Serologic Diagnosis of Celiac Disease

Policy # 00305
Original Effective Date: 01/09/2013
Current Effective Date: 10/11/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider serologic testing (e.g., IgA or IgG antibodies) in patients with signs or symptoms suggestive of celiac disease (see Clinical Manifestation of Celiac Disease) to be **eligible for coverage.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers screening of asymptomatic at risk patient groups or population-based screening for celiac disease using one or more serologic immunoglobulin A (IgA) or immunoglobulin G (IgG) measures to be **investigational.***

Based on review of available data, the Company considers genetic testing for diagnosis or evaluation of celiac disease using a multigene panel test (e.g., Celiac PLUS) to be **investigational.***

Policy Guidelines

Genetic testing is considered **investigational** when BCBSA criteria are not met, including when there is insufficient evidence to determine that the technology results in an improvement in the net health outcome.

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Genetic Counseling
Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background/Overview

Celiac disease, which is 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 250–500 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 individuals with any serologic or histologic evidence of disease.

Celiac disease is defined as inflammation of the small intestine resulting from an immunologic intolerance to gluten; i.e., the proteins derived from wheat, barley, and rye. The symptoms of the disease are markedly variable and can be broadly subdivided into intestinal and extra intestinal manifestations; the latter is thought to be related to nutrient malabsorption. For example, osteopenia and osteoporosis, which are commonly seen in adults with untreated celiac disease, are related to the impaired absorption of vitamin D and binding of intraluminal calcium and magnesium to unabsorbed dietary fatty acids, forming insoluble soaps.

Clinical Manifestation of Celiac Disease

General	Gastrointestinal	Extraintestinal
• Short stature • Weight loss • Failure to thrive • Lassitude	• Diarrhea • Steatorrhea • Flatulence • Abdominal distension • Anorexia	• Laboratory abnormalities: • Iron/folate deficiency anemia • Hypocalcemia • Skin: • Dermatitis herpetiformis

• Lethargy • Clubbing • Delayed puberty • Peripheral edema	• Nausea, vomiting • Recurrent aphthous stomatitis • Angular cheilosis • Glossitis • Hepatic steatosis	• Follicular keratosis • Pigmentation, bruising • Hematological: • Splenic atrophy • Musculoskeletal • Osteopenia, osteoporosis • Bone pain, joint pain • Dental enamel effects • Arthritis • Neurological • Peripheral neuropathy • Epilepsy • Night blindness • Reproduction • Female and male infertility • Recurrent abortion • Psychiatric • Anxiety, depression • Irritability, poor school performance

Many of the symptoms of celiac disease 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 between 6 and 24 months, following weaning, 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 celiac disease refers to the presence of malabsorption, while atypical celiac disease consists primarily of extra intestinal manifestations. Finally, silent celiac disease may be entirely asymptomatic and discovered only on biopsy or with serologic testing (see further discussion below). Celiac disease is a human leukocyte antigen (HLA)-associated disease. A 2007 review by Green and Cellier states that the alleles that encode for HLA-DQ2 or HLA-DQ8 proteins

are a necessary but not sufficient cause of celiac disease and that celiac disease will not occur in the absence of alleles (not all persons with these alleles will develop celiac disease). There is a 10% prevalence among first-degree relatives. Celiac disease is associated with a number of other conditions, including type 1 diabetes mellitus, rheumatoid arthritis, and primary biliary cirrhosis.

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 Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHN) and consisted of a series of 3 intestinal biopsies: 1 at diagnosis, 1 after 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 consistent history and serologic results, followed by a clinical response to a gluten-free diet.

While a positive biopsy result is considered the gold standard for diagnosis, serologic evaluation of patients with possible celiac disease can be used to triage the large numbers of patients with nonspecific symptoms for biopsy. More recently, there has been a trend toward using serologies to make a definitive diagnosis of celiac disease. Serologic diagnosis is focused on the detection of IgA antibodies. In the presence of gluten, the intestine produces large amounts of antibodies that are secreted intraluminally but spill over into the serum, where they can be detected. Antigliadin, antiendomysial, and tTG IgA antibodies have been most extensively studied. Gliadin is a component of gluten, while antiendomysial antibodies (referred to as EMA) are directed against the reticulin network surrounding the smooth muscle bundles of the gastrointestinal (GI) tract. Tissue transglutaminase (usually abbreviated as tTG or TTG) is the enzyme responsible for deamidation of gliadin in the lamina propria, increasing its immunogenicity and allowing interaction with HLA-DQ2 or HLA-DQ8.

Antigliadin antibodies (AGA) can be detected using an enzyme-linked immunosorbent assay (ELISA) test. EMA are detected using an indirect immunofluorescence technique that utilizes either primate esophagus or human umbilical cord as a substrate. More recently the EMA antigen has been identified as tTg, allowing the development of an ELISA-based test and a dot blot procedure that can be performed in the physician's office. A total of 2% to 3% of patients with celiac disease are IgA deficient; in these patients, IgG antibodies are assayed instead of IgA antibodies. Among the approximately 10% of cases in which clinical suspicion, serologic testing, and intestinal biopsy are

equivocal, a 2007 review by Green and Cellier suggests that negative tests for HLA-DQ2 and HLA-DQ8 (present in 90–95% and 5+% of patients with celiac disease, respectively) can rule out a diagnosis of celiac disease.

The newest serologic tests are deamidated gliadin peptide (DGP) antibody tests. Deamidation refers to a chemical reaction in which an amide group is removed from an organic compound. Deamidated gliadin is produced when gluten undergoes acid or enzymatic treatment so that tTG converts some of the glutamines to glutamic acid. Deamidated peptides are believed to be more specific to celiac disease than native peptides. Some of the DGP antibody tests are able to assay both IgA and IgG, so they can be used in patients regardless of IgA deficiency status.

DIAGNOSTIC TESTS

Celiac Disease

Previously called sprue, celiac sprue, gluten-sensitive enteropathy, gluten intolerance, nontropical sprue, or idiopathic steatorrhea, celiac disease is an immune-based reaction to gluten (water-insoluble proteins in wheat, barley, rye) that primarily affects the small intestine. Celiac disease occurs almost exclusively in patients who carry at least 1 human leukocyte antigen DQ2 or DQ8; the negative predictive value of having neither allele exceeds 98%.Serum antibodies to tissue transglutaminase, endomysium, and deamidated gliadin peptide support a diagnosis of celiac disease but diagnostic confirmation requires duodenal biopsy taken when patients are on a gluten-containing diet.

Test Description: Celiac PLUS

Celiac PLUS (Prometheus Therapeutics & Diagnostics) is a panel of 2 genetic and 5 serologic markers associated with celiac disease. Per the manufacturer, Celiac PLUS is a diagnostic test that also stratifies the future risk of celiac disease. Genetic markers (human leukocyte antigen DQ2 and DQ8) are considered predictive of the risk of developing celiac disease; serologic markers (immunoglobulin A [IgA] anti-tissue transglutaminase antibody, IgA anti-endomysial antibodies, IgA anti-deamidated gliadin peptide antibodies, IgG anti-deamidated gliadin peptide, and total IgA) are considered diagnostic for celiac disease. Celiac PLUS is intended for patients at risk for the disease (eg, with an affected first-degree relative) or with symptoms suggestive of the disease.

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Antibody testing for celiac disease is widely available, and HLA typing for celiac disease is offered by several laboratories such as Quest, LabCorp, and Prometheus.

Centers for Medicare and Medicaid Services (CMS)
No national coverage determination.

Rationale/Source

Use of serologic tests for the diagnosis of celiac disease has the potential to reduce the need for intestinal biopsies and thus improve the efficiency of diagnosis. Evidence from systematic reviews and head-to-head comparative studies using biopsy as the gold standard is adequate to conclude that tissue transglutaminase and antiendomysial antibody tests are sufficiently accurate for identifying celiac disease in patients with signs or symptoms of the disease. These tests are appropriate for use as the initial diagnostic test for celiac disease and will reduce the need for intestinal biopsy without substantially lowering the accuracy of diagnosis. There is uncertainty regarding the clinical utility of combination testing and insufficient evidence to recommend a specific combination or sequence of tests. However, a number of studies have reported an improvement in accuracy through combination testing, and the use of more than one test may be considered in some individuals with indeterminate results following testing with tTG or EMA.

In children younger than 2 years-old, the pattern of serologies appears to be different than in older individuals. One study found that, in children younger than 18 months, serologic measurement of antigliadin antibodies is more sensitive than either of the other 2 tests. Other studies have corroborated that the accuracy of tTG in children younger than 2 years is less than in adults, but these studies are not consistent in determining the optimal testing strategy in young children. Because of the reduced accuracy of tTG, other serologic tests such as AGA have potentially greater utility and may be considered medically necessary in children younger than 2 years.

There is insufficient evidence on the newer deamidated gliadin peptide (DGP) tests; fewer studies have been published, and the DGP tests have not consistently been found to be as sensitive as the tTG and antiendomysial antibody (EMA) tests. Moreover, national organizations that recommend the use of tTG and EMA tests do not yet have recommendations on DGP tests.

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Celiac Disease: Celiac PLUS
In 2013, the American College of Gastroenterology (ACG) published an evidence-based diagnostic algorithm for patients with high (>5%) or low (<5%) probability of celiac disease. In both groups of patients, IgA anti-TTG antibody is "the preferred single test for detection of celiac disease in individuals over the age of 2 years" (strong recommendation based on a high level of evidence); sensitivity and specificity of the anti-TTG IgA are both approximately 95%. For patients with high probability of disease, initial diagnostic workup comprises duodenal biopsy and anti-TTG IgA. If both tests are negative, celiac disease is unlikely; if both are positive, celiac disease is diagnosed. If results are discrepant, further workup including HLA DQ2 and DQ8 genotyping and total IgA level to rule out IgA deficiency is recommended. For patients with low probability of disease, initial diagnostic workup comprises anti-TTG IgA level and total IgA level. With 1 exception, combining several serologic tests rather than obtaining IgA anti-TTG alone is not recommended due to substantially reduced specificity for only marginally increased sensitivity (weak recommendation based on moderate evidence). In children younger than 2 years of age, however, combination testing with IgA anti-TTG and anti-DGP (both IgA and IgG) is recommended due to reduced test performance in this age group (strong recommendation based on moderate evidence). A strong recommendation (based on moderate evidence) against routine HLA DQ2 and DQ8 testing in the initial diagnostic workup of celiac disease is made; targeted HLA DQ2 and DQ8 testing is recommended for select clinical situations (e.g., discrepant serology and biopsy results [strong recommendation based on moderate evidence]).

No studies of the combined serologic and genetic Celiac PLUS test were identified.

Clinical Validity
Celiac PLUS tests for genetic and serologic factors known to be associated with celiac disease. All 7 test components are included in an evidence-based diagnostic algorithm developed by a professional medical society. However, algorithmic testing is individualized according to baseline risk of disease and is done sequentially, rather than simultaneously as in Celiac PLUS. Information about clinical validity of obtaining several serologic and genetic tests at once (i.e., Celiac PLUS) is lacking; improved sensitivity and reduced specificity may be expected.

Clinical Utility
No studies examining the clinical utility of Celiac PLUS were identified. Factors that support an indirect chain of evidence for prognostic or diagnostic utility are lacking. A comparison of clinical

and/or histopathologic outcomes using either Celiac PLUS or ACG's published diagnostic algorithm would be required to demonstrate improved health outcomes with Celiac PLUS.

Section Summary: Celiac Disease
No studies examining the clinical utility of Celiac PLUS were identified. Factors that support an indirect chain of evidence for prognostic or diagnostic utility are lacking. A comparison of clinical and/or histopathologic outcomes using either Celiac PLUS or ACG's published diagnostic algorithm would be required to demonstrate improved health outcomes with Celiac PLUS.

Supplemental Information

Practice Guidelines and Position Statements

Diagnostic Tests: Celiac Disease
In 2013, ACG published an evidence-based consensus algorithm for the diagnosis and management of celiac disease. A recommendation for genetic testing using a mutligene panel test (e.g., Celiac PLUS) was not included.

American Gastroenterological Association: In 2006, the American Gastroenterological Association issued a position statement on the diagnosis and management of celiac disease. Regarding serologic testing, they concluded that, in the primary care setting, the transglutaminase IgA antibody test is the most efficient single serologic test for diagnosing celiac disease. They state that the 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.

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition: In 2005, NASPGHAN issued a guideline on the diagnosis and treatment of celiac disease in children. They recommend testing for celiac disease as part of the differential diagnosis of children with failure to thrive and persistent diarrhea. They also recommend testing in children with non-GI symptoms of celiac disease (e.g., dermatitis herpetiformis, dental enamel hypoplasia of permanent teeth,

osteoporosis, short stature, delayed puberty, and iron-deficient anemia resistant to oral iron), and testing should be considered in children with other persisting GI symptoms. They recommend measurement of tTG IgA as initial testing and state that, although the EMA IgA test is as accurate as tTG, it is not recommended as a first-line test because it is more subject to interpretation error. In children with known selective IgA deficiency and symptoms suspicious for celiac disease, testing with tTG IgG is recommended. When serologic tests are negative, they recommend that an intestinal biopsy be considered in children with chronic diarrhea or failure to thrive who have symptoms compatible with celiac disease. Moreover, an intestinal biopsy is needed to confirm the diagnosis of celiac disease in all cases.

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. The NIH considered serologic testing as the first step in pursuing a diagnosis of celiac disease 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 celiac disease 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 gluten-free diet. Testing is indicated in individuals with GI symptoms and other signs and symptoms suggestive of celiac disease. Routine screening of asymptomatic individuals in high-risk groups (e.g., those with type 1 diabetes) was not recommended, although they stated that discussions with individual patients are warranted.

Of note as of March 28, 2017, the USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for celiac disease in asymptomatic adults, adolescents and children.

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for celiac disease in asymptomatic persons. Evidence is lacking, and the balance of benefits and harms cannot be determined.
https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/celiac-disease-screening

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01/03/2013	Medical Policy Committee review
01/09/2013	Medical Policy Implementation Committee approval. New policy.
01/09/2014	Medical Policy Committee review
01/15/2014	Medical Policy Implementation Committee approval. No change to coverage.
01/08/2015	Medical Policy Committee review
01/21/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
01/07/2016	Medical Policy Committee review
01/22/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
01/05/2017	Medical Policy Committee review. Considered archiving policy.
01/18/2017	Medical Policy Implementation Committee approval. Removed investigational statements for DGP antibody screening.
02/02/2017	Medical Policy Committee review
02/15/2017	Medical Policy Implementation Committee approval. Removed coverage statements and added population-based screening to investigational statement.
09/07/2017	Medical Policy Committee review
09/20/2017	Medical Policy Implementation Committee approval. Added that serological testing (e.g. IgA or IgG antibodies) in patients with signs or symptoms suggestive of celiac disease may be considered eligible for coverage. Added that genetic testing for diagnosis or evaluation of celiac disease using a multigene panel test (e.g., Celiac PLUS) is considered to be investigational.
09/06/2018	Medical Policy Committee review
09/19/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/03/2018	Coding update
09/05/2019	Medical Policy Committee review

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09/11/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/03/2020	Medical Policy Committee review
09/09/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/02/2021	Medical Policy Committee review
09/08/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 09/2022

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2020 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81382, 82784, 83516, 83520, 86255, 88346
HCPCS	No codes
ICD-10 Diagnosis	K90.0, Z13.21

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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 that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.