

See below for Additional Technical Information topics
Celiac Disease (HLA-DQ2 and HLA-DQ8)
Celiac Disease (Initial Testing)

Celiac Disease (HLA-DQ2 and HLA-DQ8)

Indications for Ordering

- Do not use in the initial evaluation for celiac disease (CD)
- Useful in ruling out CD (high negative predictive value) in selective clinical situations, such as
 - Equivocal small bowel histologic finding (Marsh I-II) in seronegative individuals
 - Evaluation of individuals on a gluten-free diet (GFD) not tested for CD prior to starting diet
 - Individuals with discrepant celiac-specific serology and histology
 - Strong serologic evidence and clinical suspicion and desire to avoid small bowel biopsy (eg, children)

Test Description

Polymerase chain reaction (PCR) followed by melting curve analysis

Tests to Consider

Primary test

[Celiac Disease \(HLA-DQ2, and HLA-DQ8\) Genotyping 2005018](#)

Related tests

[Celiac Disease Reflexive Cascade 2008114](#)

- Preferred reflex screening test for CD
- Depending on initial results from IgA screening, one or more of the following tests may be added for clinical interpretation
 - Tissue Transglutaminase Antibody, IgA
 - Tissue Transglutaminase Antibody, IgG
 - Endomysial Antibody, IgA by IFA
 - Deamidated Gliadin Peptide (DGP) Antibody, IgA
 - Deamidated Gliadin Peptide (DGP) Antibody, IgG
 - Celiac Disease Dual Antigen Screen
- May aid in monitoring adherence to gluten-free diet (GFD)

tTG tests

- [Tissue Transglutaminase \(tTG\) Antibody, IgA 0097709](#)
- [Tissue Transglutaminase Antibody, IgG 0056009](#)
 - Recommended single screening test for CD
 - IgA testing recommended to identify IgA deficiency prior to ordering tTG test
 - Use IgA test in individuals who are IgA competent
 - Use IgG test in individuals who are IgA deficient
 - May aid in monitoring adherence to GFD

EMA tests

- [Endomysial Antibody, IgA by IFA 0050736](#)
- [Endomysial Antibody, IgG 2005501](#)
 - Acceptable single screening test for CD
 - IgA testing recommended to identify IgA deficiency prior to ordering EMA test
 - Use IgA test in individuals who are IgA competent
 - EMA IgA is an acceptable follow-up test for weakly positive or negative tTg IgA screen
 - Use IgG test in individuals who are IgA deficient
 - May aid in monitoring adherence to GFD

DGP tests

- [Deamidated Gliadin Peptide \(DGP\) Antibody, IgA 0051357](#)
- [Deamidated Gliadin Peptide \(DGP\) Antibody, IgG 0051359](#)
 - Acceptable single screening test for CD
 - IgA testing recommended to identify IgA deficiency prior to ordering DGP test
 - Use IgA test in individuals who are IgA competent
 - Use IgG test in individuals who are IgA deficient
 - May be useful in diagnosing children <2 years who test negative for tTG and EMA antibodies
 - May aid in monitoring adherence to GFD

Dual antigen tests

[Celiac Disease Dual Antigen Screen 0051689](#)

- Acceptable single screening test for CD
- Screen includes tTG antibodies IgA and IgG, and DGP antibodies IgA and IgG

[Celiac Disease Dual Antigen Screen with Reflex 2002026](#)

- Acceptable reflexive screening test for CD
- Screen includes tTG antibodies IgA and IgG, and DGP antibodies IgA and IgG
 - Positive screen reflexes to IgA antibody testing for tTG and DGP
 - Negative IgA testing for tTG and DGP reflexes to IgG antibody testing for tTG and DGP
 - Negative screen – no further testing

Overview

Prevalence – 1/133 in U.S.

Symptoms

- Gastrointestinal
 - Diarrhea
 - Weight loss, anorexia
 - Lactose intolerance
 - Abdominal distention
- Nongastrointestinal
 - Joint pain/inflammation
 - Migraines
 - Epilepsy
 - Depression
 - Osteopenia/osteoporosis
 - Delayed puberty/short stature
 - Infertility
 - Dermatitis herpetiformis
 - Iron deficiency anemia
- Often diagnosed after a prolonged period due to
 - Variability of symptoms
 - Overlap of symptoms with other conditions

Diagnosis

Based on the following

- Classic histological findings on small bowel biopsy
- Celiac disease-associated antibodies
- Improvement with GFD
- Presence of HLA antibodies for equivocal cases

Genetics

Genes – *HLA-DQ2*, *HLA-DQ8*

Inheritance – multifactorial

Mutations

- *HLA-DQ2* (encoded by *HLA-DQA1*05* and *HLA-DQB1*02*)
 - DQ2 present in >90% of individuals with CD
 - DQ2 present in 20-30% of the general population
- *HLA-DQ8* (encoded by *HLA-DQB1*03:02*)
 - DQ8 present in ~5-10% of individuals with CD
 - DQ8 present in 10% of the general population

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity – 100%
- Clinical specificity – 3%
- Analytical sensitivity/specificity – >99%
- Negative predictive value – >99%

Results

- Positive
 - Both alleles (*HLA-DQA1*05* and *HLA-DQB1*02*) of *HLA-DQ2* heterodimer identified in a symptomatic individual
 - Supports CD diagnosis
 - Further celiac confirmation testing recommended
 - Identification of one portion of the *HLA-DQ2* heterodimer
 - Rarely observed in CD
 - If strong suspicion exists, further celiac testing may be helpful
 - *HLA-DQ8* identified in a symptomatic individual
 - Supports CD diagnosis
 - Further celiac confirmation testing recommended
- Negative
 - No copy of *HLA-DQ2* heterodimer or *HLA-DQ8* identified
 - Diagnosis of CD is likely excluded
 - No further celiac testing recommended
 - Rare exceptions to these HLA associations have been occasionally observed

Limitations

- Rare diagnostic errors may occur due to primer-site mutations
- Copy number of each detected allele will not be determined
- Alleles other than *HLA-DQ2* and *HLA-DQ8* will not be identified
- Other genetic and nongenetic factors that influence celiac disease are not evaluated

Celiac Disease (Initial Testing)

Indications for Ordering

Test for suspected celiac disease (CD) when symptoms of bloating, diarrhea, and unexplained abdominal pain are present

Test Description

Semiquantitative indirect immunofluorescence antibody (IFA)

Tests to Consider

Typical testing strategy

- Preferred initial tests are celiac disease reflexive cascade or anti-tissue transglutaminase (tTG) antibody for individuals >2 years
- EMA testing is an acceptable initial test alternative but more laborious and expensive

Primary tests

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 - Evaluation of individuals who were not tested for CD prior to starting a GFD
 - Individuals with discrepant celiac-specific serology and histology
 - Strong serologic evidence and clinical suspicion and desire to avoid small bowel biopsy (eg, children)

Disease Overview

Prevalence – 1/80-140 in Western populations

- Usually affects Caucasians of European ancestry

Age of onset – three peaks

- Infancy
- Second to third decade
- Fifth to sixth decade

Symptoms

Clinical presentation is extremely varied and tends to differ by age group

- General symptoms – anemia, fatigue, weight loss
- Pediatric symptoms – diarrhea, abdominal distention, malnutrition
 - Symptoms of malnutrition
 - Short stature
 - Anemia (typically iron deficient)
 - Defects in dentition
 - Failure to thrive
 - Developmental delay

- Adult symptoms – abdominal pain, flatulence, diarrhea, **steatorrhea** in severe cases
 - Extraintestinal symptoms
 - Fatigue and malaise (may occur independently of anemia)
 - Neurologic or psychiatric disorders
 - Neuromuscular abnormalities
 - **Infertility**
 - Mouth ulcers
 - Recurrent fetal loss
- Associated conditions
 - Osteopenic bone disease
 - Small-for-gestational-age infants
 - Dermatitis herpetiformis (DH) – symptoms of malabsorption may be absent
 - IgA deficiency
 - Increased risk of lymphoma
 - Other autoimmune disorders
 - Autoimmune adrenal disease
 - Autoimmune thyroid disease
 - Inflammatory bowel disease (IBD)
 - Primary biliary cirrhosis
 - Primary sclerosing cholangitis
 - Rheumatoid arthritis
 - Sjögren syndrome
 - Systemic lupus erythematosus (SLE)
 - Type 1 diabetes mellitus (DM)
- Higher risk in individuals with Down or Turner syndrome

Diagnostic issues

- Testing is often performed in individuals with low risk of CD, increasing the chance of false-positive indeterminate results
 - Indeterminate tTG test results pose a clinical conundrum for biopsy versus additional confirmatory testing
 - Biopsy acquisition is an invasive procedure with risks
- Addition of EMA may diminish need for biopsy in numerous individuals with indeterminate results and high suspicion of disease

- Adult CD should be confirmed with small bowel biopsy
 - Multiple biopsies of the duodenum (one or two biopsies at the bulb and at least four biopsies of the distal duodenum are recommended)
- Consider small bowel biopsy in seronegative individuals when there is strong clinical suspicion of CD

Test Interpretation

Clinical sensitivity/specificity – >99%

Results

- Positive
 - Positive result alone is not diagnostic of CD
 - Small bowel biopsy is recommended for confirmation
- In patients with suspected DH
 - Should be followed with perilesional skin biopsy for direct immunofluorescence assay
 - Results should be interpreted alongside pemphigoid and pemphigus panel tests or epithelial skin antibody tests to differentiate DH from other immunobullous skin diseases
- Negative
 - Does not rule out CD
 - HLA genotyping or small bowel biopsy is recommended in individuals with high clinical suspicion of CD

Limitations

- Correlation between celiac disease serologic tests may be variable at low antibody titers, early disease, or treatment with GFD
 - Strong clinical correlation is recommended
- At screening dilution, EMA may show prozone phenomenon
 - If suspicion for disease is strong, consider testing for tTg and/or DGP antibodies
- Sera containing anti-smooth muscle antibodies (ASMA) will interfere with the detection of EMA IgG
 - Sera should be further tested at higher dilutions
- False-negative results
 - Early disease
 - Individuals on GFD
 - Use of immunosuppression
- False-positive results
 - Consider early disease and/or specific risk for CD
- Small bowel biopsy and/or HLA DQ typing may be important in establishing a diagnosis of CD based on patient's age, clinical symptoms, and/or risk for disease