



BlueCross BlueShield
of Alabama

Name of Policy:

Serologic Diagnosis of Celiac Disease

Policy #: 161
Category: Laboratory

Latest Review Date: September 2013
Policy Grade: A

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

- 1. The technology must have final approval from the appropriate government regulatory bodies;*
- 2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
- 3. The technology must improve the net health outcome;*
- 4. The technology must be as beneficial as any established alternatives;*
- 5. The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

- 1. In accordance with generally accepted standards of medical practice; and*
- 2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
- 3. Not primarily for the convenience of the patient, physician or other health care provider; and*
- 4. 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.*

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.

Celiac disease (CD), celiac sprue, or gluten-sensitive enteropathy is a life-long, chronic malabsorption, inflammatory condition of the gastrointestinal tract that affects the small intestine in genetically susceptible individuals. CD is caused by exposure to dietary gluten in genetically pre-disposed individuals. The condition is characterized by villous atrophy, a lowering of the villous height to crypt depth ratio (normal, 3-5:1), an increase in intraepithelial lymphocytes (normal, 10-30 per 100 epithelial cells), and extensive surface cell damage and infiltration of the lamina propria with inflammatory cells. There are a wide range of presentations from asymptomatic to fatigue and vague abdominal symptoms, weight loss and diarrhea to frank malabsorption with steatorrhea. 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 and they 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 and, therefore, there is a hereditary component to the 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 three intestinal biopsies: one at diagnosis, one 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 still considered the gold standard for diagnosis, the availability of highly sensitive and specific serologic markers greatly facilitates the diagnosis of CD. These serologic tests are used to evaluate patients with suspected disease, monitor adherence and

response to a gluten-free diet, and screen patient with atypical, extraintestinal manifestations. 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 (AGA) can be detected using an ELISA test. EMA antibodies were originally detected using an 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 or a dot blot procedure. The dot blot test potentially 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. 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.

For HLA-DQ2 and HLA-DQ8 testing, refer to medical policy # 545-Human Leukocyte Antigen (HLA) Testing for Celiac Disease.

Policy:

Effective for dates of service on or after November 3, 2013:

Serologic measurement of antigliadin, antiendomysial or tissue transglutaminase antibodies meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage 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;

Serologic measurement of deamidated gliadin peptide antibodies does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** in patients with signs or symptoms suggestive of celiac disease.

Screening of asymptomatic at risk patient groups for celiac disease using one or more serologic IgA or IgG measures **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

Population screening for celiac disease using one or more serologic IgA or IgG measures **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

Effective for dates of service prior to November 3, 2013:

Serologic measurement of antigliadin or antiendomysial antibodies meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage when:

- Performed to evaluate patients with suspected disease; **OR**
- Performed to monitor patient's adherence and response to a gluten-free diet; **OR**
- Performed to evaluate patients with atypical, extraintestinal manifestations.

Screening of asymptomatic at risk patient groups for celiac disease using one or more serologic IgA or IgG measures **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

Population screening for celiac disease using one or more serologic IgA or IgG measures does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered investigational.

Blue Cross and Blue Shield of Alabama 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 Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate 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.

Key Points:

The age of presentation and prevalence of celiac disease has been altered over the last 30-40 years. The condition was previously thought to be a disease of childhood. However, adult presentation is increasingly common and celiac sprue can occur at any age.

The prevalence in different countries ranges widely. Several European studies have recently revealed values between 1:152 to 1:300 in countries that include Ireland, the United Kingdom, Italy, and Sweden. Studies from the United States have suggested that the condition affected 1:6000; however, a recent study involving serologic screening of blood donors suggested that this figure is more likely to be 1:250. Most researchers place the prevalence in the United States at 1:1000.

Serologic evaluation of celiac disease has been most widely researched in patients with nonspecific signs and symptoms of disease. In this setting, the negative predictive value is likely to be most informative, as these patients can forego a confirmatory biopsy.

Serologic diagnosis in individuals with signs or symptoms suggestive of celiac disease

National guidelines and position statements agree that serologic testing is the first step in diagnosing celiac disease and that the IgA antibody to human recombinant tissue transglutaminase (tTG) test is recommended. They all state that the IgA antibody to antiendomysium antibody (EMA) test has similar sensitivity and specificity to the tTG IgA test, but two of the national organizations mention that the EMA test is more prone to interpretation error. For individuals with known selective IgA deficiency, testing with tTG IgG and/or EMA IgG is recommended. The national organizations also agree that when test results are indeterminate, testing for the genetic markers HLA (human leukocyte antigen) -DQ2 or HLA-DQ8 is recommended. None of these guidelines and statements mentioned the newer deamidated gliadin peptide (DGP) antibody tests.

Several systematic reviews have evaluated the accuracy of commercially available serologic tests for celiac disease. In 2010, Lewis and Scott published a meta-analysis of studies in which both the tTG antibody tests and deamidated gliadin peptide (DGP) tests were performed. A total of 11 studies with 937 patients with untreated celiac disease and 1,328 individuals without known celiac disease were included. Among the controls, 636 had duodenal biopsy to exclude the presence of celiac disease. Pooled sensitivity for diagnosing celiac disease was significantly lower ($p < 0.001$) using DGP IgA tests (87.8%, 95% confidence interval [CI]: 85.6-89.9%) than tTG IgA tests (93%, 95% CI: 91.2-94.5%). The pooled specificity, 94.1% for DGP IgA and 96.5% for tTG IgA did not differ significantly. The meta-analysis did not present findings separately for individuals with and without known celiac disease. The authors concluded that, although both tests performed well, the tissue tTG antibody test out-performed the DGP antibody test and remains the serologic test of choice for diagnosing and/or excluding the diagnosis of celiac disease.

In a review of tests in children and adults published in 2005, Hill sought articles using biopsy examination as the gold standard. Of 27 studies on tTG IgA, sensitivities of 90% or more in 16 of 27 studies (range 54–100%), and specificities of 95% or more in 18 of 27 studies (range 79–100%) were reported. EMA IgA had sensitivities of 90% or more in 27 of 32 studies (range 86–100%) and specificities of 95% or more in all but 1 of 32 studies (range 90–100%). Both tests appeared to have comparable sensitivity and specificity in adults and children, although one study found the EMA IgA test less reliable in children (sensitivity 90% and specificity 98%). Hill also noted that no combination of tests was better than a single test using either EMA or tTG but that antigliadin antibody (AGA) IgA was less suitable due to generally lower test operating characteristics (sensitivity, specificity) compared to EMA IgA or tTG IgA. A 2006 meta-analysis of 32 studies of tTG antibody tests by Zintzaras and Germeis found pooled sensitivity for human tTG tests to be 94% with pooled specificities of 95% and 94% for recombinant and purified human ELISA assays, respectively. Guinea pig tTG had lower sensitivity and specificity than either human substrate sources.

Several head-to-head comparisons of serologic tests for celiac disease are described below. A study published by Naiyer and colleagues in 2009 compared the sensitivity of 4 tTG IgA assays that are commercially available in the U.S. and three deamidated gliadin peptide kits. The tTG IgA kits that were reviewed include the Inova tTG IgA, the Binding Site (recombinant human Ag), the Eurospital (recombinant human Ag) and the Immco (recombinant human Ag). The three DGP kits included were the Inova (antigliadin antibody [AGA] II-IgA), the Inova (AGA II-IgG), and the Inova (AGA-II IgA + IgG). The study used frozen serum samples from patients who were evaluated for celiac disease at a single center in the U.S. Group 1 (n=28) consisted of adult patients who had newly diagnosed (confirmed by biopsy) celiac disease. Group 2 (n=54) were patients with celiac disease who had been on a gluten-free diet for 2 to 87 months. There were two control groups. Group 3 (n=40) were healthy adults (normal controls) and Group 4 (n=57) were adult patients with hepatitis C or Crohn's disease (disease controls). Two patients from Group 1 were excluded from the analysis because biopsy results were not available. Using the manufacturer's recommended cutoff values, sensitivity of the four tTG IgA kits in patients with active celiac disease compared to disease controls ranged from 85.7% to 96.4%. The Immco kit had a specificity of 75.9%, and the other three had specificities over 90% (93.1% for the Binding Site test and 98.3% each for the Inova and Eurospital tests). There were no statistically significant differences among tests. The DGP kits had sensitivities ranging from 71.4% to 82.1% and specificities ranging from 94.8% to 98.3%, and there were no significant differences among the DGP kits. In receiver operating curve (ROC) analysis, there was a statistically significant difference between the areas under the curve (AUC) when two tTG IgA tests (by Inova and Eurospital) were compared to the Inova DGP-IgA test, favoring the tTG IgA tests. The authors mentioned that there may have been some selection bias favoring the tTG IgA tests; 23 out of 28 patients in Group 1 had initially been diagnosed with tTG IgA tests.

In 2010, Vermeersch and colleagues published a prospective study, conducted in Belgium, which compared four commercially available DGP assays and other serologic assays including three tTG IgA tests. Tests included DGP IgG assays by four companies, Euroimmun, Inova, Phadia, and The Binding Site, and IgA tests by BioRad, Phadia, and Genesis. Patients undergoing serologic tests and intestinal biopsies for symptoms of celiac disease were identified retrospectively. The sample consisted of 86 newly diagnosed celiac disease patients and 741 patients not found to have celiac disease. IgA tTG tests had been done at the time of patient presentation; other tests were performed on stored serum samples. Using cutoffs recommended by the manufacturer, the sensitivity of the four DGP IgG tests ranged from 77% to 84% and the specificity from 97% to 99%. The sensitivity of the tTG IgA tests ranged from 84% to 88%, and the specificity ranged from 92% to 98%. Overall, the diagnostic performance of the four DGP tests was comparable to the three IgG tests.

Another prospective study was published in 2010 by Sugai and colleagues; data were collected in Argentina. They conducted serology testing and duodenal biopsy in 679 adults; 161 considered high-risk (suspected but undiagnosed celiac disease) and 518 at low-risk for celiac disease (referred for routine upper gastrointestinal (GI) tract endoscopy due to non-specific symptoms not primarily related to celiac disease). The following data correspond to a cutoff of 20 U/mL for indicating a positive test. In the high-risk population, the sensitivity and specificity of the tTG IgA test was 95.2% and 97.9%, respectively. The sensitivity and specificity of the DGP IgA test was 98.4% and 92.7%, respectively. Corresponding percentages for the DGP IgG

test were 95.2% and 100%, respectively. Using ROC analysis and a cutoff of 20 U/mL, the AUC was 0.997 for the tTG IgA test, 0.995 for the DGP IgA test, and 0.989 for the DGP IgG test. A combined tTG and DGP test had a sensitivity of 100%, a specificity of 92.8%, and the AUC in ROC analysis was 0.999. In the low-risk population, sensitivities of the tTG, IgA, DGP IgA, and DGP IgG tests were 76.5%, 82.3% and 70.6%, respectively, and the specificities were 97.4%, 96.2%, and 99.0%, respectively.

Conclusions

Both tTG and EMA serologies show high accuracy for the diagnosis of celiac disease. Systematic reviews have estimated the sensitivity of these tests to be in the 85-95% range, and the specificity in the mid-90s. tTG may have a slightly higher sensitivity and may be less prone to interpretation error, and as a result, is often recommended as the initial serologic test. EMA may have a higher specificity than tTG and is often used as a second or confirmatory serologic test. Anti-gliadin antibodies have somewhat less accuracy and probably offer limited utility in addition to tTG and EMA.

Serologic testing in young children with signs and symptoms of celiac disease

A number of studies have suggested different patterns of serologic positivity in young children with celiac disease. As a result, there has been a substantial amount of research in this area in attempts to define the optimal serologic tests for this age group. Numerous studies have compared the diagnostic accuracy of various serologic tests in this population compared to the gold standard of intestinal biopsy. These studies have not reported consistent data on the accuracy of different serologic tests. A representative sample of the available studies is reviewed below.

A study by Lagerqvist and colleagues in Sweden investigated the optimal serologic test for younger children. This study used data from a population-based registry of children diagnosed with biopsy-confirmed celiac disease. A total of 430 children with celiac disease were included; two were then excluded because they had IgA deficiency, leaving 428 children in the analysis. The mean age at diagnosis was 16 months (range 7.5 months to 14 years); 327 (76%) were younger than two years at diagnosis. Two control groups were used; a disease control group consisting of 133 children admitted to the hospital on suspicion of having celiac disease but who had a negative biopsy. Four were excluded due to IgA deficiency, and 128 were included in the analysis. There was also a healthy control group of 87 children; no biopsies were performed on children in this group. In children younger than 18 months, the sensitivity of IgA antibodies against gliadin (AGA IgA) was 97% (95% CI: 94-99%), which was significantly higher than either the tTG IgA test with a sensitivity of 83% (78-88%) or the EMA IgA test, which also had a sensitivity of 83% (95% CI: 78-87%). The specificity of the AGA IgA test in the under 18 month's group was 88% (95% CI: 73-97%). This was lower (statistical significance not reported) than the tTG IgA (100%, 95% CI: 90-100%) and the EMA IgA (97%, 95% CI: 85-100%). Combining AGA IgA and tTG IgA in children under 18 months resulted in a sensitivity of 98% (when at least one of the tests was positive). The specificity of the combined test was not reported. In children 18 months or older, performance of both the tTG IgA and EMA IgA tests was better than the AGA IgA. The sensitivity of the AGA IgA test in the older age group was significantly lower (94%) than either of the other two tests, each of which had a sensitivity of 99%. Findings of this study support the policy statement that

serologic measurement of antigliadin antibodies may be considered medically necessary in children younger than 18 months of age.

A multicenter study from France evaluated whether AGA serology offered additional diagnostic accuracy when added to tTG and EMA. A total of 4,122 children were tested for celiac disease serology, and 397 had at least one positive serology with tTG, EMA, and AGA. Of these, 312 (79%) were positive for tTG, EMA, or both. There were 85 patients who were negative for both tTG and EMA, but positive for AGA. Of these 85 patients, clinical information was available for 62. Twenty-nine of the 62 children were considered to have other disorders, and a biopsy was not undertaken. An intestinal biopsy was performed in 33 patients, and only five of these were found to have celiac disease. These data suggest that AGA has limited utility in patients who are negative for tTG and EMA. A small number of additional cases of celiac disease may be identified, but the vast majority of individuals will have other disorders. Use of AGA may lead to a large number of unnecessary endoscopies with biopsy.

Panetta et al evaluated the accuracy of tTG in 169 children younger than two years-old. All patients had symptoms suggestive of celiac disease and had undergone biopsy. A total of 108 children showed biopsy evidence of celiac disease and 47 did not. At a cutoff level of 8 AU/mL, the sensitivity and specificity were 96% (95% CI: 91-99%) and 91% (95% CI: 80-98%); at a cutoff of 16 AU/mL the sensitivity and specificity were 79% (95% CI: 70-86%) and 100% (95% CI: 92-100%) – all respectively. These results suggest that the accuracy of tTG in young children is similar to that seen for older individuals.

Mubarak et al performed serologic testing in 212 children who had undergone a biopsy for workup of celiac disease, 41 of whom were younger than two years-old. Two commercial kits were used to test for deamidated gliadin peptides (DGPs), using both IgG- and IgA-based tests. The positive and negative predictive values were generally fairly high, ranging from 74-91%. These values were in the same range as tTG and EMA serologies, which had predictive values ranging from 77-97%. The single best test in children younger than age two years was IgG deamidated gliadin, which had no false positive results and thus a positive predictive value of 100%.

Hojdak et al identified 59 children who were younger than three years of age and had both serologic tests and intestinal biopsy performed. Forty-seven children had celiac disease on biopsy and 12 did not. Four serologic tests were compared on their performance characteristics: tTG, EMA, DGP, and AGA. All tests were sensitive, ranging from 96-100%. tTG had a reduced specificity of 50% and DGP had a sensitivity of only 44%, when using the manufacturer's recommended cut point. In contrast, EMA had a high specificity at 91%. ROC analysis revealed a higher AUC for EMA (96.8%) compared to 89.3% for tTG and 88.2% for DGP. The authors did not address the clinical or statistical significance of these differences in accuracy.

Conclusions

Serologic patterns of celiac disease differ in young children compared to older age groups. Some studies report a reduced sensitivity of TTG and EMA tests in children younger than two years-old, but others do not. AG antibodies, used in combination with TTG and EMA, may be

more useful in this situation because of the reduced accuracy of the other tests. Some studies report substantially improved accuracy when using AG antibodies.

Combination and/or sequential testing

Several studies have evaluated use of multiple serologic tests, either in combination or sequence, in efforts to improve upon the diagnostic accuracy of any single test.

In 2008, Hopper and colleagues conducted a prospective study in the U.K. that evaluated combinations of tTG and EMA in 2,000 adult patients without a previous history of celiac disease. Duodenal biopsy was performed in all patients and was used as the gold standard. A total of 77/2,000 (3.9%) patients were diagnosed with celiac disease based on histologic findings. Various serologic testing strategies were evaluated; results are as follows:

Serologic test	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Only tTG positive	90.9 (82.4-94.5)	90.9 (89.5-92.1)
Only EMG positive	87.0 (77.7-92.8)	98.0 (97.4-98.60)
Both positive	85.7 (76.2-91.8)	98.6 (98.0-99.0)
Either positive	92.2 (84.0-96.4)	90.3 (88.9-91.6)
If tTG positive, then EMA positive (2 step)	85.7 (76.2-91.8)	98.6 (98.0-99.0)

The tTG test alone was more sensitive than the EMA test alone, with a somewhat lower specificity. Use of a combination approach (both tests positive, either positive or a two-step approach) did not clearly improve the overall test accuracy. The authors note that the sensitivities of the tTG only and EMA only approaches were somewhat lower than in other studies but state that this may be because the current study was prospective and/or because it included a lower-risk population.

Katz et al used a combination of tTG and EMA serologies to identify celiac disease in 3,850 residents in one county in Wyoming. A total of 18 patients were positive for both tests and underwent a small bowel biopsy. On biopsy, 17 of 18 patients had evidence of celiac disease, meaning that the positive predictive value of combination testing was 94%. This study provides no information about the negative predictive values.

Basso et al evaluated a number of diagnostic algorithms using sequential serologic testing in 329 children with documented celiac disease and 374 control children. These authors set the cutoff to achieve 100% specificity and calculated the resulting sensitivity and predictive values. The most sensitive single test was IgA tTG at 75.7%. The most accurate sequence of tests was IgA tTG followed by the QUANTA Lite™ TTG/DGP screen. This sequence of testing yielded an overall accuracy of 78.7% and a negative predictive value of 97.3%.

Some authors have advocated that a high-positive titer for tTG indicates a very high sensitivity and specificity for the diagnosis of celiac disease. Using this principle, a high-positive tTG is sufficient to make the diagnosis of celiac disease, while a low-positive or negative titer should be followed up with additional serologies and/or intestinal biopsy. Mubarak et al used a cutoff for tTG of 100 U/mL in a prospective study of 183 children. These authors reported that 87/130 patients with a positive tTG had levels of at least 100 U/mL. All patients with a tTG at that

level had celiac disease, for a specificity and positive predictive value of 100%. Alessio et al performed a retrospective evaluation of 412 consecutively referred patients who underwent small bowel biopsy for suspected celiac disease. A tTG ratio of at least seven times normal was found to correctly classify all patients as celiac disease, yielding a specificity and positive predictive value of 100%.

Conclusions:

Sequential and combination testing has the potential to improve the diagnostic accuracy of serology compared to any single test alone. When positive serology is defined as both tTG and EMA being positive, the specificity will improve to close to 100% but with some loss of sensitivity. Using the tests sequentially yields similar diagnostic accuracy. Raising the positive threshold for tTG to high levels, e.g., five to ten times normal, results in a very high specificity, raising the potential that a high-positive result on tTG may be sufficient as a single diagnostic test for celiac disease.

Screening asymptomatic at-risk patient groups for celiac disease using serologic testing

Screening that targets at-risk subpopulations was undertaken by Catassi et al. in a multicenter prospective case-finding study of internal medicine and primary care practices in North America. A number of at-risk groups were identified using self-reported questionnaires at the time of office visit; they include those previously listed in this policy, as well as infertility, epilepsy, chronic fatigue, irritable bowel syndrome, recurrent abdominal pain or bloating, and unexplained anemia. Serum tTG IgA testing was performed in 976 adults and was followed by EMA IgA if high (>7.0 arbitrary units) (n=30). The 22 patients with EMA-positive tests were then advised to undergo intestinal biopsy and human leukocyte antigen (HLA) testing. Of 15 biopsies performed, 15 cases of celiac disease were diagnosed. Diagnosis of celiac disease increased from 0.27 cases/1,000 visits in the 12 months preceding the study to 8.6 cases/1,000 visits during the study. This study does not adequately address the question of the potential value of screening for celiac disease in populations considered at high risk.

Population screening for celiac disease using serologic testing

A feasibility study from Europe for a population-based screening program of six year-olds was reported by Korponay-Szabó et al. Nurses performed rapid testing for IgA and tTG and laboratory testing for tTG IgA, IgA-EMA, and EMA IgG among 2,676 of 3,518 eligible children in a county in Hungary. Five children had been diagnosed with celiac disease prior to the study and were not included. Thirty-two new cases of celiac disease were diagnosed (in 25 of 28 with a positive rapid test result, in six of 14 with negative rapid test but positive on all laboratory tests, and in one of one with negative rapid test, negative IgA tests but positive IgG test). The rapid test had a sensitivity of 78.1% and a specificity of 100%. Seropositive cases missed by the rapid test had no villous atrophy on biopsy or were IgA deficient (n=1). None of the 32 newly diagnosed children were previously judged chronically ill, but they had common clinical problems found in untreated celiac disease, such as underweight, iron deficiency, and autoimmune thyroid disease. A gluten-free diet was prescribed for all children, and at six-month follow-up, their mean hemoglobin values and body mass index had increased significantly. A screening program should have clear benefits of an early diagnosis and effective treatment. Case finding and subsequent adherence to a gluten-free diet may improve

symptoms and quality of life for those affected, while other health improvements are unknown. Additional studies may help delineate the long-term clinical benefits of a screening program.

Summary

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 two 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 anti gliadin antibodies is more sensitive than either of the other two tests. Other studies have corroborated that the accuracy of tTG in children younger than two 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 two 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.

Practice Guidelines and Position Statements

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 antiendomysial antibodies (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-gastrointestinal 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 two-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 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 U.S. Preventive Services Task Force (USPSTF) related to screening for celiac disease in children or adults.

Key Words:

Celiac disease, CD, celiac sprue, serologic tests

Approved by Governing Bodies:

FDA approved

Benefit Application:

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

ITS: Home Policy provisions apply

FEP contracts: Special benefit consideration may apply. Refer to member's benefit plan.

Pre-certification/Pre-determination requirements: Not 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
86255	Fluorescent noninfectious agent antibody; screen, each antibody
86256	Fluorescent noninfectious agent antibody; titer, each antibody
86816	HLA typing; DR/DQ, Single Antigen
88347	Immunofluorescent study, each antibody; indirect method

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Policy History:

Medical Policy Group, May 2004

Medical Policy Administration Committee, June 2004 (2)

Available for comment June 28-August 11, 2004

Medical Policy Group, May 2007 (1)

Medical Policy Group, November 2008 (2)

Medical Policy Group, February 2009 (1)

Medical Policy Administration Committee, March 2009

Available for comment March 4-April 17, 2009

Medical Policy Group, September 2010 (1)

Medical Policy Group, January 2012 (1): Update to Key Points and References related to MPP update; no change in policy statement

Medical Policy Panel, January 2013

Medical Policy Group, September 2013 (1): Deaminated gliadin peptide antibodies are considered investigational and verbiage is added to policy statement, rest of policy statement reconfigured for clarification purposes, along with the addition of tissue transglutaminase to coverage criteria; addition of CPT codes 81377, 81382 and 81383 related to genetic testing for HLA-DQ2/8; update to Key Points and References

Medical Policy Administration Committee, September 2013

Available for comment September 19 through November 2, 2013

Medical Policy Group, January 2014 (1) Removed all aspects of HLA-DQ testing related to celiac disease and created new policy #545; no other changes noted to policy

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case by case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.