

# Graves' Disease and Thyroid Stimulating Immunoglobulins: An Improved Diagnostic Tool?

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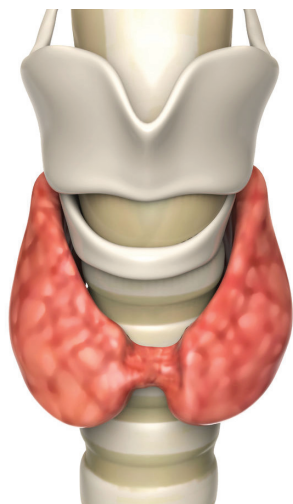
*Helicobacter pylori* Serologic Testing to Be Discontinued

*"Quality in Laboratory Diagnosis"*



# Graves' Disease and Thyroid Stimulating Immunoglobulins: An Improved Diagnostic Tool?

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Graves' disease, one of the most common forms of hyperthyroidism, has an incidence of approximately 5 in 10,000 people per year, affecting 13 million, and targets women seven times as often as men. <sup>(1)</sup> Graves' disease is an autoimmune disorder caused by the presence of thyroid-stimulating immunoglobulins (TSI) that bind to the TSH receptor on the thyroid cells

and stimulate the uncontrolled production of thyroid hormone.

Although the presence of TSI in the serum of patients known to have Graves' disease is significant to the disease, the direct screening for this autoantibody has not been used as a primary tool in its diagnosis. Rather, the diagnosis is typically derived from the clinical history, the physical examination and a panel of diagnostic tests, which includes the measurement of serum levels of thyroid stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4) or free T4. This has been the case because the direct measurement of TSI is relatively complex (tissue culture followed by radioimmuno-assay), is relatively expensive, has a longer turn-around time, and is subject to some assay interferences. Nonetheless, detecting the presence of TSI in the blood can be a powerful diagnostic tool for the differential diagnosis of Graves' disease. <sup>(2)</sup>

TSI measurements are also used to monitor the response to Graves' disease therapy <sup>(3)</sup>, predication of remission or relapse <sup>(4)</sup>, confirmation of Graves' ophthalmopathy <sup>(5)</sup>, and prediction of hyperthyroidism in neonates. <sup>(6)</sup> Incorporating a TSI assay into existing diagnostic algorithms has been shown to reduce overall direct costs of Graves' disease diagnosis by up

to 43%, with the net cost of avoiding misdiagnosis reduced by up to 85%.<sup>(7)</sup>

Recently, an automated semi-quantitative assay, which detects only TSI, the specific cause of Graves' disease pathology, has become available. <sup>(8)</sup> The manufacturer evaluated serum samples from 361 treated and untreated hyperthyroid Graves' disease patients, and 404 individuals with other thyroid or autoimmune diseases. At a cut-off of 0.55 IU/L, the clinical sensitivity and specificity for Graves' disease were 98.6% and 98.5% respectively. In comparison, the clinical sensitivity and specificity of the current tissue culture/radioimmunoassay procedure is 92.0% and 99.4%, with 7.6% invalid (null) results. <sup>(9)</sup>

The clinical sensitivity and specificity of assays can, at times, appear to be abstract or confusing. Let me share two clinical examples from our in house analytical validation.

**Patient #1:** Currently demonstrating clinical symptoms of hyperthyroidism. TSH = <0.01 mIU/L (reference range: 0.4 – 4.5 mIU/L), free T4 = 1.25 ng/dL (reference range: 0.8 – 1.8 ng/dL), free T3 = 3.7 pg/mL (reference range: 2.3 -4.2 pg/mL). Thus, this patient is clinically symptomatic, has a low TSH, but a normal free T4 and free T3. Follow up studies were TSI by bioassay = <89 % of baseline (reference range: <140%), thyroid scan: consistent with Graves' disease. Final clinical diagnosis: Graves' disease. TSI by chemiluminescence = 0.925 IU/L (>0.55 IU/L is consistent with Graves' disease.)

**Patient #2:** Currently asymptomatic. Referred to an endocrinologist for low TSH and presumed subclinical hyperthyroidism. TSH = 0.01 mIU/L (reference range: 0.4 – 4.5 mIU/L), free T4 = 2.53 ng/dL (reference range: 0.8 - 1.8 ng/dL). Follow up studies were ultrasound, which showed a slightly enlarged thyroid and TSI by bioassay: <89 % of baseline (reference range: <140%). Final clinical diagnosis:

“goiter”. TSI by chemiluminescence = 7.98 IU/L (>0.55 IU/L is consistent with Graves’ disease).

We believe that the TSI assay by chemiluminescence accurately confirms the diagnosis of Graves’ disease in Patient #1 and strongly suggests the development of Graves’ disease in Patient #2, despite the normal TSI bioassay. The use of this new direct TSI assay can make the differential diagnosis of Graves’ disease faster and easier, allowing patients to be diagnosed and treated sooner.

This assay is available from Warde Medical Laboratory as Test Code TSI, effective June 28, 2016.

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# Helicobacter pylori Serologic Testing to Be Discontinued

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The serologic evaluation for IgG antibodies to *Helicobacter pylori* (*H. pylori*) has come under increased scrutiny in the last several years. Evidence is mounting that when non-invasive testing is indicated for detection of *H. pylori* infection, the urea breath test (UBT) and the *H. pylori* stool antigen test (SAT) provide superior performance characteristics for the documentation of infection.<sup>(1-3)</sup> Although the UBT and SAT may be affected by previous proton pump inhibitor (PPI) or antimicrobial therapy, they likely have sensitivity, specificity, and positive predictive value (PPV) well in excess of 90% for the detection of active *H. pylori* infection.<sup>(1)</sup> On the other hand, serologic screening for *H. pylori* infection has cited sensitivity in the range of 76 to 84%, with specificity in the range of 79 to 90%.<sup>(1, 4, 5)</sup> While the prevalence of *H. pylori*

infection worldwide is high—likely in the range of 50%-- prevalence in the United States and other developed nations is lower. At prevalence rates of 20 to 30% (as is the case for many regions of the US), there is evidence that the positive predictive value of *H. pylori* serologic testing may dip to about 50%, substantially limiting its clinical utility.<sup>(1, 5)</sup> Furthermore, serologic testing cannot be used to monitor disease after therapy, since IgG antibodies may persist for many years following the eradication of infection.<sup>(1-3)</sup>



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For the last decade or so, both the American Gastroenterology Association (AGA) and the American College of Gastroenterology (ACG) have recommended either the UBT or SAT as an initial step in the workup of possible *H. pylori* infection.<sup>(1, 3)</sup> Current diagnostic algorithms for the non-invasive assessment of patients for possible *H. pylori* infection no longer include serologic evaluation.<sup>(6)</sup> In the face of accumulating evidence on this topic, large national reference laboratories such as Quest Diagnostics, Mayo Medical Laboratories, and ARUP no longer offer *H. pylori* serologic testing on their test menus, and many insurance companies no longer cover patients' costs for this testing.

In light of an emerging consensus that serologic testing for *H. pylori* is not clinically useful, Warde Medical Laboratory will discontinue its *H. pylori* IgG antibody assay effective September 1, 2016. For the initial non-invasive (non-endoscopic) workup of *H. pylori*, either the UBT or the SAT is now recommended. For best results from these assays, the use of PPIs, bismuth-containing compounds, or antibiotics should be discontinued for two weeks prior to testing. Additional information on ordering and collection requirements for these tests may be obtained by contacting Warde client services at 800-760-9969.

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Volume 26 Issue 2, 2016

## The Warde Report

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