Human Leukocyte Antigen Testing for Celiac Disease

Description

Celiac disease (CD) is currently diagnosed by serology, medical history and response to a gluten free diet (GFD), with confirmation by small intestinal biopsy. Human Leukocyte Antigen (HLA) testing may be useful for ruling out disease in symptomatic patients when findings of other tests are inconclusive.

Background

CD, also referred to as celiac sprue or gluten-sensitive enteropathy, is a relatively common disorder that has variable clinical expression. Population-based screening surveys suggest a prevalence of 1 in 250 to 500 in most countries, including the U.S. However, this prevalence may vary widely depending on how the disease is defined, ie, whether only clinically apparent cases are considered, as opposed to including all individuals with any serologic or histologic evidence of disease.

CD is characterized by inflammation of the small intestine resulting from an immunologic intolerance to gluten (ie, the proteins derived from wheat, barley, and rye). The symptoms of the disease are markedly variable and can be broadly subdivided into intestinal and extraintestinal manifestations; the latter is thought to be related to nutrient malabsorption. For example, osteopenia and osteoporosis, which are commonly seen in adults with untreated CD, are related to the impaired absorption of vitamin D and binding of intraluminal calcium and magnesium to unabsorbed dietary fatty acids, forming insoluble soaps. The only treatment for celiac disease is lifelong adherence to a GFD.

Many of the symptoms of CD (eg, diarrhea, abdominal pain and weight loss) are nonspecific and are often overlooked. In addition, the disease may develop at any time in life, from infancy to very old age. In children, the disease typically presents following weaning between 6 and 24 months, and is characterized by abnormal stools, poor appetite, and irritability. In adults, diarrhea is the main presenting symptom, but presenting symptoms may be entirely nonspecific, such as anemia or infertility. Typical or classical CD refers to the presence of malabsorption, while atypical CD consists primarily of extraintestinal manifestations.

CD is a human leukocyte antigen (HLA) -associated disease. Approximately 90% to 95% of patients with CD carry the HLA-DQ2 allele and the remaining 5% to 10% carry the HLA-DQ8 allele. However, not all people with one of these 2 alleles will develop CD. It is believed that approximately 25% to 40%
of the general population of the U.S. carries either the HLA-DQ2 or HLA-DQ8 allele but only about 3% of individuals carrying the DQ2/DQ8 alleles will develop gluten intolerance. (1, 2)

Given the nonspecific nature of the symptoms, definitive diagnosis has been based on the results of small intestinal biopsies showing a flattened intestinal mucosa in association with an inflammatory infiltrate. Diagnostic criteria were first established in 1969 by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHN) and consisted of a series of 3 intestinal biopsies: at diagnosis, after institution of GFD, and the third after a repeat gluten challenge. This cumbersome method of diagnosis was revised in 1990 by simplifying the diagnostic criteria to a positive biopsy at presentation in conjunction with consistent history and serologic results, followed by a clinical response to a GFD. (3)

While a positive biopsy result is considered the criterion standard for diagnosis, serologic evaluation of patients with possible CD, together with a consistent clinical history and a positive response to a gluten-free diet, can sometimes be adequate for diagnosis. Serologic studies are also useful in triaging the large numbers of patients with nonspecific symptoms for biopsy. In approximately 10% of cases in which clinical suspicion suggests CD, serologic testing, and intestinal biopsy are nondiagnostic, either because the results of serology and biopsy are discordant, or because both tests are negative despite persistent symptoms suggestive of CD. In these cases, HLA testing may be useful for ruling out a diagnosis of celiac disease.

**Regulatory Status**

HLA typing for celiac disease is offered by several laboratories such as Quest, LabCorp, and Prometheus. There are several methods that are used for HLA typing including Simple Sequence-specific-Primer, Polymerase Chain Reaction (PCR), reverse dot blot hybridization, and real-time PCR.

**Related Policies**

6.01.33 Wireless Capsule Endoscopy as a Diagnostic Technique in Disorders of the Small Bowel, Esophagus, and Colon

**Policy**

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

HLA-DQ2 and HLA-DQ8 testing may be considered **medically necessary** to rule out celiac disease in:

- patients with discordant serologic and histologic (biopsy) findings; or
- patients with persistent symptoms despite negative serology and histology.

HLA-DQ2 and HLA-DQ8 testing for celiac disease is considered **investigational** in all other situations.
Serologic Diagnosis in Individuals with Signs or Symptoms Suggestive of Celiac Disease

National guidelines and position statements agree that serologic testing is the first step in diagnosing celiac disease (CD) and that the immunoglobulin (Ig) A antibody to human recombinant tissue transglutaminase (tTG) test is recommended. (4-6) They state that the IgA antibody to antiendomysium antibody (EMA) test has similar sensitivity and specificity to the tTG IgA test, but two of the national organizations mention that the EMA test is more prone to interpretation error. For individuals with known selective IgA deficiency, testing with tTG IgG and/or EMA IgG is recommended. The national organizations also agree that when test results are indeterminate, testing for the genetic markers HLA-DQ2 or HLA-DQ8 is recommended.

Several studies have established that human leukocyte antigen (HLA) typing has a high sensitivity and a high negative predictive value for the diagnosis of CD. For example, a 2007 prospective study by Hadithi et al included a total of 463 patients who were referred for evaluation of CD. (7) Sixteen (3.5%) of the 463 patients met ESPGHN diagnostic criteria for CD (ie, characteristic histologic findings) (Marsh III) on small-bowel biopsy and unequivocal symptom resolution after initiating a gluten-free diet. All 16 patients were positive for HLA-DQ2 and/or HLA-DQ8. In contrast, 192 of 227 (43%) of patients who did not meet diagnostic criteria for celiac disease were positive for 1 or both of these alleles. Testing positive for HLA-DQ2 or HLA-DQ8 had a positive predictive value of 7.7% (95% confidence interval [CI], 4.5% to 12%) and a negative predictive value of 100% (95% CI, 98.6 to 100%).

In 2014, Pallav et al published a retrospective report of HLA testing in 256 patients with known or suspected CD. (8) Taking into account all available clinical and laboratory data, a total of 44 patients were diagnosed with CD and, in 173 patients, CD was ruled out. A final diagnosis could not be obtained in 39 of 256 (15%) patients. HLA-DQ2 or DQ8 was absent in 40% of non-CD patients and 2 CD patients. The negative predictive value was 98%. A total of 154 patients were found to carry HLA-DQ2 or DQ8 alleles. Forty-two of the 44 patients diagnosed with CD tested positive for 1 or both of the HLA alleles, with a test sensitivity of 95.5%. The diagnostic accuracy data are somewhat limited by the 15% of patients without a definitive diagnosis.

Practice Guidelines and Position Statements

American College of Gastroenterology (ACG): A 2013 guideline on the diagnosis and management of CD stated the following on HLA testing:

1. HLA-DQ2/DQ8 testing should not be used routinely in the initial diagnosis of CD (Strong recommendation, moderate level of evidence).
2. HLA-DQ2/DQ8 genotyping testing should be used to effectively rule out the disease in selected clinical situations (Strong recommendation, moderate level of evidence).
3. Examples of such clinical situations include but are not limited to:
   - Equivocal small-bowel histological finding (Marsh I-II) in seronegative patients
   - Evaluation of patients on a gluten-free diet (GFD) in whom no testing for CD was done before GFD
- Patients with discrepant celiac-specific serology and histology
- Patients with suspicion of refractory CD where the original diagnosis of celiac remains in question
- Patients with Down's syndrome.’ (9)

European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHN): A 2012 guideline on the diagnosis of CD stated that HLA-DQ2/HLA-DQ8 testing should be offered to patients with an uncertain diagnosis of celiac disease eg, those with negative CD-specific antibodies and mild infiltrate changes in small-bowel specimens. A negative finding renders celiac disease highly unlikely in these individuals. (10)

The National Institute for Health and Clinical Excellence (NICE): A 2009 guideline by this U. K.-based organization on CD includes the following statement on HLA typing:

"Do not use human leukocyte antigen (HLA) DQ2/DQ8 testing in the initial diagnosis of coeliac disease. (However, its high negative predictive value may be of use to gastrointestinal specialists in specific clinical situations." (11)

American Gastroenterological Association: In 2006, the American Gastroenterological Association issued a position statement on the diagnosis and management of CD. Regarding serologic testing, they concluded that, in the primary care setting, the transglutaminase immunoglobulin (Ig) A antibody test is the most efficient single serologic test for diagnosing CD. They state that the antiendomysial antibodies (EMA) IgA test is more time-consuming and operator dependent than the tTG. If IgA deficiency is strongly suspected, testing with IgG EMA and/or tTG IgG antibody test is recommended. If serologic test results are negative and celiac disease is still strongly suspected, providers can test for the presence of the disease-associated HLA alleles and, if present, perform small intestinal mucosal biopsy. Alternatively, if signs and symptoms suggest that small intestinal biopsy is appropriate; patients can proceed to biopsy without testing for HLA alleles. (5)

National Institutes of Health (NIH): The NIH issued a Consensus Development Conference Statement in June 2004 based on a 2-day meeting and literature reviews by the University of Ottawa Evidence-based Practice Center. NIH considered serologic testing as the first step in pursuing a diagnosis of CD and stated that the best tests are the tTG IgA and EMA IgA tests, which they considered to be of equivalent accuracy. In individuals with suggestive symptoms and negative tTG IgA or EMA tests, consider an IgA deficiency and, if identified, it is recommended that a tTG IgG or EMA IgG be performed. When diagnosis is uncertain due to indeterminate test results, an option according to the NIH statement is to test for the genetic markers HLA-DQ2 or HLA-DQ8. Biopsy of the proximal small bowel is indicated in those with a positive CD antibody test, except those with biopsy-proven dermatitis herpetiformis. No specific approach was suggested when there is positive serology and normal biopsy findings. Options include additional biopsies, repeat serology testing, and a trial of a GFD. Testing is indicated in individuals with gastrointestinal symptoms and other signs and symptoms suggestive of celiac disease. (4)
U.S. Preventive Services Task Force Recommendations

As of April 2015, there are no recommendations from the U.S. Preventive Services Task Force (USPSTF) related to screening for celiac disease in children or adults.

Summary

Several studies have reported that the sensitivity and negative predictive value of HLA testing for celiac disease is 100%, meaning that this test is highly accurate for ruling out CD. In contrast, a substantial number of patients who do not have CD carry the HLA-DQ2 and/or HLA-DQ8 alleles, resulting in suboptimal specificity, meaning that this test is less accurate for confirming the diagnosis. National recommendations and study data support the conclusion that HLA typing is useful for ruling out celiac disease when patients have discordant serologic and histologic (biopsy) findings or when patients have persistent symptoms despite negative serology and histology. Thus, HLA typing may be considered medically necessary in these situations and is otherwise considered investigational.

Medicare National Coverage

There is no national coverage determination.

References

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Subject: Human Leukocyte Antigen Testing for Celiac Disease  
Page: 6 of 6


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<thead>
<tr>
<th>Date</th>
<th>Action</th>
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This policy was approved by the FEP® Pharmacy and Medical Policy Committee on September 18, 2015 and is effective October 15, 2015.

Signature on file
Deborah M. Smith, MD, MPH