

## Evidence Based Guideline

### Serologic Diagnosis of Celiac Disease

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### Description of Procedure or Service

Celiac disease is currently diagnosed by a positive small intestinal biopsy with consistent history and serologic results. A variety of serologic tests are available; some may be more accurate than others or more appropriate for use in certain patient populations.

#### Background:

Celiac disease, which may also be referred to as celiac sprue or gluten-sensitive enteropathy, may be defined as small intestinal inflammation resulting from an immunologic intolerance to gluten; i.e., the proteins derived from wheat, barley, and rye. The diagnosis is confirmed when there is a clinical and histologic improvement on a strict gluten-free diet, and relapse when dietary gluten is reintroduced. As summarized in the following table, 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 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 Manifestations of Celiac Disease

General	Gastrointestinal	Extraintestinal
Short stature	Diarrhea, steatorrhea, flatulence	Laboratory abnormaltilites <ul style="list-style-type: none"> <li>• Iron and folate deficiency anemia</li> <li>• hypocalcemia</li> </ul>
Weight loss	Abdominal distention	Skin <ul style="list-style-type: none"> <li>• Dermatitis herpetiformis</li> <li>• Follicular keratosis</li> <li>• Pigmentation, bruising</li> </ul>
Failure to thrive	Anorexia, nausea, vomiting	Hematological <ul style="list-style-type: none"> <li>• Splenic atrophy</li> </ul>
Lassitude, lethargy	Recurrent aphthous stomatitis	Musculoskeletal <ul style="list-style-type: none"> <li>• Osteopenia, osteoporosis</li> <li>• Bone pain, joint pain</li> <li>• Dental enamel effects</li> <li>• Arthritis</li> </ul>
Clubbing	Angular chelosis, glossitis	Neurological <ul style="list-style-type: none"> <li>• Peripheral neuropathy</li> <li>• Epilepsy</li> <li>• Night blindness</li> </ul>
Delayed puberty	Hepatic steatosis	Reproduction <ul style="list-style-type: none"> <li>• Female and male infertility</li> <li>• Recurrent abortion</li> </ul>

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Edema	Psychiatric <ul style="list-style-type: none"><li>• Anxiety, depression</li><li>• Irritability, poor school performance</li></ul>
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As noted in the table, 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 extraintestinal manifestations. Finally, silent celiac disease may be entirely asymptomatic and discovered only on biopsy or with serologic testing (see further discussion below). For example, population-based screening serologic surveys suggest a prevalence of 1 in 250–500 in most countries, including the United States. Celiac disease is an 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, there has been considerable interest in the serologic evaluation of patients with possible celiac disease, in part as a technique to triage the large number of patients with nonspecific symptoms for biopsy. 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 tissue transglutaminase 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 tract. Tissue transglutaminase 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 can be detected using an ELISA test. EMA antibodies are detected using an indirect immunofluorescence technique, using either primate esophagus or human umbilical cord as a substrate. More recently the EMA antigen has been identified as the tissue enzyme tissue transglutaminase (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 where clinical suspicion, serologic testing, and intestinal biopsy are equivocal, the 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 tissue transglutaminase converts some of the glutamines to glutamic acid. Deamidated peptides are believed to be more specific to celiac disease than native peptides. A limitation of human antigen-based tTG tests for diagnosing celiac disease is that they have relatively low specificity and can result in false-positive findings in patients with

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chronic liver disease, inflammatory bowel disease, diabetes and other conditions. 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.

### Regulatory Status

Antibody testing for celiac disease is widely available and HLA typing for celiac disease if offered by several laboratories such as Quest, LabCorp and Prometheus.

***\*\*\*Note: This Evidence Based Guideline is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

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Serologic measurement of tissue transglutaminase or antiendomysial antibodies may be appropriate in patients with signs or symptoms suggestive of celiac disease.

Serologic measurement of antigliadin antibodies may be appropriate in children under 18 months of age with signs or symptoms suggestive of celiac disease.

HLA-DQ2 and HLA-DQ8 testing may be appropriate to rule out celiac disease in patients with discordant serologic and histologic (biopsy) findings or if persistent symptoms warrant testing despite negative serology and histology.

## Medical Evidence regarding Serologic Diagnosis of Celiac Disease indicates it is not recommended in the following situations

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Serologic measurement of deamidated gliadin peptide antibodies is not recommended in patients with signs or symptoms suggestive of celiac disease.

The use of more than one antibody test is not recommended.

The use of one or more serologic IgA or IgG measures is not recommended for:

- Screening of asymptomatic at risk patient groups for celiac disease OR
- Population screening for celiac disease.

## Rationale

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Use of serology tests, if accurate, reduces the need for multiple biopsies. Evidence from systematic reviews and head-to-head comparative studies using biopsy as the gold standard concludes that there is sufficient evidence that tissue transglutaminase and antiendomysial antibody tests are reasonably accurate for identifying celiac disease in patients with signs or symptoms of the disease. One study found that, in children under 18 months old, serologic measurement of antigliadin antibodies is more sensitive than either of the other 2 tests. 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 EMA tests. Moreover, national organizations that recommend the use of tTG and EMA tests do not yet have recommendations on DGP tests. There is insufficient evidence that any combination of serology tests is superior to use of a single test. The evidence is also insufficient that serology testing of asymptomatic high-risk individuals or population screening of asymptomatic individuals improves the net health outcome.

The National Institutes of Health 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

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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 gastrointestinal 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 December 2010, there are no recommendations from the USPSTF (US Preventive Services Task Force) related to screening for celiac disease in children or adults.

### Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

### Billing/Coding/Physician Documentation Information

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This guideline may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable codes: There are no specific CPT codes describing the serologic diagnosis of celiac disease.*

*CPT 83516 would describe an ELISA test, a common component of the serologic diagnosis.*

*Testing for antiendomysial antibodies is evolving toward the detection of tTg antibodies used and ELISA test (see above); however, some laboratories may still use an indirect immunofluorescent study described by CPT code 88347.*

### Scientific Background and Reference Sources

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Green PH, Cellier C. Celiac disease. *N Engl J Med* 2007; 357(17):1731-43

American Gastroenterologic Association medical position statement: celiac sprue. *Gastroenterology* 2001; 120(6):1522-5

Walker-Smith JA, Guandalini S, Schmitz J, et al. Revised criteria for diagnosis of coeliac disease. *Arch Dis Child* 1990; 65(8):909-11

National Institutes of Health. NIH consensus development conference on celiac disease. Consensus development conference statement June 28-30, 2004. Available online at: <http://consensus.nih.gov/2004/2004CeliacDisease118.html.htm>.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.30, 1/13/2011

# Serologic Diagnosis of Celiac Disease

## Policy Implementation/Update Information

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5/10/11 New Evidence Based Guideline issued. Serologic measurement of tissue transglutaminase or antiendomysial antibodies may be appropriate in patients with signs or symptoms suggestive of celiac disease. Serologic measurement of antigliadin antibodies may be appropriate in children under 18 months of age with signs or symptoms suggestive of celiac disease. HLA-DQ2 and HLA-DQ8 testing may be appropriate to rule out celiac disease in patients with discordant serologic and histologic (biopsy) findings or if persistent symptoms warrant testing despite negative serology and histology. Serologic measurement of deamidated gliadin peptide antibodies is not recommended in patients with signs or symptoms suggestive of celiac disease. The use of more than one antibody test is not recommended. The use of one or more serologic IgA or IgG measures is not recommended for: Screening of asymptomatic at risk patient groups for celiac disease OR Population screening for celiac disease. Specialty Matched Consultant Advisory Panel review 4/27/11. (adn)

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