MEDICAL POLICY

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POLICY TITLE	SEROLOGIC DIAGNOSIS OF CELIAC DISEASE
POLICY NUMBER	MP-2.228

Original Issue Date (Created):	**May 3, 2004**
Most Recent Review Date (Revised):	**September 24, 2013**
Effective Date:	**November 1, 2013**

I. POLICY

Serologic measurement of tissue transglutaminase or antiendomysial antibodies may be considered **medically necessary** in patients with signs or symptoms suggestive of celiac disease.

Serologic measurement of antigliadin antibodies may be considered **medically necessary** in children less than 24 months of age with signs or symptoms suggestive of celiac disease.

HLA-DQ2 and HLA-DQ8 testing may be considered **medically necessary** 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.

The following are considered **investigational** as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with these procedures:

- Screening of asymptomatic at risk patient groups for celiac disease using one or more serologic IgA or IgG measures.
- Population screening for celiac disease using one or more serologic IgA or IgG measures.
- Serologic measurement of deamidated gliadin peptide antibodies in patients with signs or symptoms suggestive of celiac disease.

II. PRODUCT VARIATIONS

[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

[N] Capital Cares 4 Kids
[N] PPO
[N] HMO
[N] SeniorBlue HMO
[N] SeniorBlue PPO
[N] Indemnity
[N] SpecialCare
[N] POS
[Y] FEP PPO*

The FEP program dictates that all drugs, devices or biological products approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational. Therefore, FDA-approved drugs, devices or biological products may be assessed on the basis of medical necessity.

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III. DESCRIPTION\BACKGROUND

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 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 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.

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Clinical Manifestation of Celiac Disease

General	Gastrointestinal	Extraintestinal
• Short stature • Weight loss • Failure to thrive • Lassitude • Lethargy • Clubbing • Delayed puberty • Peripheral edema	• Diarrhea • Steatorrhea • Flatulence • Abdominal distension • Anorexia • Nausea, vomiting • Recurrent apthous stomatitis • Angular cheilosis • Glossitis • Hepatic Steatosis	Laboratory abnormalities Iron/folate deficiency anemia Hypocalcemia Skin Dermatitis herpetiformis 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 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 U.S. 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 a10% 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 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 (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. Antiendomysial antibodies (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 (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.

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 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 is offered by several laboratories such as Quest, LabCorp, and Prometheus.

IV. RATIONALE

The most recent update with literature review for this policy includes the period up to December 2012.

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. (3-5) 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. (6) 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 outperformed 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. (7) 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 1 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 Germenis 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. (8) 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 3 deamidated gliadin peptide kits. (9) 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 3 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 2 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 4 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 3 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 2 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 4 commercially available DGP assays and other serologic assays including 3 tTG IgA tests. (10) Tests included DGP IgG assays by 4 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 4 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 4 DGP tests was comparable to the 3 IgG tests.

Another prospective study was published in 2010 by Sugai and colleagues; data were collected in Argentina. (11) 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. (12) A total of 430 children with celiac disease were included; 2 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 2 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 months 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 1 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 2 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 (13) 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 5 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. (14) evaluated the accuracy of tTG in 169 children younger than 2 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. (15) performed serologic testing in 212 children who had undergone a biopsy for workup of celiac disease, 41 of whom were younger than 2 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 2 years was IgG deamidated gliadin, which had no false positive results and thus a positive predictive value of 100%.

Hojsak et al. (16) identified 59 children who were younger than 3 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 2 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. (17) 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 EMA 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 2-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 because the current study was prospective and/or because it included a lower-risk population.

Katz et al. (18) 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. (19) 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 (20) 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. (21) performed a retrospective evaluation of 412 consecutively referred patients who underwent small bowel biopsy for suspected celiac disease. A tTG ratio of at least 7 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., 5-10 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. (22) 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 6 year-olds was reported by Korponay-Szabó et al. (23) 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 6 of 14 with negative rapid test but positive on all laboratory tests, and in 1 of 1 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 6-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 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.

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. (4)

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. (5)

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 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. (3)

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

V. DEFINITIONS

INTRALUMINAL means within the lumen of any tubular structure or organ.

MALABSORPTION is a disordered or inadequate absorption of nutrients from the intestinal tract, especially the small intestine. The syndrome may be associated with or due to a number of diseases, including those affecting the intestinal mucosa, such as infections, tropical sprue, celiac disease, pancreatic insufficiency, or lactase deficiency. It may also be due to surgery such as gastric resection and ileal bypass, or to antibiotic therapy, such as neomycin.

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital for benefit information.

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VII. DISCLAIMER

Capital's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

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IX. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

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CPT Codes®								
83516	86816	86817	88347					

ICD-9-CM Diagnosis Code*	Description
579.0	CELIAC DISEASE

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

The following ICD-10 diagnosis codes will be effective October 1, 2013:

ICD-10-CM Diagnosis Code*	Description
K90.0	Celiac disease

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

X. POLICY HISTORY

MP 2.228	**CAC 10/28/03**
	CAC 5/31/05
	CAC 5/30/06
	CAC 9/26/06
	CAC 9/25/07
	CAC 9/30/08
	CAC 9/29/09 Consensus Review
	CAC 11/30/10 Consensus Review
	CAC 11/22/11 Adopting BCBSA. Added new policy statement indicating that serologic measurement of deamidated gliadin peptide antibodies is investigational. Other medically necessary and investigational policy statements remain unchanged.
	Admin Change 1/26/12 The following administrative changes were made to reflect 1:2012 BCBSA policy change. Policy statement removed indicating the use of combination tests is <u>not medically necessary</u>. The age limit for the policy statement regarding testing in children was changed from 18 months to 24 months.
	7/25/13 Admin coding review complete--rsb
	CAC 9-24-13 Consensus. No change to policy statements. References updated.

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	Rationale Section added. Deleted FEP variation referencing policy manual. Standard FEP variation inserted.

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