2.04.95	Human Leukocyte Antigen Testing for Celiac Disease		
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Section:	2.0 Medicine	**Page:**	Page 1 of 12

Policy Statement

I. Human leukocyte antigen *(HLA)-DQ2* and *HLA-DQ8* testing may be considered **medically necessary** to rule out celiac disease in:
   A. Individuals with persistent symptoms despite negative serology and histology
   B. Individuals with discordant serologic and histologic (biopsy) findings

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

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

- N/A

Description

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.

Related Policies

- Wireless Capsule Endoscopy for Gastrointestinal (GI) Disorders

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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.

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Rationale

Background

Diagnosis

Celiac disease (CD), also referred to as celiac sprue or gluten-sensitive enteropathy, is a relatively common disorder with variable clinical expression. Population-based screening surveys suggest a worldwide prevalence of 1% with approximately 2 million people affected in the U.S.[1,] However, this prevalence may vary widely depending on how the disease is defined, and whether only clinically apparent cases are considered, as opposed to including all people with any serologic or histologic evidence of disease.

Celiac disease is characterized by inflammation of the small intestine resulting from an immunologic intolerance to gluten (i.e., 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 CD is lifelong adherence to a gluten-free diet.

Many symptoms of CD (e.g., diarrhea, abdominal pain, 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.

Celiac disease is associated with the human leukocyte antigen (HLA). 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 1 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 people carrying the *DQ2* or *DQ8* alleles will develop gluten intolerance.[2,3,]

Given the nonspecific nature of the symptoms, the 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 and consisted of a series of 3 intestinal biopsies: at diagnosis, after the institution of a gluten-free diet, 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 a consistent history and serologic results, followed by clinical response to a gluten-free diet.[4,]

Testing

While a positive biopsy result is considered the criterion standard for diagnosis, the 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 CD.

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National guidelines and position statements recommend serologic testing as the first step in diagnosing CD and recommend the immunoglobulin (Ig) A antibody to human recombinant tissue transglutaminase test. [5,6,7,8,] Guidelines have indicated that the IgA antibody to anti-endomysium antibody test has similar sensitivity and specificity as the tissue transglutaminase IgA test, but national organizations have indicated that the anti-endomysium antibody test is more prone to interpretation error. For subjects with known selective IgA deficiency, testing with tissue transglutaminase IgG and/or anti-endomysium antibody IgG is recommended.

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Genetic Testing for Symptoms Suggestive of Celiac Disease

Clinical Context and Test Purpose

The purpose of genetic testing for the human leukocyte antigen (HLA) genes *HLA-DQ2* and *HLA-DQ8* of individuals with symptoms suggestive of celiac disease (CD) are to rule out CD in:

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

The following PICO was used to select literature to inform this review.

Populations

The relevant populations of interest are individuals with persistent symptoms of CD despite negative serology and histology and those with discordant serologic and histologic (biopsy) findings.

Interventions

The test being considered is genetic testing for the HLA genes *HLA-DQ2* and *HLA-DQ8.* 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. Commercial testing is available from numerous companies.

Comparators

The following practice is currently being used to diagnose CD: clinical management without genetic testing.

Outcomes

The general outcomes of interest are test validity, other test performance measures, and change in disease status.

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The potential beneficial outcomes of primary interest would be the avoidance of all downstream consequences that occur with a lack of correct diagnoses such as the use of ineffective disease management options or the gain of benefits that occur with a correct diagnosis such as the use of appropriate and effective disease management options. Implementation of an empirical gluten-free diet in individuals with clinical ambiguity may not only be ineffective but may also lead to inconvenience without any benefit. An early confirmed diagnosis can avoid delays in appropriate treatment and lifestyle changes and subsequent avoidance of morbidity associated with the disease. False-positive or false-negative test results can lead to the initiation of unnecessary treatment and adverse events from that treatment or undertreatment.

Genetic testing for *HLA-DQ2* and *HLA-DQ8* alleles may be performed at any point during a lifetime.

Study Selection Criteria

For the evaluation of the clinical validity of this test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Reviews

A report conducted by Maglione et al (2016) for the Agency of Healthcare Research and Quality indicated that HLA testing could be used to rule out CD with close to 100% sensitivity.[9,] The report cited the 2013 American College of Gastroenterology estimates[10,] of negative predictive value (NPV) of the *HLA-DQ2* and *-DQ8* combination test at over 99%. In the Agency report, 2 studies were cited on the accuracy of HLA testing; a large 2013 prospective cohort study found that HLA testing had a sensitivity of 100% and specificity of 18.2%. A 1999 cohort study also reported a sensitivity of 100% and a specificity of 33.3%.

Prospective and Retrospective Studies

Several studies have established that HLA typing has high sensitivity and a high NPV for the diagnosis of CD. Werkstetter et al (2017) reported on the results of a large, international prospective study to validate a biopsy free approach for diagnosis of CD in symptomatic children with levels of immunoglobulin A against tissue-transglutaminase (TGA-IgA) 10 times or more the upper limit of normal, confirmed by positive findings for *HLA-DQ2*, *-DQ8*, and endomysium antibodies.[11,] The primary aim was to determine whether the nonbiopsy approach would identify children with CD with a positive predictive value (PPV) above 99% in clinical practice. Data on symptoms, total IgA, TGA, endomysium antibodies, and biopsy findings (reference standard) were collected from 803 consecutive pediatric patients (≤18 years) on a gluten-containing diet. When results were concordant, cases were classified as a proven CD. Those with low TGA-IgA levels (3 times or below the upper limit of normal) but without other features of CD were classified as no CD. Biopsy analyses were performed and reviewed in a blinded manner. Inconclusive cases were regarded as not having CD. Data were analyzed for 707 children (65.1% girls; median age, 6.2 years); 645 were diagnosed with CD, 46 were found not to have CD, and 16 had inconclusive results. Test results of TGA-IgA 10 times or more the upper limit of normal, detection of endomysium antibodies, and any symptom identified children with CD (n=399) with a PPV of 99.75% (95% confidence interval [CI], 98.61% to 99.99%); the PPV was 100% (95% CI, 98.68% to 100%) when only malabsorption symptoms were used instead of any symptom (n=278). The inclusion of HLA analyses did not increase accuracy.

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Oliveira et al (2022) evaluated serologic tests as markers of CD in a retrospective cohort study in 94 children with type 1 diabetes mellitus who underwent screening for CD. Type 1 diabetes mellitus confers high risk for CD and baseline propensity for *HLA-DQ2* or *-DQ8* positivity was assessed.[12,] Data for HLA testing were missing in 42 patients. Among the 52 patients with available results, 44 (84.6%) were positive for *HLA-DQ2* or *-DQ8.* Four (4.3%) patients screened positive for CD by IgA or IgG antibodies against TGA or endomysium, all of whom underwent biopsy and had histology consistent with CD. Of these 4 patients diagnosed with CD, 3 had undergone HLA testing, all of whom were positive for *HLA-DQ2* or *-DQ8*, corresponding to 100% sensitivity and NPV. Specificity and PPV of HLA testing for CD were 16.6% and 9.1%, respectively.

Pallav et al (2014) retrospectively assessed HLA testing in 256 patients with known or suspected CD.[13,] Taking into account all available clinical and laboratory data, 44 out of 256 patients were diagnosed with CD. Celiac disease was ruled out in 173 patients and a final diagnosis could not be obtained in 39 (15%) of 256 patients. *HLA-DQ2* or *-DQ8* alleles were absent in 40% of patients without CD and 2 patients with CD. The NPV 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.

A prospective study by Hadithi et al (2007) included a total of 463 patients who were referred for evaluation of CD.[14,] Sixteen (3.5%) of the 463 patients met European Society of Paediatric Gastroenterology, Hepatology and Nutrition diagnostic criteria for CD (i.e., characteristic histologic findings) (Marsh III) on small bowel biopsy and experienced unequivocal symptom resolution after initiating a gluten-free diet. All 16 patients were positive for *HLA-DQ2* and/or *HLA-DQ8*. In contrast, 192 (43%) of 447 patients who did not meet diagnostic criteria for CD were positive for 1 or both of these alleles. Testing positive for *HLA-DQ2* or *HLA-DQ8* had a PPV of 7.7% (95% CI, 4.5% to 12%) and a NPV of 100% (95% CI, 98.6% to 100%).

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Randomized controlled trials assessing the use of *HLA* testing were not identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

HLA-DQ2 and *HLA-DQ8* genotype testing in patients who are suspected of CD with discordant serologic and histologic results or in those who are symptomatic of CD but test negative for serologic and histologic tests has clinical utility based on a chain of evidence. Confirming exclusion of a diagnosis of CD in clinically ambiguous patients may lead to avoidance of improper or ineffective interventions, including the implementation of a gluten-free diet. For patients in whom CD is excluded as a diagnosis, this further allows the implementation of appropriate diagnostic strategies to ascertain true etiologies of their symptoms (i.e., microscopic colitis, Crohn disease).

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Section Summary: Genetic Testing for Symptoms Suggestive of Celiac Disease

In individuals who are suspected of having CD and have negative or discordant serologic and biopsy findings, several studies have reported that the sensitivity and NPV of *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. One prospective study found that testing positive for *HLA-DQ2* or *HLA-DQ8* had a NPV of 100% (95% CI, 98.6% to 100%) but a PPV of 7.7% (95% CI, 4.5% to 12%). Confirming exclusion of a diagnosis of CD in clinically ambiguous patients may lead to avoidance of improper or ineffective interventions, including the implementation of a gluten-free diet. For patients in whom CD is excluded as a diagnosis, this further allows the implementation of appropriate diagnostic strategies to ascertain true etiologies of their symptoms.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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."[10,]

The American College of Gastroenterology guideline for diagnosis and management of celiac disease was updated in 2023; the recommended diagnostic approach did not change since the 2013 guideline.[8,]

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)."[15,]

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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."[16,]

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."[17,]

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.[18,] 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.[19,] 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

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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.[20,] 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.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in September 2023 did not identify any ongoing or unpublished trials that would likely influence this review.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Comorbidities
  - Activity and functional limitations
  - Family history if applicable
  - Reason for procedure/test/device, when applicable
  - Pertinent past procedural and surgical history
  - Past and present diagnostic testing and results
  - Prior conservative treatments, duration, and response
  - Treatment plan (i.e., surgical intervention)
- Consultation and medical clearance report(s), when applicable
- Radiology report(s) and interpretation (i.e., MRI, CT, discogram)
- Laboratory results
- Other pertinent multidisciplinary notes/reports: (e.g., psychological or psychiatric evaluation, physical therapy, multidisciplinary pain management) when applicable

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed
- Procedure report(s)

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Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	81370	HLA Class I and II typing, low resolution (e.g., antigen equivalents); HLA-A, -B, -C, -DRB1/3/4/5, and -DQB1
	81371	HLA Class I and II typing, low resolution (e.g., antigen equivalents); HLA-A, -B, and -DRB1 (e.g., verification typing)
	81372	HLA Class I typing, low resolution (e.g., antigen equivalents); complete (i.e., HLA-A, -B, and -C)
	81373	HLA Class I typing, low resolution (e.g., antigen equivalents); one locus (e.g., HLA-A, -B, or -C), each
	81374	HLA Class I typing, low resolution (e.g., antigen equivalents); one antigen equivalent (e.g., B*27), each
	81375	HLA Class II typing, low resolution (e.g., antigen equivalents); HLA-DRB1/3/4/5 and -DQB1
	81376	HLA Class II typing, low resolution (e.g., antigen equivalents); one locus (e.g., HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each
	81377	HLA Class II typing, low resolution (e.g., antigen equivalents); one antigen equivalent, each
	81378	HLA Class I and II typing, high resolution (i.e., alleles or allele groups), HLA-A, -B, -C, and -DRB1
	81379	HLA Class I typing, high resolution (i.e., alleles or allele groups); complete (i.e., HLA-A, -B, and -C)
	81380	HLA Class I typing, high resolution (i.e., alleles or allele groups); one locus (e.g., HLA-A, -B, or -C), each
	81381	HLA Class I typing, high resolution (i.e., alleles or allele groups); one allele or allele group (e.g., B*57:01P), each
	81382	HLA Class II typing, high resolution (i.e., alleles or allele groups); one locus (e.g., HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each
	81383	HLA Class II typing, high resolution (i.e., alleles or allele groups); one allele or allele group (e.g., HLA-DQB1*06:02P), each
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
02/01/2016	BCBSA Medical Policy Adoption
06/01/2017	Policy revision without position change

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01/01/2018	Policy revision without position change
01/01/2019	Policy revision without position change
02/01/2020	Annual review. No change to policy statement. Literature review updated.
02/01/2024	Policy reactivated. Previously archived from 09/01/2020 to 01/31/2024.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

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Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
Reactivated Policy **Policy Statement:** N/A	**Human Leukocyte Antigen Testing for Celiac Disease 2.04.95** **Policy Statement:** I. Human leukocyte antigen *(HLA)-DQ2* and *HLA-DQ8* testing may be considered **medically necessary** to rule out celiac disease in: A. Individuals with persistent symptoms despite negative serology and histology B. Individuals with discordant serologic and histologic (biopsy) findings II. *HLA-DQ2* and *HLA-DQ8* testing for celiac disease is considered **investigational** in all other situations.

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