulates the thyroid to produce and release thyroid hormones regulating metabolic homeostasis.

T3: Triiodothyronine; a thyroid hormone.

T4: Thyroxine; a thyroid hormone.

TSHR: Thyroid stimulating hormone receptor; activation by TSH or TSAbs results in the production and release of T3 and T4 from the thyroid.

TSAb: TSH receptor stimulating antibody; stimulates T3 and T4 release in the absence of TSH.

TBAb: TSH receptor blocking antibody; prevents TSH binding and stimulation of the TSH receptor, reducing the release of T3 and T4 by the thyroid.

HT: Hashimoto's thyroiditis; an autoimmune disease that causes hypothyroidism and is marked by goiter, weight gain, cold intolerance, fatigue, and constipation.

TRAb assay: TSH receptor antibody immunoassay; detects both TSAbs and TBAbs.

TSAb Bioassay: Cell-based assay designed to preferentially detect TSAbs.

Bridge assay: The IMMULITE 2000 TSI immunoassay, which uses genetically engineered chimeric TSH receptors lacking the primary TBAb binding site to capture and label TSAbs in patient serum samples. The Bridge assay is designed to reduce TBAb detection with the objective of more specifically detecting TSAbs.

Comparison of the bridge assay to 2nd and 3rd generation TRAb assays

Evaluation of the first fully automated immunoassay method for the measurement of stimulating TSH receptor autoantibodies in Graves' disease.

Tozzoli R, D'Aurizio F, Villalta D, Giovanella L. CCLM 2016;55(1):58-64. DOI: 10.1515/cclm-2016-0197

Objective

- Evaluate the ability of the IMMULITE 2000 TSI assay (bridge assay) to differentiate untreated Graves' disease patients from patients with other thyroid diseases and nonthyroid autoimmune diseases.
- Compare the IMMULITE 2000 TSI assay to the second-generation TRAK Human TRAb radioimmunoassay (BRAHMS Thermo Scientific) and the third generation Elecsys/Cobas Anti-TSH Receptor electro-chemiluminescence IMA (TRAb ECLIA, Roche Diagnostics).

Methods

- Retrospective evaluation of patients (age not specified) with untreated Graves' disease diagnosed according to American Thyroid Association guidelines.
- Also tested patients with other thyroid disease (autoimmune thyroiditis, multinodular non-toxic goiter), patients with non-thyroid autoimmune diseases (rheumatoid arthritis, systemic lupus, chronic autoimmune gastritis, celiac disease), and healthy controls <30 years meeting the NACB guidelines for normal thyroid function.
- Used ROC analysis to determine the best cut-off level.
- Correlation and agreement were used to compare the three assays.

Results

- The suggested cut-off according to ROC analysis was 0.54 IU/L, which aligns with the Siemens Healthineers recommended cut-off of 0.55 IU/L.
- The IMMULITE 2000 TSI assay accurately identified all patients with Graves' disease (Figure 2).
- Positive results were obtained for three patients without Graves' disease but who had other autoimmune diseases (Figure 2). The authors suggest that these might not be false positive results as both blocking antibodies and stimulating antibodies have been observed in non-Graves' disease and euthyroid patients in other studies.
- The difference between median TSI in patients with and without Graves' disease was statistically significant.
- Passing & Bablok analysis indicated good correlation between IMMULITE 2000 TSI and each of the other two assays, however with a negative bias. The two TRAb assays correlated well with minimal bias.

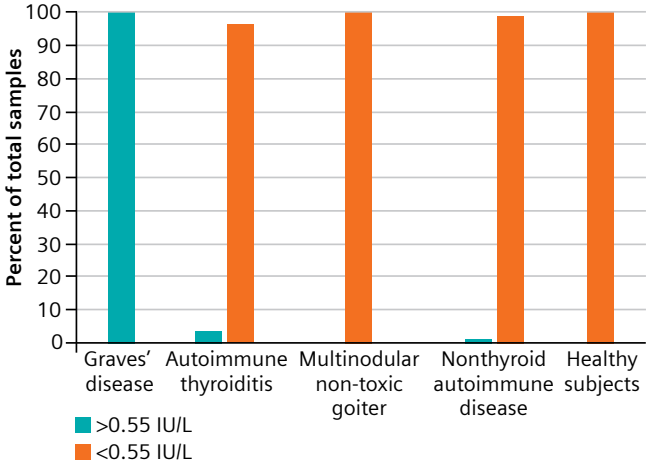
Authors' conclusions

"[T]he diagnostic performance of fully automated [IMMULITE 2000 TSI assay] in GD patients is at least comparable to that of current TRAb assays, with a trend toward a better accuracy. As a consequence, it may be adopted in clinical practice for the differential diagnosis of hyperthyroidism…and to assess patients with Graves' orbitopathy."

Significance

- **The diagnostic sensitivity of the IMMULITE 2000 TSI assay determined in this study was 100%, which is higher than the sensitivity reported in other studies for the two compared TRAb assays.**

Figure 2. IMMULITE 2000 TSI results demonstrating high sensitivity and specificity for diagnosing Graves' disease.



Comparison of the bridge assay to 3rd generation assays

Clinical Evaluation of the First Automated Assay for the Detection of Stimulating TSH Receptor Autoantibodies.

Allelein S, Ehlers M, Goretzki S, et al. Horm Metab Res 2016;48:795–801. DOI: 10.1055/s-0042-121012

Objective

Retrospectively compare the performance of the IMMULITE 2000 TSI assay (bridge assay) to the Roche anti-TSHR (TRAb) assay in clinical practice.

Methods

- Samples were analyzed from patients diagnosed with Graves' disease, autoimmune thyroiditis, nonautoimmune nodular thyroid disease, thyroid cancer (differentiated, poorly differentiated, or anaplastic), as well as from patients with no history of thyroid disease.
- Approximately 13% of the Graves' disease samples were from newly diagnosed patients. The remainder were from patients already receiving therapy. Samples were collected between 3 and 12 months of initial diagnosis.
- Decision thresholds were determined using receiver operator characteristics (ROC) analysis.
- Sensitivity was calculated using samples taken from patients diagnosed with Graves' disease.
- Specificity was calculated using samples taken from healthy individuals and patients with different thyroid diseases (excluding GD patients).

Results

- Confirmed the 0.55 IU/L cutoff determined by Siemens Healthineers is highly sensitive for making a new Graves' disease diagnosis, and highly specific for differentiating between Graves' disease and other thyroid diseases.
- The sensitivity and specificity (Figure 3) for the IMMULITE 2000 TSI assay was calculated three different ways:

1. Based on data from newly diagnosed patients, only, at the Siemens Healthineers recommended cutoff.
2. Based on data for all Graves' disease patients at a cutoff that is lower than recommended by Siemens Healthineers but determined to be optimal according to the study's ROC analysis.
3. Based on data for all Graves' disease patients at the Siemens Healthineers recommended cutoff.

- PPV and NPV (Figure 3) were greater than 93% in all analyses, indicating that the 0.55 IU/L cutoff is effective for both rule-in and rule-out of Graves' disease.
- The IMMULITE 2000 TSI assay detected 3% more patients with new or existing Graves' disease than the Roche anti-TSHR assay.
- Overall correlation between the IMMULITE 2000 TSI assay and the Roche anti-TSHR assay was high but less than 90%.

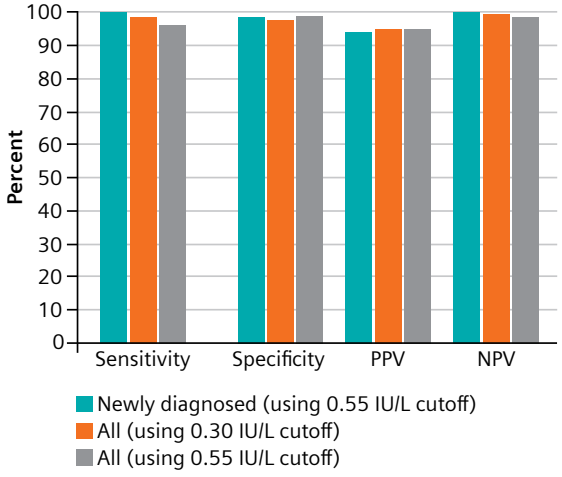
Authors' conclusions

"Our results demonstrate the new automated bridge assay to detect sTRAb with high sensitivity (in diagnosing GD) and specificity (in discriminating it from other thyroid diseases)."

Significance

- **Confirms the high clinical sensitivity and specificity of the IMMULITE 2000 TSI assay.**
- **Suggests that the IMMULITE 2000 TSI assay is a little more sensitive than the Roche anti-TSHR assay for diagnosing Graves' disease patients.**

Figure 3. Performance characteristics of the IMMULITE 2000 TSI assay based on contrived cohorts.



Stimulating TSH receptor autoantibodies immunoassay: analytical evaluation and clinical performance in Graves' disease.

Autilio C, Morelli R, Locantore P, et al. Ann Clin Biochem. 2018;55(1):172-7. DOI: 10.1177/0004563217700655

Objective

- Evaluate the analytical and clinical performance of the IMMULITE 2000 TSI assay (bridge assay) for diagnosing Graves' disease and detecting relapse following treatment, and compare it to the performance of Roche Elecsys/Cobas Anti-TSH Receptor (TRAb) electro-chemiluminescence immunoassay.

Methods

- Prospective evaluation of patients (age not specified) with suspected Graves' disease or other thyroid disorder treated in a single clinic over the course of one year. Results were compared to remnant donated blood from apparently healthy subjects.
- Final diagnosis was made based on the American Thyroid Association guidelines. Patients were diagnosed with Graves' disease, atrophic thyroiditis, chronic autoimmune thyroiditis (CAT), or multinodular non-toxic goiter.
- LoD, LoQ, and LoB were determined for each assay according to the CLSI EP17-A protocol.
- ROC analysis was used to determine the best cut-off for differentiating patients with Graves' disease from patients with other thyroid diseases and healthy individuals with the highest possible diagnostic sensitivity and specificity.
- The method comparison was conducted using the ROC-determined cut-off for IMMULITE 2000 TSI assay (bridge assay) and the Roche recommended cut-offs for the Cobas anti-TSHR (TRAb) assay.

Results

- The LoB, LoD, LoQ, and %CVs for intra- and inter-assay precision determined in the study and by Siemens Healthineers were almost identical (Table 1).
- The cut-off determined by the study group was similar to the cut-off determined by Siemens Healthineers.
- The sensitivity and specificity for Graves' disease using the study cut-off were in alignment with the sensitivity and specificity determined by Siemens Healthineers at the slightly lower cut-off recommended in the instructions for use (IFU).
- Only one false-negative (individual with mild hyperthyroidism) and two false-positive results were generated using the study cut-off. The authors point out that at least one of the false-positive results could reflect accurate detection of stimulating antibodies as other studies support the presence of stimulating antibodies in CAT.
- Passing & Bablok analysis indicated 98% correlation between IMMULITE 2000 TSI assay and the Roche TRAb assay, with a small but negative IMMULITE bias. This was attributed to the difference in assay formats (bridge vs TRAb).
- More false-negative and false-positive results were observed using the Roche assay at its manufacturer-recommended cut-off than with the IMMULITE 2000 TSI assay.

Authors' conclusions

"[T]he test allows to accurately detect very low values of analyte, apart from identifying GD patients correctly. The highest analytical sensitivity that has emerged could make this method the elective one..."

Significance

- **The study offers additional confirmation of the IMMULITE 2000 TSI assay's superior sensitivity, specificity, and clinical diagnostic accuracy over the Roche anti-TSHR assay.**
- **The high functional and clinical sensitivity make the IMMULITE 2000 TSI assay a valuable tool both for initial diagnosis and for diagnosing recurrence in the patient who is no longer being treated.**

Table 1. Similarity between assay characteristics determined in the study and reported in the Siemens Healthineers IFU.

	Cut-off (IU/L)	Sensitivity (%)	Specificity (%)	LoB (IU/L)	LoD (IU/L)	LoQ (IU/L)	Intra-assay % CV	Interassay % CV
IMMULITE 2000 TSI IFU	0.55	98.6	98.5	0.03	0.06	0.10	3.5–7.0	5.0–8.3
IMMULITE 2000 TSI Study	0.57	98.0	99.9	0.04	0.07	0.14	4.2–5.9	4.5–7.2
Roche anti-TSHR	1.75	96	99	NR*	NR	0.9	NR	NR

*NR=Value not reported in study article.

Diagnostic accuracy of a new fluoroenzyme immunoassay for the detection of TSH receptor autoantibodies in Graves' disease.

Villalta, D., D'Aurizio, F., Da Re, M. et al. Autoimmun Highlights 2018; 9:3. DOI: 10.1007/s13317-018-0102-4

Objective

- Evaluate the diagnostic accuracy of a new third generation automatic fluorescence enzyme immunoassay, the ELiA anti-TSHR assay (Thermo Fischer Scientific) for TSHR antibody measurement in GD, in comparison to two current immunoassays: the BRAHMS TRAK RIA (TRAb) and the IMMULITE 2000 TSI assay (bridge assay).

Methods

- Evaluated sera from patients with untreated GD, treated GD (1–12 months of treatment), GD and Graves' orbitopathy (GD/GO), non-toxic multinodular goiter (NTMG), Hashimoto's thyroiditis (HT), toxic adenoma or toxic multinodular goiter (TA/TMG), non-thyroid autoimmune diseases (NTAD: systemic lupus erythematosus, rheumatoid arthritis, autoimmune gastritis, celiac disease), and normal controls (NC).
- Determined clinical sensitivity and specificity for all assays.
- Used ROC analysis to determine cut-off for the ELiA assay.

Results (Table 2)

- Cut-off for the ELiA assay (3.8 IU/L) is higher than any other 2nd or 3rd generation TRAb assay, and almost 7 x greater than the IMMULITE 2000 TSI assay cut-off.
- The Clinical sensitivity of the ELiA assay was 94.7% for untreated GD patients, 76% for treated GD patients, and 86.7% for GD/GO. Specificity was 99.6%
- The IMMULITE 2000 TSI assay sensitivity determined in the study was 100% and the specificity was 98.2% using the recommended 0.55 IU/L cut-off.

Authors' conclusions

"The diagnostic sensitivity of ELiA™ –TSHR assay for GD resulted high, though slightly lower than those of the TRAK™ and TSI™ Immulite [sic] assays. In all probability, this is associated to the lower analytical sensitivity of the ELiA™–TSH-R assay, as shown by the high cut-off (3.8 IU/L)."

Significance

- **This study was done to support the ELiA assay, however the results indicate that it is not as sensitive as the IMMULITE 2000 TSI assay and confirms the very high sensitivity and specificity of the IMMULITE 2000 TSI assay.**
- **The high cutoff indicates that the ELiA assay has lower functional sensitivity.**
- **While the ELiA assay appears to have slightly higher specificity than the IMMULITE 2000 TSI assay, this difference is likely not statistically significant. In addition, several other studies have demonstrated higher specificity for the IMMULITE 2000 TSI assay than reported in this study.**

Table 2. Summary of IMMULITE 2000 TSI assay clinical sensitivity and specificity results determined in the above four studies.

Reference	GD patients (n)	Patients with other thyroid or autoimmune diseases (n)	Healthy individuals (n)	Assay Cut-off (IU/L)	Clinical Sensitivity (%)	Clinical Specificity (%)
IMMULITE 2000 TSI US IFU	361[a]	404	0	0.55	98.6	98.5
Tozzoli et al. 2017	72[b]	191	120	0.54[c]	100	98.7
Allelein et al. 2016	266[b]	180	41	0.55	100	99
Autilio et al. 2018	46[b]	49	50	0.57[c]	98.0	99.9
Villalta et al. 2018	57[b]	213	120	0.55	100	98.2

a. Treated and untreated patients
b. Untreated patients, only
c. Determined in study using ROC analysis

Comparison to the Thyretain bioassay

Analytical and Clinical Validation of Two Commercially Available Immunoassays Used in the Detection of TSHR Antibodies.

Kemble DJ, Jackson T, Morrison M, et al. JALM 2017;2(3):345-55. DOI:10.1373/jalm.2017.024067

Objective

- Compare the clinical performances of the Thyretain TSI bioassay and two automated immunoassays: the Roche Anti-TSHR antibody (TRAb) assay (performed on Cobas e601) and the IMMULITE 2000 TSI assay (bridge assay).
- Evaluate the analytical performance of the two automated assays.

Methods

- Prospective evaluation of patients (age not specified) referred for TSI testing using the Thyretain assay.
- Automated assay results were obtained on site. Thyretain assay results were generated at a reference laboratory.
- Approximately 65% of samples were evaluated by all three methods.
- An extended sample set was used to compare the Thyretain TSI bioassay and the Siemens Healthineers IMMULITE 2000 TSI assay against the final diagnosis.
- Discordant samples (at least one automated assay not aligned with Thyretain result) were compared to clinical history if available. For samples without clinical history, biochemical thyroid status was assessed by determining TSH and free T4 (FT4) levels, and in some cases, anti-thyroid peroxidase (aTPO).
- Compared imprecision for the Siemens Healthineers and Roche assays at their respective cut-offs for diagnosing Graves' disease.
- Evaluated the degree of HCG cross-reactivity for all three assays.

Results

- All strongly positive samples according to Thyretain were also positive according to both automated assays.
- There were fewer discrepant results between the Thyretain bioassay and the IMMULITE 2000 TSI assay employing a bridge assay format (16%) than between the Thyretain bioassay and Roche anti-TSHR assay (28%) when the bioassay results were low-positive (Table 3).
- There were fewer discrepant results between the Thyretain bioassay and Roche anti-TSHR assay (13%) than between the Thyretain bioassay and the IMMULITE 2000 TSI assay employing a bridge assay format (16%) when the bioassay results were negative (Table 4). Following review of clinical history, the authors noted that all of the Thyretain-negative/IMMULITE-positive samples were collected from patients with a diagnosis of Graves' disease who were being treated or previously treated with methimazole or propylthiouracil.
- In comparison, using clinical history for resolution, only 50% of Thyretain-negative/Roche-positive samples were found to have come from patients with a history of Graves' disease.
- None of the assays were susceptible to HCG interference for the concentrations tested. Both immunoassays demonstrated good imprecision in line with what is reported in the manufacturers' IFUs.

Authors' conclusions

"The 3 commercially available anti-TSHR autoantibody measurement methods demonstrated equivalent performance in patients with untreated Graves' disease."

"[T]he Siemens TSI assay more frequently generated results consistent with clinical history, results of other laboratory tests, and imaging studies than the Thyretain Bioassay and Roche anti-TSHR assay."

Significance

- **The IMMULITE 2000 TSI assay (bridge assay) appears to be more sensitive for detecting stimulating antibodies associated with Graves' disease.**
- **The IMMULITE 2000 TSI assay results might align more reliably with clinical presentation and patient history than results obtained with either the Thyretain bioassay or the automated Roche anti-TSHR assay.**

Table 3. Agreement between each immunoassay and the bioassay.

	Agreement with Thyretain bioassay		
Immunoassays	Positive (%)	Negative (%)	Total (%)
Roche Anti-TSHR assay (TRAb)	84.4	86.9	85.2
IMMULITE 2000 TSI assay (Bridge)	91.1	84.2	88

Table 4. Resolution of discordant results for patients with known clinical history. Results in agreement with clinical history or biomarker results are highlighted in orange, uncertain interpretation in gray.

Patient	Thyretain bioassay	Roche Anti-TSHR assay (TRAb)	IMMULITE 2000 TSI assay (bridge)	Interpretation based on clinical history or TSH and FT4 results
1	Negative	Negative	Positive	GD receiving therapy
2	Negative	Negative	Positive	GD receiving therapy, TPO positive
3	Negative	Positive	Negative	Thyroiditis
4	Negative	Not tested	Positive	Previous GD, therapy discontinued
5	Negative	Positive	Positive	GD receiving therapy
6	Negative	Not tested	Positive	Previous GD, therapy discontinued
7	Negative	Negative	Positive	GD, currently pregnant
8	Negative	Positive	Positive	GD receiving therapy and euthyroid
9	Negative	Not tested	Positive	GD receiving therapy
10	Negative	Not tested	Positive	Pregnant, GD, receiving therapy
15	Positive	Negative	Negative	Uncertain diagnosis: possible GD or toxic nodular goiter
21	Positive	Not tested	Negative	Previous GD, therapy discontinued. TPO positive, Hashimoto's thyroiditis

Product availability may vary from country to country and is subject to varying regulatory requirements. Please contact your local representative for availability.

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