BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.95 Human Leukocyte Antigen Testing for Celiac Disease

Annual Effective Policy Date: January 1, 2024

Original Policy Date: December 2023

Related Policies:

6.01.33 - Wireless Capsule Endoscopy for Gastrointestinal (GI) Disorders

Human Leukocyte Antigen Testing for Celiac Disease

Description

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Celiac disease (CD) is currently diagnosed by serology, medical history, and response to a gluten-free diet, 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.

OBJECTIVE

The objective of this evidence review is to assess whether human leukocyte antigen (*HLA)-DQ2* and *HLA-DQ8* genotype testing improves the net health outcome in patients who are suspected of having celiac disease or have symptomatic celiac disease.

POLICY STATEMENT

Human leukocyte antigen *(HLA)-DQ2* and *HLA-DQ8* testing may be considered **medically necessary** to rule out celiac disease in:

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

HLA-DQ2 and *HLA-DQ8* testing for celiac disease is considered **investigational** in all other situations.

POLICY GUIDELINES

None

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Some Plans may have contract or benefit exclusions for genetic testing. Serologic diagnosis of celiac disease may be offered by reference laboratories specializing in the evaluation of gastrointestinal diseases.

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Several methods are used for HLA typing, including simple sequence-specific-primer, polymerase chain reaction, reverse dot blot hybridization and real-time polymerase chain reaction. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

RATIONALE

Summary of Evidence

For individuals who are suspected of having celiac disease (CD) and have negative or discordant serologic and biopsy findings, the evidence includes a systematic review and several retrospective and prospective cohort studies. Relevant outcomes are test validity, other test performance measures, and changes in disease status. Several studies have reported that the sensitivity and negative predictive value (NPV) of Human leukocyte antigen (*HLA)-DQ2* and *HLA-DQ8* genotype testing for CD approached 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. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Gastroenterology

In 2013, a guideline from the American College of Gastroenterology stated the following:

"1. *HLA-DQ2/DQ8* testing should not be used routinely in the initial diagnosis of CD [celiac disease] (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 in whom no testing for CD was done before gluten-free diet
- Patients with discrepant celiac-specific serology and histology
- Patients with suspicion of refractory CD where the original diagnosis of celiac remains in question."[9,]

National Institute for Health and Care Excellence

The 2009 NICE guidance, which was updated in 2015, on celiac disease (CD) included the following statement on human leukocyte antigen (HLA) typing:

"Do not use human leukocyte antigen (*HLA) DQ2* (*DQ2.2* and *DQ2.5*)/*DQ8* testing in the initial diagnosis of coeliac disease in non-specialist settings.

Only consider using *HLA DQ2* (*DQ2.2* and *DQ2.5*)/*DQ8* testing in the diagnosis of coeliac disease in specialist settings (for example, in children who are not having a biopsy, or in people who already have limited gluten ingestion and choose not to have a gluten challenge)."[14,]

American Gastroenterological Association Institute

In 2021, the American Gastroenterological Association (AGA) Institute released a clinical practice update on the evaluation and management of patients with suspected enteropathy, but negative serologic test results for CD and included the following statement on HLA genetic testing:

"In cases of suspected seronegative CeD [celiac disease], genetic testing should be performed to determine whether the patient carries an HLA genotype (DQ2 or DQ8) that is compatible with developing CeD...HLA genetic testing is most helpful for patients if results are negative, as this excludes the possibility of seronegative CeD as a diagnosis. However, compatible genetics infer that the patient has a risk of developing CeD, but these results cannot stand alone as a diagnostic criterion."[15,]

These guidelines also recommend that a gastroenterologist or CD specialist review and evaluate all reported and tested alleles before determining that a patient is HLA-negative.

In 2019, the clinical practice update on diagnosis and management of CD from the AGA Institute stated the following on human leukocyte antigen (HLA) gene testing:

"Determination of *HLA-DQ2/DQ8* has a limited role in the diagnosis of CD. Its value is largely related to its negative predictive value to rule out CD in patients who are seronegative in the face of histologic changes, in patients who did not have serologic confirmation at the time of diagnosis, and in those patients with a historic diagnosis of celiac disease; especially as very young children prior to the introduction of celiac-specific serology."[16,]

In 2006, the AGA Institute issued their original position statement on the diagnosis and management of CD. Regarding serologic testing, the Institute concluded that, in the primary care setting, the transglutaminase immunoglobulin (Ig) A antibody test is the most efficient single serologic test for diagnosing CD.[6,] The guidelines indicated that the antiendomysial antibodies IgA test is more time-consuming and operator dependent than the tissue transglutaminase (tTG) test. If IgA deficiency is strongly suspected, testing with IgG antiendomysium antibody (EMA) and/or tTG IgG antibody test is recommended. If serologic test results are negative and CD is still strongly suspected, providers can test for the presence of the disease-associated HLA alleles and, if present, perform a 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.

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

In 2016, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition, in conjunction with the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition, released a clinical report on the diagnosis and treatment of gluten-related disorders. Regarding HLA tests, the authors stated that HLA testing should not be used as an initial test used for diagnosis of CD.[17,] This testing should be reserved for patients where discrepancies are found between their serological and histologic findings, or when patients have commenced a gluten-free diet prior to any testing. In these patients, if neither *HLA-DQ2* nor *DQ8* is found upon testing, the diagnosis of CD is unlikely.

National Institutes of Health

In 2004, the National Institutes of Health issued a consensus statement based on a meeting and an independent literature review.[5,] The National Institutes of Health 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 the Institutes considered to be of equivalent accuracy. In patients with suggestive symptoms and negative tTG IgA or EMA tests, it was recommended that consideration be given to IgA deficiency and, if identified, that a tTG IgG or EMA IgG be performed. When the diagnosis of CD is uncertain because of indeterminate results, testing for certain genetic markers (HLA haplotypes) was recommended to stratify individuals into high- or low-risk for CD. Greater than 97% of individuals with CD have the *DQ2* and/or *DQ8* marker, compared with about 40% of the general population. Therefore, an individual negative for *DQ2* or *DQ8* would be extremely unlikely to have CD (high negative predictive value). Biopsy of the proximal small bowel was indicated in those with a positive CD antibody test, except those with biopsy-proven dermatitis herpetiformis. No specific approach was suggested when there was a positive serology and normal biopsy findings. Options included additional biopsies, repeat serology testing and a trial of a gluten-free diet. Testing was indicated in patients with gastrointestinal tract symptoms and other signs and symptoms suggestive of CD.

U.S. Preventive Services Task Force Recommendations

The US Preventative Service Task Force (2017) released guidelines on screening adults and children for CD.[18,] These guidelines reviewed the use of tTG IgA testing followed by an intestinal biopsy to screen asymptomatic patients. Genotype testing was not discussed. The overall conclusion of this review was that the current balance of evidence was insufficient to assess benefits and harms resulting from screening for CD.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2023	New policy	Policy updated with literature review through September 20, 2022; references added. Minor editorial refinements to policy statements; intent unchanged. FEP Benefit change. New FEP Policy