Policy Statement

HLA-DQ2 and HLA-DQ8 testing may be considered **medically necessary** to rule out celiac disease in **either** of the following:
- Patients with persistent symptoms despite negative serology and histology
- Patients 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

**Genetics Nomenclature Update**
The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society’s nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology: “pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign” to describe variants identified that cause Mendelian disorders.

<table>
<thead>
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<th>Table PG1. Nomenclature to Report on Variants Found in DNA</th>
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<td><strong>Previous</strong></td>
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<th>Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification</th>
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<td><strong>Variant Classification</strong></td>
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<tr>
<td>Variant of uncertain significance</td>
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<tr>
<td>Likely benign</td>
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<tr>
<td>Benign</td>
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ACMG: American College of Medical Genetics and Genomics, AMP: Association for Molecular Pathology.

**Genetic Counseling**
Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.
Coding
The following is the specific code range for human leukocyte antigen gene testing:

- **81370-81383**

One laboratory that performs this testing lists the following coding online:

- **81377 x 2**: HLA Class II typing, low resolution (e.g., antigen equivalents); one antigen equivalent, 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

Other laboratory websites suggest that the testing be reported with code 81383 x 2 alone or with 81377 x 2.

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 to Diagnose Disorders of the Small Bowel, Esophagus, and Colon

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. 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 Clinical Laboratory Improvement Amendments 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

Background

Diagnosis

Celiac disease (CD) 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.

CD 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 one of these two 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.1,2

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 a presentation in conjunction with the consistent history and serologic results, followed by clinical response to a gluten-free diet.3

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.

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.4,5,6 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.

Genetic Testing for Symptoms Suggestive of Celiac Disease

Clinical Context and Test Purpose

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 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, i.e., whether only clinically apparent cases are considered, as opposed to including all people with any serologic or histologic evidence of disease.

The purpose of genetic testing for the human leukocyte antigen (HLA) genes HLA-DQ2 and HLA-DQ8 of individuals with symptoms suggestive of 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 questions addressed in this evidence review are: (1) Is there evidence that genetic testing of individuals with signs or symptoms suggestive of CD with persistent symptoms despite negative serology and histology or individuals with discordant serologic and histologic (biopsy) findings or individuals to rule out CD has clinical validity?; and (2) Does genetic testing of such individuals change patient management in a way that improves outcomes as a result of diagnostic testing?

The following PICOs were used to select literature to inform this review.

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

Interventions
The relevant intervention is genetic testing for the HLA genes HLA-DQ2 and HLA-DQ8. Commercial testing is available from numerous companies. Ordering and interpreting genetic testing may be complex and is best done by experienced specialists such as gastroenterologists. Most patients are likely to be tested in an outpatient setting. Referral for genetic counseling is important for the explanation of the genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Comparators
The following practice is currently being used to diagnose CD: clinical management without genetic testing, which is administered in an outpatient setting.

Outcomes
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 delayed treatment of appropriate treatment and lifestyle changes and subsequent avoidance of morbidity associated with the disease. False-positive or -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.

**Technical Reliability**

Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**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).

**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

**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. The report cited the 2013 American College of Gastroenterology estimates 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 found that HLA testing had a sensitivity of 100% and specificity of 18.2% and a 1999 cohort 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. For example, 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 plus 10 times the upper limit of normal levels of immunoglobulin A against tissue transglutaminase (TGA-IgA) (aka serologic marker) and positive finding for HLA-DQ2 and -DQ8. 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 TGA-IgA levels of three times or below the upper limit of normal low 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. Use of test results including TGA-IgA 10 times or more the upper limit of normal, a positive result from the test for endomysium antibodies, and any symptom identified children with CD (n=399) yielded 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.

Pallav et al (2014) retrospectively assessed HLA testing in 256 patients with known or suspected CD.\(^9\) Taking into account all available clinical and laboratory data, 44 patients were diagnosed with CD, and in 173 patients CD was ruled out. A final diagnosis could not be obtained in 39 (15%) of 256 patients. HLA-DQ2 or-DQ8 alleles were absent in 40% of non-CD patients and 2 CD patients. 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 one 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.\(^10\) 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 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 227 patients who did not meet diagnostic criteria for CD were positive for one 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%).

**Section Summary: Clinically Valid**

More than 99% of patients with CD have HLA-DQ2 and/or DQ8 compared with about 25% to 40% of the general population. Thus, CD is highly unlikely in patients without these haplotypes. 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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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).

**Summary of Evidence**

For individuals who are suspected of having CD and have negative or discordant serologic and biopsy findings, the evidence includes several retrospective and prospective cohort studies. The
relevant outcomes are test validity, other test performance measures, and change in disease status. 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Supplemental Information
Practice Guidelines and Position Statements

**American College of Gastroenterology**
The guidelines from the American College of Gastroenterology (2013) addressing the diagnosis and management of celiac disease (CD) stated the following on human leukocyte antigen (HLA) gene testing:

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.

**National Institute for Health and Care Excellence**
The 2009 guidance, which was updated in 2015, from the National Institute for Health and Care Excellence on CD included the following statement on 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).”

**American Gastroenterological Association Institute**
The American Gastroenterological Association Institute (2006) issued a 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. The guidelines indicated that the antiendomysial antibodies IgA test is more time-consuming and operator dependent than the tissue transglutaminase (tTG). 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.

**National Institutes of Health**
The National Institutes of Health (2004) issued a consensus statement based on a meeting and an independent literature review. 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. 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 2019 did not identify any ongoing or unpublished trials that would likely influence this review.

References


**Documentation for Clinical Review**

Please provide the following documentation (if/when requested):

- 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**

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

**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. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

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### HCPCS
None

### ICD-10 Procedure
None

## Policy History

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

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## 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 (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.

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.