BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Serologic Diagnosis of Celiac Disease

Policy #: 161
Latest Review Date: May 2023
Category: Laboratory

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Blue Advantage will treat **serologic measurement of antigliadin, antiendomysial or tissue transglutaminase antibodies** as a **covered** benefit when:

- Performed to evaluate patients with signs or symptoms suggestive of celiac disease; **OR**
- Performed to monitor patient's adherence and response to a gluten-free diet

Blue Advantage will treat **serologic measurement of deamidated gliadin peptide antibodies** as a **non-covered benefit** and as **investigational** in patients with signs or symptoms suggestive of celiac disease.

Blue Advantage will treat **screening of asymptomatic at risk patient groups for celiac disease** using one or more serologic IgA or IgG measures as a **non-covered** benefit and as **investigational**.

Blue Advantage will treat **population screening for celiac disease** using one or more serologic IgA or IgG measures as a **non-covered** benefit and as **investigational**.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

Celiac disease is an immune disorder in which individuals are unable to tolerate gluten, a protein found in wheat, rye, and barley. Diagnosis is made based on the biopsy and histopathologic examination of the small intestine. Blood tests may be used to select individuals for biopsy and to aid in diagnosis. Celiac disease is characterized by an abnormal proximal small intestinal mucosa, and it is associated with a permanent intolerance to gluten. Both the symptoms and abnormal small intestinal mucosal morphology resolve with removal of gluten from the diet.

Because the symptoms of celiac disease are nonspecific they are often overlooked. In addition, the disease may develop at any time in life, from infancy to very old age. In adults, diarrhea is the main presenting symptom, but presenting symptoms may be entirely nonspecific, such as anemia or infertility. Celiac disease is associated with a number of other conditions, including Type 1 diabetes mellitus, rheumatoid arthritis, and primary biliary cirrhosis.

KEY POINTS:

The most recent literature update was performed through May 17, 2023.

Summary of Evidence

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 diagnostic test for celiac disease and will reduce the need for intestinal biopsy without substantially lowering the accuracy of diagnosis. It should be noted, however, that the most important initial step in diagnosis is recognition of the many clinical features that can be associated with the disease.

In children younger than two years-old, the pattern of serologies appears to be different than in older individuals. Evidence found that in children younger than 18 months, serologic measurement of antigliadin antibodies (AGA) is the most sensitive testing.

The evidence for serologic measurement of deamidated gliadin peptide antibodies (DGP) for celiac disease remains controversial and unproven as superior to the gold standard of using biopsy results. Of studies identified, evidence has been found with conflicting results. There is a need for well-designed trials to prove the clinical utility of this testing. The evidence is insufficient to prove an improvement in net health outcomes for this technology.

Practice Guidelines and Position Statements

American Gastroenterological Association (AGA)

In 2013, the AGA issued the following position statement on the diagnosis and management of celiac disease:

Many individuals with celiac disease may have no symptoms at all. Celiac disease is usually detected by serologic testing of celiac-specific antibodies. The diagnosis is confirmed by duodenal mucosal biopsies. Both serology and biopsy should be performed on a gluten-containing diet. The treatment for celiac disease is primarily a gluten-free diet (GFD), which requires significant patient education, motivation, and follow-up. Non-responsive celiac disease occurs frequently, particularly in those diagnosed in adulthood. Persistent or recurring symptoms should lead to a review of the patient's original diagnosis to exclude alternative diagnoses, a review of the GFD to ensure there is no obvious gluten contamination, and serologic testing to confirm adherence with the GFD. In addition, evaluation for disorders associated with celiac disease that could cause persistent symptoms, such as microscopic colitis, pancreatic exocrine dysfunction, and complications of celiac disease, such as enteropathy-associated lymphoma or refractory celiac disease, should be entertained. Newer therapeutic modalities are being studied in clinical trials, but are not yet approved for use in practice. Given the incomplete response of many patients to a GFD-free diet as well as the difficulty of adherence to the GFD over the long term, development of new effective therapies for symptom control and reversal of inflammation and organ damage are needed. The prevalence of celiac disease is increasing worldwide and

many patients with celiac disease remain undiagnosed, highlighting the need for improved strategies in the future for the optimal detection of patients.

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN)
In 2016, NASPGHAN issued the following guideline on the diagnosis and treatment of celiac disease in children:

To screen patients for celiac disease (CD), measurement of the immunoglobulin A (IgA) tissue transglutaminase antibody is the preferred test. Total serum IgA level should be measured to exclude selective IgA deficiency and to avoid false-negative test results. Patients with positive serologic test results should be referred to a gastroenterologist for endoscopic small intestinal biopsies to confirm the diagnosis. Testing for human leukocyte antigens DQ2 and DQ8 can help exclude the diagnosis. A gluten-free diet should not be started before confirming the diagnosis of CD. Serologic testing is very useful for screening patients with suspected CD. Early diagnosis is essential to prevent complications of CD.

National Institutes of Health (NIH)
According to a 2004 NIH Consensus Panel Statement on celiac disease, serological testing is the first step in pursuing a diagnosis of CD. The Consensus Statement said that the best available tests are the IgA anti-human tissue transglutaminase (TTG) and anti-endomesial IgA antibodies (EMA). According to the NIH Consensus Statement, the antigliadin IgA and IgG antibody tests are no longer routinely recommended because of their lower sensitivity and specificity.

The European Society of Pediatric Gastroenterology and Nutrition (ESPGHAN)
The European Society of Pediatric Gastroenterology and Nutrition has established criteria for definitive diagnosis of CD. In children younger than two years of age, the criteria state diagnosis would be made only when reintroduction of gluten into the diet, after the intestinal mucosa has become normal, causes the mucosa again to become abnormal, with or without symptoms. In children older than two years of age, the criteria state a second challenge with gluten is not required if the initial biopsy is positive.

According to 2020 guidelines, a no-biopsy approach is appropriate for children with TGA-IgA values ≥10 times the upper limit of normal with appropriate tests and positive endomysia antibodies (EMA-IgA) in a second serum sample.

U.S. Preventive Services Task Force Recommendations
Not applicable.

KEY WORDS:
Celiac disease, CD, celiac sprue, serologic tests, DGP, deamidated gliadin peptide, tTG, tissue transglutaminase, AGA, antigliadin antibodies, EMA, antiendomysial antibodies

APPROVED BY GOVERNING BODIES:
This testing is approved by the United States FDA.

BENEFIT APPLICATION:
Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

CURRENT CODING:
CPT codes:

82784	Gammaglobulin; IgA, IgD, IgG, IgM, each
83516	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen, qualitative or semiquantitative; multiple step method
83518	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen, qualitative or semiquantitative; single step method (e.g., reagent strip)
83520	Immunoassay, analyte, quantitative; not otherwise specified
86231	Endomysial antibody (EMA), each immunoglobulin (Ig) class (Effective 01/01/22)
86255	Fluorescent noninfectious agent antibody; screen, each antibody
86256	Fluorescent noninfectious agent antibody; titer, each antibody
86258	Gliadin (deamidated) (DGP) antibody, each immunoglobulin (Ig) class (Effective 01/01/22)
86364	Tissue transglutaminase, each immunoglobulin (Ig) class (Effective 01/01/22)
86816	HLA typing; DR/DQ, Single Antigen
88346	Immunofluorescence, per specimen; initial single antibody stain procedure
88350	each additional single antibody stain procedure (List separately in addition to code for primary procedure)

REFERENCES:

1. Alessio MG TE, Brusca I, et al. Correlation between IgA tissue transglutaminase antibody ratio and histological finding in celiac disease. J Pediatr Gastroenterol Nutr 2012; 55(1):44-49.
2. American Gastroenterological Association Medical Position Statement: Celiac sprue. Gastroenterology 2001; 120(6): 1522-5.
3. American Gastroenterological Association. AGA Institute Medical Position Statement on the Diagnosis and Management of Celiac Disease. Gastroenterology 2006; 131: 1977-1980.
4. Basso D, Guariso G, Bozzato D et al. New screening tests enrich anti-transglutaminase results and support a highly sensitive two-test based strategy for celiac disease diagnosis. Clin Chim Acta 2011; 412(17-18):1662-7.
5. Catassi C, Kryszak D, et al. Detection of Celiac disease in primary care: A multicenter case-finding study in North America. Am J Gastroenterol, July 2007; 102(7): 1454-1460.
6. Catassi, G. N., Pulvirenti, A., Monachesi, C., Catassi, C., & Lionetti, E. (2021). Diagnostic Accuracy of IgA Anti-Transglutaminase and IgG Anti-Deamidated Gliadin for Diagnosis of Celiac Disease in Children under Two Years of Age: A Systematic Review and Meta-Analysis. Nutrients, 14(1), 7.
7. Diós, Á., Srinivasan, B., Gyimesi, J., Werkstetter, K., Valenta, R., Koletzko, S., & Korponay-Szabó, I. R. (2022). Changes in Non-Deamidated versus Deamidated Epitope Targeting and Disease Prediction during the Antibody Response to Gliadin and Transglutaminase of Infants at Risk for Celiac Disease. International journal of molecular sciences, 23(5), 2498.
8. Farrell R, et al. Diagnosis of celiac sprue. Am J of Gastroenterology 2001; 96(12): 3237-46.
9. Farrell RJ and Kelly CP. Current concepts: Celiac sprue. N Engl J Med 2002; 346(3); 180-8.
10. Fasano A and Catassi C. Current approaches to diagnosis and treatment of celiac disease: An evolving spectrum. Gastroenterology 2001; 120(3): 636-51.
11. Foucher B, Johanet C, Jego-Desplat S et al. Are Immunoglobulin A anti-gliadin antibodies of any help in the diagnosis of coeliac disease in children below 2 years-old? a French multicenter study. J Pediatr Gastroenterol Nutr 2012; 54(1):110-2.
12. Green PH, Cellier C. Celiac disease. NEJM, October 25, 2007; 357: 1731-1743.
13. Hill ID, Dirks MH, Liptak GS et al. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2005; 40(1):1-19.
14. Hill ID. What are the sensitivity and specificity of serologic tests for celiac disease? Do sensitivity and specificity vary in different populations? Gastroenterology, April 2005; 128(4 Suppl 1): S25-32.
15. Hojsak I, Mozer-Glassberg Y, Segal Gilboa N et al. Celiac Disease Screening Assays for Children Younger than 3 Years of Age: The Performance of Three Serological Tests. Dig Dis Sci 2011.
16. Hopper AD, Hadjivassiliou M, Hurlstone DP et al. What is the role of serologic testing in celiac disease? A prospective, biopsy-confirmed study with economic analysis. Clin Gastroenterol Hepatol 2008; 6(3):314-20.

17. Husby S, Koletzko S, Korponay-Szabó IR, et al; ESPGHAN Working Group on Coeliac Disease Diagnosis; ESPGHAN Gastroenterology Committee; European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr. 2012;54(1):136-160.
18. IOM (Institute of Medicine). 2011. Clinical Practice Guidelines We Can Trust. Washington, DC: The National Academies Press.
19. Katz KD, Rashtak S, Lahr BD et al. Screening for celiac disease in a North American population: sequential serology and gastrointestinal symptoms. Am J Gastroenterol 2011; 106(7):1333-9.
20. Kelly, Ciaran P. (2018). Diagnosis of celiac disease in adults. In Grover, Shilpa (Ed.), UpToDate. Retrieved September 14, 2018 from www.uptodate.com/contents/diagnosis-of-celiac-disease-in-adults
21. Korponay-Szabo IR, Szabados K, Pusztai 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.
22. Lagerqvist C, Dahlbom I, Hansson T et al. Antigliadin immunoglobulin A best in finding celiac disease in children younger than 18 months of age. J Pediatr Gastroenterol Nutr 2008; 47(4):428-35.
23. Lewis NR, Scott BB. Meta-analysis: deamidated gliadin peptide antibody and tissue transglutaminase antibody compared as screening tests for coeliac disease. Aliment Pharmacol Therap 2010; 31(1):73-81.
24. Mir, B. A., Majeed, T., Singh, A., Rajput, M. S., Kumar, A., & Chauhan, A. (2022). Emerging Biomarkers for Screening and Management of Celiac Disease. BioMed research international, 2022, 2756242.
25. Mubarak A WV, Gmelig-Meyling FH, et al. Tissue transglutaminase levels above 100 U/ml and celiac disease: a prospective study. World J Gastroenterol 2012; 18(32):4399-403.
26. Mubarak A, Gmelig-Meyling FH, Wolters VM et al. Immunoglobulin G antibodies against deamidated-gliadin-peptides outperform anti-endomysium and tissue transglutaminase antibodies in children <2 years age. APMIS 2011; 119(12):894-900.
27. Naiyer AJ, Hernandez L, Ciaccio EJ et al. Comparison of commercially available serologic kits for the detection of celiac disease. J Clin Gastroenterol 2009; 43(3):225-32.
28. NIH consensus development conference on celiac disease. Consensus development conference statement. 2004. Available online at: consensus.nih.gov/2004/2004CeliacDisease118.html.htm. Last accessed March 2010.
29. Panetta F, Torre G, Colistro F et al. Clinical accuracy of anti-tissue transglutaminase as screening test for celiac disease under 2 years. Acta Paediatr 2011; 100(5):728-31.
30. Pietzak A, et al. Celiac disease: Going against the grain. Nutrition in Clinical Practice 2001; 16:335-44.
31. Rashid, M, Lee, J. Serologic testing in celiac disease; practical guide for clinicians. Can Fam Physician. 2016 Jan; 62(1): 38–43.

32. Rashtak S, Ettore MW, Homburger HA, Murray JA. Comparative usefulness of deamidated gliadin antibodies in the diagnosis of celiac disease. Clin Gastroenterol Hepatol. 2008 Apr;6(4):426-32; quiz 370. Epub 2008 Mar 4.
33. Rubio-Tapia, Alberto, MD; Hill, Ivor D, MD; Kelly, Ciarán P, MD; Calderwood, Audrey H, MD; Murray, Joseph A, MD. ACG Clinical Guidelines: Diagnosis and Management of Celiac Disease. American Journal of Gastroenterology: May 2013:Volume 108:Issue 5:p.656–676
34. Sblattero D, et al. Human recombinant tissue transglutaminase ELISA: An innovative diagnostic assay for celiac disease. Am J of Gastroenterology 2000; 95(5): 1253-57.
35. Sugai E, Moreno ML, Hwang HJ et al. Celiac disease serology in patients with different pretest probabilities: is biopsy avoidable? World J Gastroenterol 2010; 16(25):3144-52.
36. Vermeersch P, Geboes K, Marien G et al. Diagnostic performance of IgG anti-deamidated gliadin peptide antibody assays is comparable to IgA anti-tTG in celiac disease. Clin Chim Acta 2010; 411(13-14):931-5.
37. Walburga D, et al. Autoantibodies to tissue transglutaminase as predictors of celiac disease. Gastroenterology 1998; 115:1317-21.
38. Walker-Smith JA GS, Schmitz J et al. Revised criteria for diagnosis of coeliac disease. Report of Working Group of European Society of Paediatric Gastroenterology and Nutrition. Arch Dis Child 1990; 65(8):909-11.
39. Zanini B, Lanzarotto F, Mora A, Bertolazzi S, Turini D, Cesana B, Donato F, Ricci C, Lonati F, Vassallo F, Scarcella C, Lanzini A. Five year time course of celiac disease serology during gluten free diet: results of a community based "CD-Watch" program. Dig Liver Dis. 2010;42(12):865. Epub 2010 Jul 2.
40. Zintzaras E and Germenis AE. Performance of antibodies against tissue transglutaminase for the diagnosis of celiac disease: Meta-analysis. Clinical and Vaccine Immunology, February 2006, vol. 13, No. 2, pp. 187-192.

POLICY HISTORY:

Adopted for Blue Advantage, March 2005
Available for comment May 1-June 14, 2005
Medical Policy Group, May 2007
Medical Policy Group, November 2008
Medical Policy Group, February 2009
Available for comment April 16-May 30, 2009
Medical Policy Group, September 2010
Medical Policy Group, January 2012
Medical Policy Group, September 2013
Available for comment September 19 through November 2, 2013
Medical Policy Group, January 2014
Medical Policy Group, December 2015
Medical Policy Group, June 2018

Medical Policy Group, September 2018 **(9)**: Updates to Key Points, References, added Key Words DGP, deamidated gladin peptide, TG, tissue transglutaminase, AGA, antigliadin antibodies, EMA, antiendomysial antibodies. No change to policy statement.
Medical Policy Group, June 2019
Medical Policy Group, May 2021
Medical Policy Group, October 2021: Reviewed by consensus. No new published peer-reviewed literature available that would alter the coverage statement in this policy.
Medical Policy Group, November 2021: 2022 Annual Coding Update. Added CPT codes 86231, 86258, 86364 to the Current Coding section.
Medical Policy Group, May 2022: Reviewed by consensus. No new published peer-reviewed literature available that would alter the coverage statement in this policy.
Medical Policy Group, May 2023: Reviewed by consensus. No new published peer-reviewed literature available that would alter the coverage statement in this policy.
UM Committee, December 2023: Policy approved by UM Committee for use for Blue Advantage business.
