Autoimmune Thyroid Disease

**Indications for Ordering**
- Differentiate autoimmune-mediated thyroid disease (eg, Hashimoto thyroiditis, Graves disease [GD]) from other etiologies for hypo- or hyperthyroidism
- Predict risk of fetal thyroid dysfunction in mothers with history of GD
- Establish an autoimmune cause for recurrent miscarriage

**Test Description**

**Thyroid Stimulating Immunoglobulin (TSI)**
- Semiquantitative bioassay – TSHR-expressing cell line with a modified G protein (GNAS)
  - Improves sensitivity by increasing cAMP levels following receptor stimulation
- Quantitative chemiluminescent immunoassay – detects cAMP

**Thyroid Stimulating Hormone Receptor Antibody (TRAb)**
- Quantitative electrochemiluminescent immunoassay

**Thyroid Peroxidase (TPO) Antibody**
- Quantitative chemiluminescent immunoassay

**Thyroglobulin (TG) Antibody**
- Quantitative chemiluminescent immunoassay

**Tests to Consider**

**Typical testing strategy**
Autoimmune thyroid testing performed when hypo- or hyperthyroidism or subclinical hypo- or hyperthyroidism is suspected based on clinical signs/symptoms and thyroid function testing (TSH and free T4) (see guidelines below)

**Primary tests**

**Thyroid Stimulating Immunoglobulin 0099430**
- Acceptable testing for autoimmune thyroid disease
- Prognostic marker for relapse of GD or remission following drug therapy
- Support GD diagnosis in difficult (euthyroid) cases
- Predict risk of thyroid dysfunction in newborns of mothers with GD

**Thyroid Stimulating Hormone Receptor Antibody (TRAb) 2002734**
- Acceptable test for autoimmune thyroid disease
- Aids in the differentiation of GD from factitious thyrotoxicosis, postpartum thyroiditis, or toxic nodular goiter
- Prognostic marker for relapse of GD or remission following drug therapy
- Predict risk of thyroid dysfunction in newborns of mothers with GD
- Evaluate for the presence of euthyroid GD ophthalmopathy

**Thyroid Peroxidase (TPO) Antibody 0050075**
- Primary test for Hashimoto thyroiditis
- Secondary testing for GD
  - Aids in the differentiation of GD from factitious thyrotoxicosis, postpartum thyroiditis, or toxic nodular goiter
- Predict progression to hypothyroidism in individuals with subclinical hypothyroidism
- Evaluate individuals with recurrent miscarriage, with or without infertility issues

**Thyroglobulin Antibody 0050105**
- Diagnose autoimmune thyroid disease when TPO antibody measurements are negative and a high clinical suspicion exists for autoimmune thyroid disease
- Predict progression to hypothyroidism in individuals with subclinical hypothyroidism (eg, Hashimoto thyroiditis)

**Thyroid Antibodies 0050645**
- Test panel composed of TPO and TG antibody tests

**Disease Overview**

**Prevalence**
- GD – <1%
  - Most common cause of hyperthyroidism in U.S.
- Hashimoto thyroiditis-associated hypothyroidism – 1-2%
- Both diseases affect women more than men

**Age of onset**
- GD – 20-40 years
- Hashimoto thyroiditis-associated hypothyroidism – 40-60 years
Symptoms

Hypothyroidism
- Fatigue, weakness
- Weight gain
- Cold intolerance
- Constipation
- Dry, brittle skin and nails
- Depression

Hyperthyroidism
- Hyperactivity
- Weight loss
- Heat intolerance
- Anxiety
- Hair loss
- Irritability
- Pretibial myxedema (GD)
- Exophthalmos (GD)

Physiology

GD
- Anti-TSH receptor IgG autoantibodies bind to the TSH receptor
  - Activation and subsequent secretion of thyroxine (T4) and triiodothyronine (T3)
    - Hyperthyroidism develops
- TSH levels fall due to T3/T4 feedback to the hypothalamus and pituitary

Hashimoto thyroiditis
- Autoimmune destruction of thyrocytes
  - Autoantibodies against TPO, TG, and TSHR antibodies likely contribute to the destruction of thyroid tissue
  - Hypothyroidism develops

Prognostic issues

GD and pregnancy
- Women with GD treated with radioactive iodine or thyroidectomy prior to pregnancy
  - Test for anti-TRAb antibodies
    - During the first trimester and at 20-26 weeks (if initially elevated) OR
    - Only at 20-26 weeks
  - Antibody-positive mothers – at risk for fetal/infant hypothyroidism

Test Interpretation

Sensitivity/specificity

Thyroid Stimulating Hormone Receptor Antibody (TRAb)
- Analytical sensitivity – 0.9 IU/L limit of detection
- Analytical specificity – 88.9%

Thyroid Peroxidase (TPO) Antibody
- Analytical sensitivity – 0.25 IU/mL limit of detection
- Clinical sensitivity
  - GD – ~75%
  - Hashimoto thyroiditis – >90%

Results

GD
- Positive – elevated TSI antibodies and/or TRAb
  - Consistent with autoimmune thyroid disease
  - GD likely if individual has signs/symptoms and biochemical evidence of hyperthyroidism
- Negative – no evidence of TSI antibodies and/or TRAb
  - NOT consistent with GD

Hashimoto thyroiditis
- Positive – elevated TPO and/or TG antibodies
  - Consistent with autoimmune thyroid disease
  - Hashimoto thyroiditis likely if individual has signs/symptoms and biochemical evidence of hypothyroidism
  - Elevated TPO antibodies in individual with subclinical hypothyroidism
    - Associated with an increased risk of developing hypothyroidism versus those without elevated TPO antibody titers
- Negative – no evidence of TPO and/or thyroglobulin antibodies
  - NOT consistent with Hashimoto disease

Limitations

Thyroid Stimulating Immunoglobulin (TSI)
- Blocking antibodies specific to TSHR may decrease TSI antibody levels
  - Net response is most likely physiologic
  - TSH serum levels ≥6 mU/L may cause a false-positive result

Thyroglobulin Antibody
Presence of other nonthyroid autoimmune diseases may cause a false-positive result

References

- Hyperthyroidism and Other Causes of Thyrotoxicosis: Management Guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists (May/June 2011)
- Clinical Practice Guidelines for Hypothyroidism in Adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association (Nov/Dec 2012)