

Title

Serological Diagnosis of Celiac Disease¹

Description

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 soaps¹.

Clinical Manifestation of Celiac Disease

General

Gastrointestinal

Extraintestinal

Short stature

Diarrhea, steatorrhea, flatulence

Laboratory abnormalities:

Iron and folate deficiency anemia
Hypocalcemia

Weight loss

Abdominal distention

Skin:

Dermatitis herpetiformis
Follicular keratosis
Pigmentation, bruising

Failure to thrive

Anorexia, nausea, vomiting

Hematological:

Splenic atrophy

Lassitude, lethargy

Recurrent aphthous stomatitis

Musculoskeletal:

Osteopenia, osteoporosis
Bone pain, joint pain
Dental enamel effects
Arthritis

Clubbing

Angular chelosis, glossitis

Neurological:

Peripheral neuropathy
Epilepsy
Night blindness

Delayed puberty

Hepatic steatosis

Reproduction:

Female and male infertility
Recurrent abortion

Edema

Psychiatric:
Anxiety, depression
Irritability, poor school performance

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 (1) 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. (See reference 5 in the Rationale section.)

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 (1) 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.

When services are covered for commercial products and for Medicare HMO Blue, Medicare PPO Blue, and Blue Medicare PFFS PlusRx

We cover serologic measurement of tissue transglutaminase or antiendomysial antibodies in patients with signs or symptoms suggestive of celiac disease.

We cover serologic measurement of antigliadin antibodies in children under 18 months of age with signs or symptoms suggestive of celiac disease.

We cover HLA-DQ2 and HLA-DQ8 testing 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.

When services are not covered for commercial products or for Medicare HMO Blue, Medicare PPO Blue, and Blue Medicare PFFS PlusRx

We do not cover the use of more than one antibody test as it is considered not medically necessary.

We do not cover screening of asymptomatic at risk patient groups for celiac disease using one or more serologic IgA or IgG measures.

We do not cover population screening for celiac disease using one or more serologic IgA or IgG measures.

Individual consideration

All our medical policies are written for the majority of people with a given condition. Each policy is based on medical science. For many of our medical policies, each individual's unique clinical circumstances may be considered in light of current scientific literature. For consideration of an individual patient, physicians may send relevant clinical information to:

For services already billed

Blue Cross Blue Shield of Massachusetts
Provider Appeals
PO Box 986065
Boston, MA 02298

Prior to performance of service

Blue Cross Blue Shield of Massachusetts
Case Creation/Medical Policy
One Enterprise Drive
Quincy, MA 02171
Tel: 1-800-327-6716
Fax: 1-888-641-5330

Authorization Information

For Managed Care members:

- No authorization is required for this service; *see Managed Care Guidelines for additional requirements.*

For Indemnity and PPO members:

- No authorization is required for this service; *see Indemnity and PPO Guidelines for additional requirements.*

Managed Care Guidelines

All authorization requirements are determined by the individual's subscriber certificate, explanation of coverage, or summary plan description, however;

- **For Medicare HMO Blue members:** The service must meet the criteria for coverage noted in this policy, be medically necessary, prescribed by a plan physician and provided by a network provider.
- **For Medicare HMO Blue members:** Referrals are required for all visits to a specialist.
- For all other Managed Care plans, any specialist visit requires a referral, except for visits performed by OB/GYN specialists.
- Authorization is required for an inpatient admission.

Indemnity and PPO Guidelines

All authorization requirements are determined by the individual's subscriber certificate, explanation of coverage, or summary plan description, however;

- Authorization is required for an inpatient admission.
- Authorizations are not required for most outpatient services as determined by the individual's subscriber certificate.
- Referrals to a specialist are not required.

Other information

For our Medical Technology Assessment Guidelines, see document [#350](#).

Coding information

Procedure codes are from current CPT, HCPCS Level II, Revenue Code, and/or ICD-9-CM manuals, as recommended by the American Medical Association, Centers for Medicare and Medicaid Services and American Hospital Associations. Blue Cross Blue Shield Association national codes may be developed when appropriate.

The following codes are included below for informational purposes. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

CPT codes:

There are no specific CPT codes describing the serologic diagnosis of celiac disease. The following code would describe an ELISA test, a common component of the serologic diagnosis:

- **83516:** Immunoassay for analyte other than infectious agent antibody or infectious agent antigen, qualitative or semiquantitative; multiple-step method.

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 the following code:

- **88347:** Immunofluorescent study, each antibody; indirect method

Policy update history

New policy, effective 11/01/09.

References

References for footnote 1:

1. Green PH, Cellier C. Celiac disease. *N Engl J Med* 2007; 357(17):1731-43.
2. Farrell RJ, Kelly CP. Celiac sprue. *N Engl J Med* 2002; 346(3):180-8.
3. Fasano A, Catassi C. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. *Gastroenterology* 2001; 120(3):636-51.
4. American Gastroenterologic Association medical position statement: celiac sprue. *Gastroenterology* 2001; 120(6):1522-5.
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.
6. Hill ID. What are the sensitivity and specificity of serologic tests for celiac disease? Do sensitivity and specificity vary in different populations? *Gastroenterology* 2005; 128(4 suppl 1):S25-32.
7. Zintzaras E, Germainis AE. Performance of antibodies against tissue transglutaminase for the diagnosis of celiac disease: meta-analysis. *Clin Vaccine Immunol* 2006; 13(2):187-92.
8. Rostom A, Murray JA, Kagnoff MF. American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease. *Gastroenterology* 2006; 131(6):1981-2002.

9. Catassi C, Kryszak D, Louis-Jacques O et al. Detection of Celiac disease in primary care: a multicenter case-finding study in North America. *Am J Gastroenterol* 2007; 102(7):1454-60.
10. Korponay-Szabó IR, Szabados K, Pusttai J et al. Population screening for coeliac disease in primary care by district nurses using a rapid antibody test: diagnostic accuracy and feasibility study. *BMJ* 2007; 335(7632):1244-7.

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Footnotes

¹ Based on BCBSA policy # 2.04.30, Serological Diagnosis of Celiac Disease, issued 5/08.