TRICORE

CELIAC DISEASE TESTING

Celiac disease (CD), or gluten-sensitive enteropathy, is a nonallergic, autoimmune-mediated sensitivity to gluten in genetically susceptible individuals. Initial testing for CD typically includes assessment of the serum immunoglobulin A (IgA) level, followed by the appropriate tissue transglutaminase (tTG) antibody test (IgA or IgG, depending on whether or not the patient is IgA deficient). Duodenal biopsy remains the gold standard for diagnostic confirmation of CD, and HLA-DQ2 and HLA-DQ8 genotyping may be useful in risk estimation or disease exclusion. CD risk varies among ethnicities and geographic regions, suggesting that environmental and/or lifestyle risk factors may play a role in disease etiology.

INDICATIONS FOR TESTING

Children and Adolescents

Unexplained gastroenterologic symptoms, poor growth, delayed puberty, iron-deficiency anemia, and abnormal liver testing in children or adolescents warrant testing for CD. Children and adolescents with a specific risk factor for CD should be tested as well, even if they are asymptomatic. Risk factors include autoimmune disorders (type 1 diabetes mellitus, autoimmune thyroiditis, autoimmune liver disease), syndromes associated with CD (Down, Turner, or Williams syndromes), selective IgA deficiency, and first-degree relatives with CD.

Adults

Unexplained gastrointestinal symptoms, unexplained iron deficiency, dermatitis herpetiformis, recurrent aphthous stomatitis, early-onset osteoporosis, delayed puberty/unexplained short stature, or alopecia areata prompt CD testing in adults. Adults with a risk factor for CD should also be tested, even if asymptomatic. Risk factors in adults include family history of CD, syndromes associated with CD (Down syndrome, Turner syndrome), autoimmune disease associated with CD (eg, type 1 diabetes mellitus, thyroid disease, inflammatory bowel disease, or selective IgA deficiency.

CRITERIA FOR DIAGNOSIS

The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) has suggested the following criteria for the diagnosis of CD :

- Positive anti-tTG, anti-deamidated gliadin peptide (DGP), or endomysial antibody (EMA) serologic test, plus biopsy consistent with CD, or
- HLA-DQ2 or HLA-DQ8 positivity in the presence of CD symptoms and high levels of anti-tTG antibodies (more than 10 times the upper limit of normal)

The patient should be on a gluten-containing diet when undergoing any serologic CD test or biopsy.

The American College of Gastroenterology, the World Gastroenterology Association, and the American Gastroesophageal Association have issued similar criteria for CD diagnosis.

LABORATORY TESTING

Diagnosis

IgA Deficiency Testing

The concentration of serum IgA is performed first. If the patient is IgA deficient, serologic testing will be performed using IgG tests to prevent false-negative antibody results.

Tissue Transglutaminase Antibodies and Deamidated Gliadin Peptide Antibodies

The anti-tTG IgA test is the recommended screening test for IgA-competent individuals with possible CD, particularly in patients older than 3 years. The higher the level, the greater the likelihood that the result is a true positive. The anti-DGP IgA test can increase the sensitivity of anti-tTG IgA with a slight decrease in specificity. If both are negative and there is strong suspicion of CD, testing for anti-DGP IgG should be considered, particularly in patients less than 3 years of age. To rule out transient seropositivity, patients with low antibody levels but normal small-intestine mucosa should have serologic tests repeated in 6 months while continuing to consume gluten. In patients with IgA deficiency, anti-tTG IgG and anti-DGP IgG testing is performed.

Note: Children under 3 years of age with sufficient total IgA will have anti-tTg IgA and anti-DGP IgA performed. If both are negative, anti-DGP IgG with be performed reflexively.

[1] Husby S, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr 2012;54:136-160.

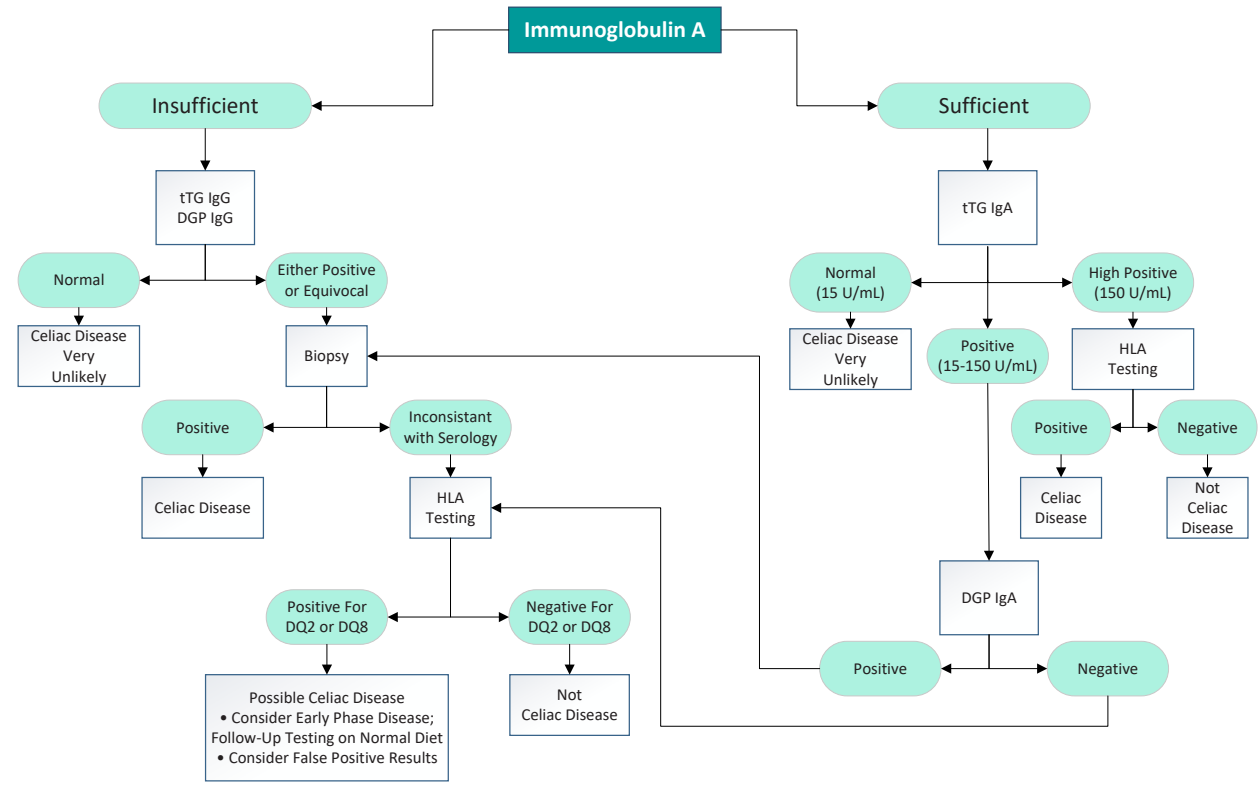
HLA Genotyping

Associations of HLA-DQ2 and HLA-DQ8 with CD are among the strongest HLA-disease associations discovered. HLA-DQ2 is present in approximately 90% of patients with CD whereas the remaining 5-10% of patients with CD carry HLA-DQ8. The presence of HLA-DQ2 or HLA-DQ8 is necessary but not sufficient for the development of CD. Although the presence of these genes cannot confirm CD, their absence essentially excludes CD. HLA genotyping is not necessary for routine laboratory evaluation of CD due to its low positive predictive value, but testing may be indicated in patients at risk for CD, individuals who are repeatedly seropositive but biopsy negative, and patients avoiding biopsy. HLA typing is useful for ruling out CD in individuals who belong to groups at risk for the disease, such as first-degree relatives of patients with confirmed CD, or individuals with other conditions known to be associated with CD, such as autoimmune diseases, type I diabetes, liver and thyroid disease, and diseases associated with chromosomal abnormalities, such as Williams, Turner, and Down syndromes.

Monitoring

Monitoring should be performed to assess therapeutic response to change in diet and patient compliance with diet. Monitoring tests include the same serologic tests recommended for diagnosis. Anti-tTG or anti-DGP can be used, depending on previous results, to monitor adherence to a gluten-free diet. In cases of IgA deficiency, IgG testing should be used. Testing is recommended every 3-6 months after initial diagnosis until abnormal baseline results have normalized or until patient is clinically stabilized, then every 1-2 years. If antibody levels remain elevated after more than 12 months on a gluten-free diet, consider repeating biopsy. A decline in antibody levels may correlate with normalization of the intestinal villi.

Celiac Disease Testing Algorithm



tTG IgA	Tissue Transglutaminase Antibody, IgA
tTG IgG	Tissue Transglutaminase Antibody, IgG
DGP IgA	Deamidated Gliadin Peptide Antibody, IgA
DGP IgG	Deamidated Gliadin Peptide Antibody, IgG
HLA	Celiac Disease Genotyping (HLA-DQ2 and HLA-DQ8)

TRICORE

CELIAC DISEASE TESTING, continued

TRICORE TEST INFORMATION

TEST NAME	CELIAC DISEASE PANEL WITH REFLEX	HLA GENETIC TESTING FOR CELIAC DISEASE, DQA AND DQB LOCI
Test Code	CELIAC	HLACEL
Test Components	IgA, serum tTG, IgA or IgG DGP, IgA or IgG	HLA-DQ genes (HLA-DQA1 and HLA-DQB1)
Specimen Type	whole blood	whole blood
Acceptable Container Type	gold top tube (SST)	lavender top tube (EDTA)
Stability	ambient: 8 hours refrigerated: 7 days frozen: 1 year	ambient: 5 days refrigerated: 5 days frozen: unacceptable
Specimen Processing	Allow specimen to clot for 20-30 minutes and then centrifuge. If using a non-gel barrier tube, separate serum into a transport tube and refrigerate.	Do not centrifuge. Do not open or share tube.
Shipping Instructions	refrigerated	ambient