Celiac Disease Testing

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<th>Policy Number: APEA – G2043 – Celiac Disease Testing</th>
<th>Initial Presentation Date: 7/01/2020</th>
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**Policy Description**

Celiac disease is a hereditary, chronic autoimmune disorder triggered by the ingestion of gluten, a protein found in wheat, rye, and barley. When an individual with celiac disease ingests gluten, the body mounts an immune response that attacks the small intestine. These attacks lead to damage on the villi within the small intestine, inhibiting nutrient absorption (CDF, 2018).

**Related Policies**

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<td>AHS-G2121</td>
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**Indications and/or Limitations of Coverage**

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request

1. Serologic testing for the diagnosis of celiac disease **MEETS COVERAGE CRITERIA** with the IgA anti-tissue transglutaminase (TTG) and the total IgA test for individuals with a suspicion of celiac disease as defined as having ONE of the following:
   a. Unexplained chronic or intermittent diarrhea
   b. Unexplained weight loss
   c. Unexplained chronic or intermittent abdominal pain or bloating
   d. Down syndrome
   e. Dermatitis herpetiformis
   f. Unexplained iron deficiency anemia
   g. Unexplained liver transaminase elevations
h. Primary biliary cirrhosis
i. Autoimmune hepatitis
j. Unexplained osteoporosis or low bone density
k. Other conditions that may be associated with non-classical CD
l. Asymptomatic first- and second-degree relatives of individuals with documented CD

2. Testing for IgA endomysial antibodies **MEETS COVERAGE CRITERIA** in individuals at risk for celiac disease (as defined above) when IgA anti-TTG is negative.

3. Testing for IgG anti-TTG **MEETS COVERAGE CRITERIA** in individuals with clinical suspicion of celiac disease, as defined above, with an IgA deficiency.

4. Testing for IgA and IgG antibodies to deamidated gliadin peptides **MEETS COVERAGE CRITERIA** for the diagnosis of celiac disease in children under 2 years of age with a clinical suspicion of celiac disease as defined above and in those over 2 years of age as a substitute for anti-TTG testing.

5. Genetic testing for HLA DQ2 and DQ8 **MEETS COVERAGE CRITERIA** for:
   a. Symptomatic individuals for whom other testing is undiagnostic or
   b. Symptomatic individuals with positive serology tests who are unable to undergo biopsy evaluation

6. Biopsy of the small intestine **MEETS COVERAGE CRITERIA** for confirmation of celiac disease for individuals at high risk for celiac disease regardless of the result of celiac disease serology testing.

7. Rapid antigen point-of-care testing for anti-TTG **DOES NOT MEET COVERAGE CRITERIA**.

8. Panel testing, multiplex, or multi-analyte testing (for more than two analytes) for the diagnosis or the evaluation of celiac disease **DOES NOT MEET COVERAGE CRITERIA**.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient’s illness.


10. Testing of stool or saliva samples for the evaluation of celiac disease **DOES NOT MEET COVERAGE CRITERIA**.

11. Serologic testing using an HLA-DQ-gluten tetramer-based assay, including flow cytometry-based HLA-DQ-gluten tetramer assays, **DOES NOT MEET COVERAGE CRITERIA**.

**Scientific Background**

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK, 2016) provides the following statistics for celiac disease:

- An estimated 1 in 141 Americans has celiac disease
Majority of people are unaware of their status

Can affect all races, but higher rate in Caucasians

Can affect both genders, but higher rate in females

More common among people with Down syndrome, Turner syndrome, and type 1 diabetes

Patients with celiac disease are at risk for Addison’s disease, Hashimoto’s disease, primary biliary cirrhosis, and type 1 diabetes

Clinical presentation of celiac disease is varied and age-dependent. In children, failure to thrive, malnutrition, diarrhea, abdominal pain, and distension is a common presentation of celiac disease. In adults, abdominal pain, diarrhea or constipation, bloating, and excessive gas are commonly seen. Other gastrointestinal symptoms include unexpected weight loss and distension (Kelly, 2019).

Serologic tests are useful in diagnosing celiac disease with IgA anti-tissue transglutaminase (tTG-IgA) antibody being the preferred serologic test for patients. Antibodies for assessment of celiac disease generally fall into one of two categories: autoantibodies (tTG-IgA, anti-endomysial antibody [EMA-IgA] or antibodies targeting gliadin (DGP-IgA or IgG). Endomysial antibodies bind to a tissue transglutaminase and produce a characteristic staining pattern. Similarly, anti-endomysial antibodies bind to tTG-2, another tissue transglutaminase. The other category of celiac antibodies involve gliadin, which is a component of gluten. Traditional antigliadin antibody tests (AGA-IgA, AGA-IgG) yielded a false positive rate of up to 20%, so they have been replaced with a deamidated gliadin peptide (DGP) (Kelly, 2019).

Celiac disease also has a genetic component. The two primary genetic factors are the human leukocyte antigen (HLA)-DQ2 and DQ8 alleles. These genes highlight the role of T cells and the immune response in celiac disease (Tye-Din, Galipeau, & Agardh, 2018). 90-95% of CD patients have the HLA-DQ2 protein encoded by HLA-DQA1*05 and DQB1*02 alleles. The remaining CD patients have mutations in the HLA-DQ8 protein encoded by the HLA-DQA1*03 and DQB1*03:02 alleles. Stankovic et al noted that the absence of susceptible HLA-DQ genotypes makes CD “very unlikely, close to 100%” (Stankovic et al., 2014). However, the use of genotyping in diagnosing CD is not without controversy. Paul and colleagues (Paul, Hoghton, & Sandhu, 2017) report that 25-40% of white Caucasians are positive for the HLA-DQ2/DQ8 haplotype but that only 0.1-1% of the population will develop celiac disease. They note that the European guidelines released in 2012 recommend genotyping for HLA-DQ2/DQ8 in children with very high anti-TTG titers, but the authors recommend the following: “HLA-DQ2/DQ8 testing must not be done to ‘screen’ or ‘diagnose’ children with coeliac disease (Paul et al., 2017).”

Serologic and histologic HLA-DQ testing requires the patient to be on a gluten-containing diet, which can be a disadvantage to testing. Recently, testing for HLA-DQ-gluten tetramer-based assays using flow-cytometry have been developed that reportedly can be accurate whether the patient is on a gluten-containing or gluten-free diet. The assay has a reported 97% sensitivity and 95% specificity for patients on a gluten-free diet as compared to controls (patients without celiac disease). The authors conclude, “This test would allow individuals with suspected celiac disease to avoid gluten challenge and duodenal biopsy, but requires validation in a larger study (Sarna et al., 2018).” Other markers, such as wheat sIgE, have been incorporated into molecular panels for CD, such as the one offered by TrueHealth (TrueHealth, 2019). Still other tests focus on subfractions of the gliadin molecule apart from the typical alpha-gliadin portion (Cyrex, 2017). Finally, direct-to-consumer (DTC) testing exists for celiac disease as well. The FDA-approved 23andme panel includes celiac disease. This test detects a single nucleotide polymorphism in HLA-DQA1 (FDA, 2017).

Validity and Utility
Olen et al (2012) evaluated diagnostic performance and actual costs in clinical practice of immunoglobulin (Ig)G/IgA DGP (deamidated gliadin peptide antibodies) as a complement to IgA-TTG for the diagnosis of pediatric CD. The authors identified 278 children with CD that went duodenal biopsy. Sensitivity and specificity for tTG were 94% and 86% respectively, but corresponding values for DGP were 91% and 26%. Positive predictive values were 88% for tTG and 51% for DGP. The authors concluded that for diagnosing CD, TTG is superior to DGP, even in children younger than 2 years. Combining TTG and DGP does not provide a better trade-off between number of missed cases of CD, number of unnecessary duodenal biopsies, and cost than TTG alone (Olen et al., 2012).

Sakly et al (2012) evaluated the usefulness of anti-DGP antibodies (a-DGP), in the diagnostic of celiac disease. Their study included 103 untreated CD patients of all ages and 36 CD patients under a gluten-free diet. The specificity of A-DGP for IgG was 93.6% and for IgA was 92% as compared to the 100% for each by anti-endomysium antibodies (AEA) and TTG. The authors concluded that the findings of this study showed “that a-DGP increases neither the sensitivity nor the specificity of AEA and [TTG] (Sakly et al., 2012)”.  

Bufler et al evaluated the diagnostic performance of three serological tests for CD. 91 children with CD contributed 411 sera samples and were compared to 98 healthy controls. Transglutaminase type 2(TG2)-IgA, deamidated gliadin peptide (DGP)-IgG and DGP-IgA were measured. Sensitivity for diagnosis was high for TG2-IgA and DGP-IgG (>90%) but lower for DGP-IgA. Specificity was >97% for all three. Non-adherence to a gluten-free diet was best indicated by positive TG2-IgA. The authors concluded that “combined testing for TG2-IgA and DGP-IgG does not increase the detection rate of CD in IgA competent children compared to TG2-IgA only” (Bufler et al., 2015).

Silvester et al performed a meta-analysis to evaluate the "sensitivity and specificity of tTG IgA and EMA IgA assays in identifying patients with celiac disease who have persistent villous atrophy despite a gluten-free diet (GFD)". The authors identified 26 studies for inclusion. The assays were found to have high specificity for identifying patients with persistent villous atrophy (0.83 for tTG IgA, 0.91 for EMA IgA, but with low sensitivity (0.50 for tTG IgA, 0.45 for EMA IgA). No significant difference was seen between pediatric and adult patients. The authors concluded that "we need more-accurate non-invasive markers of mucosal damage in children and adults with celiac disease who are following a GFD” (Silvester et al., 2017).

A 2018 report (Selleski et al., 2018) shows that only some of the DQ2/DQ8 alleles were significantly different between pediatric CD patients and pediatric non-CD patients. 97% of the CD patients were positive for at least either DQ2 or DQ8; however, 29.9% of the non-CD patients were also positive for DQ2. In fact, “No significant association was found between DQ2.2 variant and celiac disease in the studied population (Selleski et al., 2018).” Previously, high regard had been given to DQ2.2 variant as being a predisposing variant for CD (Mubarak et al., 2013). Finally, a rapid nucleic acid amplification test using multiplex ligation-dependent probe amplification (MLPA) to detect HLA-DQ2.2, HLA-DQ2.5, and HLA-DQ8 has been developed with a reported 100% specificity for those particular genotypes (Vijzelaar et al., 2016), but this test has not been FDA-approved for use in the United States.

Bajor et al performed a meta-analysis focusing on the association between the HLA-DQB1*02 gene doses and the characteristics of CD. The authors identified 24 studies for inclusion in the review and observed that homozygosity of the DQB1*02 allele led to more frequent classical CD (odds ratio [OR] 1.758). The gene dosing effect was more prominent in children (OR: 2.082) Atrophic histology (Marsh grade 3) was more prevalent with a double dose compared to a zero dose (OR: 2.626). No gene dosing effect was seen with diarrhea, age at diagnosis, severity of villous atrophy, or type 1 diabetes. The authors concluded that “A double dose of HLA-DQB1*02 gene seems to predispose patients to developing classical CD and villous atrophy. Risk stratification by HLA-DQB1*02 gene dose requires further clarification due to the limited available evidence” (Bajor et al., 2019).
Guidelines and Recommendations

2013 American College of Gastroenterology (ACG)

The American College of Gastroenterology (ACG) recommends to test for celiac disease in the following (Rubio-Tapia, Hill, Kelly, Calderwood, & Murray, 2013):

1. “Patients with symptoms, signs, or laboratory evidence suggestive of malabsorption, such as chronic diarrhea with weight loss, steatorrhea, postprandial abdominal pain and bloating, should be tested for CD. (Strong recommendation, high level of evidence)”

2. “Patients with symptoms, signs, or laboratory evidence for which CD is a treatable cause should be considered for testing for CD. (Strong recommendation, moderate level of evidence)”

3. “Patients with a first-degree family member who has a confirmed diagnosis of CD should be tested if they show possible signs or symptoms or laboratory evidence of CD. (Strong recommendation, high level of evidence)”

4. “Patients with type I diabetes mellitus should be tested for CD if there are any digestive symptoms, or signs, or laboratory evidence suggestive of celiac disease. (Strong recommendation, high level of evidence)”

5. “Celiac disease should be sought among the explanations for elevated serum aminotransferase levels when no other etiology is found, (Strong recommendation, high level of evidence)”

6. “Consider testing of asymptomatic relatives with a first-degree family member who has a confirmed diagnosis of CD (Conditional recommendation, high level of evidence)”

The ACG guidelines indicate that “Immunoglobulin A (IgA) anti-tissue transglutaminase (TTG) antibody is the preferred single test for detection of CD in individuals over the age of 2 years.” Also, if there is “a high probability of CD wherein the possibility of IgA deficiency is considered, total IgA should be measured.” Additionally, “an alternative approach is to include both IgA and IgG-based testing, such as IgG-deamidated gliadin peptides (DGPs), in these high-probability patients.” In those patients with low or deficient IgA, the ACG recommends “IgG-based testing (IgG DGPs and IgG TTG).” The guidelines also indicate that all serological testing should be done while the individual is on a gluten-containing diet.

Intestinal biopsy is recommended by the ACG for individuals with positive serology testing and for those with a clinical presentation consistent with CD, “even if the serologies are negative.”

Although antibodies directed against native gliadin are not recommended for the primary detection of CD,” the ACG notes that “when screening children younger than 2 years of age for CD, the IgA TTG test should be combined with DGP (IgA and IgG).”

With regard to HLA-DQ2 / DQ8 genotype testing, the ACG recommends that it “should not be used routinely in the initial diagnosis of CD” but rather “should be used to effectively rule out the disease in selected clinical situations” such as, “equivocal small-bowel histological finding (Marsh I-II) in seronegative patients; evaluation of patients on a GFD in whom no testing for CD was done before GFD; patients with discrepant celiac-specific serology and histology; patients with suspicion of refractory CD where the original diagnosis of celiac remains in question; or patients with Down’s syndrome... Because HLA-DQ2 is present in approximately 25%-30% of the white population, testing for CD with either HLA-DQ type is not useful because the PPV is only about 12%. “ Concerning HLA typing, “HLA typing and histological response may help to rule out or confirm the diagnosis of CD in patients with sero-negative CD.”

The ACG does not recommend stool or salivary testing, indicating that are not validated for use in the diagnosis of CD.
The ACG advocates monitoring of adherence to a gluten-free diet, based on “a combination of history and serology.” Additionally, “upper endoscopy with intestinal biopsies is recommended for monitoring in cases with lack of clinical response or relapse of symptoms despite a GFD.”

Celiac Disease Diagnostic Testing Algorithm (Rubio-Tapia et al., 2013)

2019 American Gastroenterological Association (AGA)

Relative to ongoing monitoring of individuals with celiac disease, the AGA recommends periodic serologic testing.

The AGA published an update on CD testing in 2019. Their new “best practice advice” is as follows:

- “Best Practice Advice 1: Serology is a crucial component of the detection and diagnosis of CD, particularly tissue transglutaminase–immunoglobulin A (TG2-IgA), IgA testing, and less frequently, endomysial IgA testing.”
- “Best Practice Advice 2: Thorough histological analysis of duodenal biopsies with Marsh classification, counting of lymphocytes per high-power field, and morphometry is important for diagnosis as well as for differential diagnosis.”
- “Best Practice Advice 2a: TG2-IgA, at high levels (> ×10 upper normal limit) is a reliable and accurate test for diagnosing active CD. When such a strongly positive TG2-IgA is combined with a positive endomysial antibody in a second blood sample, the positive predictive value for CD is virtually 100%. In adults, esophagogastroduodenoscopy (EGD) and duodenal biopsies may then be performed for purposes of differential diagnosis.”
- “Best Practice Advice 3: IgA deficiency is an infrequent but important explanation for why patients with CD may be negative on IgA isotype testing despite strong suspicion. Measuring total IgA levels, IgG deamidated gliadin antibody tests, and TG2-IgG testing in that circumstance is recommended.”
• “Best Practice Advice 4: IgG isotype testing for TG2 antibody is not specific in the absence of IgA deficiency.”

• “Best Practice Advice 5: In patients found to have CD first by intestinal biopsies, celiac-specific serology should be undertaken as a confirmatory test before initiation of a gluten-free diet (GFD).”

• “Best Practice Advice 6: In patients in whom CD is strongly suspected in the face of negative biopsies, TG2-IgA should still be performed and, if positive, repeat biopsies might be considered either at that time or sometime in the future.”

• “Best Practice Advice 7: Reduction or avoidance of gluten before diagnostic testing is discouraged, as it may reduce the sensitivity of both serology and biopsy testing.”

• “Best Practice Advice 8: When patients have already started on a GFD before diagnosis, we suggest that the patient go back on a normal diet with 3 slices of wheat bread daily preferably for 1 to 3 months before repeat determination of TG2-IgA.”

• “Best Practice Advice 9: Determination of HLA-DQ2/DQ8 has a limited role in the diagnosis of CD. Its value is largely related to its negative predictive value to rule out CD in patients who are seronegative in the face of histologic changes, in patients who did not have serologic confirmation at the time of diagnosis, and in those patients with a historic diagnosis of CD; especially as very young children before the introduction of celiac-specific serology” (Steffen Husby, Murray, & Katzka, 2019).

2012 European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESP-GHAN) (S. Husby et al., 2012)

The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESP-GHAN) recommends that CD testing be considered for: “children and adolescents with the otherwise unexplained symptoms and signs of chronic or intermittent diarrhoea, failure to thrive, weight loss, stunted growth, delayed puberty, amenorrhea, iron-deficiency anaemia, nausea or vomiting, chronic abdominal pain, cramping or distension, chronic constipation, chronic fatigue, recurrent aphthous stomatitis (mouth ulcers), dermatitis herpetiformis-like rash, fracture with inadequate traumas/osteopenia/osteoporosis, and abnormal liver biochemistry.” Testing should also be offered to “asymptomatic children and adolescents with an increased risk for CD such as type 1 diabetes mellitus (T1DM), Down syndrome, autoimmune thyroid disease, Turner syndrome, Williams syndrome, selective immunoglobulin A (IgA) deficiency, autoimmune liver disease, and first-degree relatives with CD.”

ESP-GHAN recommends that “the initial test be IgA class anti-TG2 from a blood sample. If total serum IgA is not known, then this also should be measured.” If the individual has humoral IgA deficiency, “at least 1 additional test measuring IgG class CD-specific antibodies should be done (IgG anti-TG2, IgG anti-DGP or IgG EMA.” They also note that “tests measuring antibodies against DGP may be used as additional tests in patients who are negative for other CD-specific antibodies but in whom clinical symptoms raise a strong suspicion of CD, especially if they are younger than 2 years,” and “tests for the detection of IgG or IgA antibodies against native gliadin peptides (conventional gliadin antibody test) should not be used for CD diagnosis.” They also indicate that “tests for the detection of antibodies of any type in faecal samples should not be used.”

For individuals with “severe symptoms and a strong clinical suspicion of CD” and negative serology testing, “small intestinal biopsies and HLA-DQ testing are recommended.”

With regard to the evaluation of asymptomatic children and adolescents with CD-associated conditions, ESP-GHAN recommends HLA testing “should be offered as the first line test,” due to its high negative predictive value. “If the patient is DQ8 and/or DQ2 positive, homozygous for only the b chains of the HLA-DQ2 complex (DQ81_0202), or HLA testing is not done, then an anti-TG2 IgA test and total IgA determination should be performed, but preferably not before the child is 2 years old. If antibodies are negative, then repeated testing for CD-specific antibodies is recommended.”
ESP-GHAN also recommends that in asymptomatic individuals at increased genetic risk for CD “duodenal biopsies with the demonstration of an enteropathy should always be part of the CD diagnosis.” As an initial step, “it is recommended that the more specific test for EMA be performed. If the EMA test is positive, then the child should be referred for duodenal biopsies. If the EMA test is negative, then repeated serological testing on a normal gluten-containing diet in 3 to 6 monthly intervals is recommended.” Testing of infants, as with all serologic testing for CD, should be done only when the individual is on a gluten-containing diet.

**2015 North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) (Hill et al., 2016)**

NASPGHAN updated their recommendations in 2015 (published in 2016) for gluten-related disorders, including CD, wheat allergy (WA), and nonceliac gluten sensitivity (NCGS). Concerning who should be tested for gluten-related disorders, “Children with symptoms consistent with gluten-related disorders, or who have self-identified relief of symptoms when avoiding gluten, should undergo testing for CD and/or WA before the elimination of dietary gluten. CD should be an early consideration in those with typical gastrointestinal symptoms such as chronic diarrhea, abdominal pain, distension, and weight loss.” The table below outlines their recommendations for considering CD testing:

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Associated conditions</th>
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<tbody>
<tr>
<td>Abdominal pain</td>
<td>First-degree relatives of those with CD</td>
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<tr>
<td>Abdominal distension</td>
<td>Type 1 diabetes</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Autoimmune thyroid disease</td>
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<tr>
<td>Constipation</td>
<td>Autoimmune liver disease</td>
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<tr>
<td>Growth failure or deceleration</td>
<td>Trisomy 21</td>
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<tr>
<td>Weight loss</td>
<td>Williams syndrome</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Turner syndrome</td>
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<tr>
<td>Elevated hepatic transaminases</td>
<td>IgA deficiency</td>
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<tr>
<td>Iron deficiency anemia</td>
<td>Juvenile chronic arthritis</td>
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<tr>
<td>Unexplained osteopenia</td>
<td></td>
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<tr>
<td>Dental enamel defects</td>
<td></td>
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<tr>
<td>Recurrent aphthous stomatitis</td>
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<tr>
<td>DH</td>
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*CD = celiac disease; DH = dermatitis herpetiformis; IgA = immunoglobulin A.

“Children belonging to groups known to be at increased risk for CD may initially have no symptoms, or very minor symptoms, despite having intestinal histologic changes that are characteristic for CD. Included in these groups are first-degree relatives of an index case, people with trisomy 21, Turner syndrome, Williams syndrome, and IgA deficiency, and those with other autoimmune conditions (Hill et al., 2016).”

For initial testing, they recommend the TTG-IgA antibody test due to its reliability and cost-effectiveness. They note that co-testing for serum IgA can be performed to “identify those who have selective IgA deficiency”; however, “use of a panel of antibodies instead of a single tTG-IgA test is not recommended. Although this approach may be associated with a marginal increase in the sensitivity of the test, it decreases the specificity and significantly increases the costs (Hill et al., 2016).” Testing for serum antibodies against gliadin is less sensitive, reliable, and specific as compared to TTG and EMA.

They do not recommend genetic testing for HLA variants as an initial diagnostic test or screening for CD since up to 40% of the general population contains one of the variant alleles. “Testing for HLA-DQ2/8 is best reserved for patients in whom there is a diagnostic dilemma, such as when there is a discrepancy between the serological and histologic findings or when a GFD [gluten-free diet] has been started before any testing (Hill et al., 2016).”

They do not recommend the use of rapid, point-of-care tests for TTG since these tests do not allow for the quantitative analysis of the antibody.
2015, 2016 National Institute for Health and Care Excellence (NICE, 2015, 2016)

The National Institute for Health and Care Excellence (NICE) recommends CD serologic testing in symptomatic young people and adults with the following algorithm (NICE, 2015):

1. First test for total serum IgA and TTG
2. Next test for IgA endomysial antibodies (EMA) if TTG is inconclusive (i.e. weakly positive)
3. “Consider using IgG EMA, IgG deamidated gliadin peptide (DGP) or IgG tTG if IgA is deficient”

For children with suspected CD, they recommend:

1. First test for total serum IgA and TTG
2. “Consider using IgG EMA, IgG DGP or IgG tTG if IgA is deficient”

NICE also recommends offer CD testing for people with any of the following:

- Autoimmune thyroid disease
- Persistent unexplained abdominal or gastrointestinal symptoms
- Irritable bowel syndrome
- Type 1 diabetes
- First-degree relatives (parents, siblings or children) with coeliac disease
- Other symptoms indicative of possible CD, including faltering growth in children, prolonged fatigue, unexpected weight loss, severe or persistent mouth ulcers, unexplained dietary deficiencies

NICE also recommends considering CD testing for people with the following:

- Metabolic bone disorder
- Unexplained neurological symptoms
- Unexplained subfertility or recurrent miscarriage
- Down’s syndrome or Turner’s syndrome
- Dental enamel defects
- Persistent elevated hepatic enzymes of unknown etiology

They do note that “People who are following a normal diet (containing gluten) should be advised to eat gluten in more than 1 meal every day for at least 6 weeks before testing for coeliac disease (NICE, 2016).”

NICE indicates that HLA testing should not be done as part of the initial testing. Also, “Only consider using HLA DQ2 (DQ2.2 and DQ2.5)/DQ8 testing in the diagnosis of coeliac disease in specialist settings (for example, in children who are not having a biopsy, or in people who already have limited gluten ingestion and choose not to have a gluten challenge) (NICE, 2015).”

2017 US Preventive Services Task Force (Bibbins-Domingo et al., 2017)

The United States Preventative Services Task Force (Bibbins-Domingo et al., 2017) recently published guidelines on the screening of asymptomatic populations for celiac disease and found that:

“The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for celiac disease in asymptomatic persons. Evidence is
lacking, and the balance of benefits and harms cannot be determined.” However, it was noted that: “Persons at increased risk for celiac disease include those who have a positive family history (eg, a first- or second-degree relative), with an estimated prevalence of 5% to 20%, and persons with other autoimmune diseases (eg, type 1 diabetes mellitus, inflammatory luminal gastrointestinal disorders, Down syndrome, Turner syndrome, IgA deficiency, and IgA nephropathy). Several specialty societies recommend screening in these populations.”


The WGO published guidelines on CD testing in 2017. A cascade with “resource-sensitive” options is listed.

The “Gold Standard” lists the following items for diagnosis of CD:

- Celiac disease-specific antibodies: assessment and intestinal biopsy
- Anti-tTG IgA or anti-EMA IgA, and total IgA to exclude IgA deficiency
- In case of selective IgA deficiency, IgG-based tests should be used: anti-DGP, anti-tTG, or EMA (the latter 2 are highly sensitive, but with lower specificity)
- Symptomatic patients with a positive serological test or a titer just below the cut-off (borderline) should be referred for endoscopy with multiple duodenal biopsies to confirm or exclude the diagnosis of celiac disease. Pitfalls in histologic diagnosis are common, and findings are characteristic, but not specific
- Asymptomatic patients with a positive serological test should be retested after consuming a gluten-containing diet for 3 months, to confirm persistent seropositivity before referral for endoscopy

The following items are listed for management of CD:

- Follow-up monitoring, including antibody tests (anti-tTG IgA or DGP-IgG in case of IgA deficiency): after 3 to 6 mo in the first year and once a year thereafter in stable patients responding to the gluten-free diet

The WGO also notes that although the presence of HLA risk alleles is “necessary” for celiac disease, it is insufficient for CD development. However, it does have a high negative predictive value, in that absence of those risk alleles excludes CD as a diagnosis.

The WGO notes two main groups of serological markers for untreated CD:

- Autoantibodies targeting the auto-antigen: EMA and anti-tTG antibodies
- Antibodies targeting the offending agent (gliadin): anti- bodies against synthetic deamidated gliadin peptides (anti-DGPs)

A summary of the characteristics of CD antibody tests is listed below:
The WGO also lists several conditions associated with a higher risk of CD. Those conditions are as follows:

- Type 1 diabetes mellitus
- Autoimmune thyroid disease
- Autoimmune liver disease
- Down syndrome
- Turner syndrome
- Williams syndrome
- Selective IgA deficiency
- Unexplained elevated serum aminotransferase levels

The WGO also recommends that first-degree relatives of index (affected) patients to be screened for CD.

Finally, the WHO recommends against use of urine, stool, or saliva measurements in clinical practice, as they have a “lower performance” than blood-based tests (Bai & Ciacci, 2017).

**European Society for the Study of Coeliac Disease (ESsCD, 2019)**

The ESsCD published guidelines on CD, including recommendations on serological and genetic testing. These recommendations are listed below:

- “Adult patients with symptoms, signs or laboratory evidence suggestive of malabsorption should be tested with serology for CD. (Strong recommendation, high level of evidence)”
Screening of asymptomatic first-degree family member of CD patient is recommended. If available, HLA-typing may be offered as the first-line test; if negative, no further work-up is needed. (Conditional recommendation, high level of evidence)

CD should be excluded in patients with unexplained elevation of serum aminotransferase levels. (Strong recommendation, high level of evidence)

T1DM should be screened regularly for CD. (Strong recommendation, high level of evidence)

IgA-TG2 antibody is the preferred single test for detection of CD at any age. (Strong recommendation, high level of evidence)

Total IgA level needs to be measured concurrently with serology testing to determine whether IgA levels are sufficient. (Strong recommendation, moderate level of evidence)

In patients with selective total IgA-deficiency, IgG-based testing (IgG-DGPs or IgG-TG2) should be performed at diagnosis and follow-up. (Strong recommendation, moderate level of evidence)

All diagnostic serologic testing should be done while patients on a gluten-containing diet. (Strong recommendation, high level of evidence)

Antibodies directed against native gliadin (AGA) are not recommended for the primary detection of CD. (Strong recommendation, high level of evidence)

Intestinal-permeability tests are neither sensitive nor specific and are not recommended for CD diagnosis. (Strong recommendation, moderate level of evidence)

Serum I-FABP might be useful in identifying dietary non-adherence and unintentional gluten intake. (Strong recommendation, moderate level of evidence)

A newly diagnosed adult CD patient should undergo testing to uncover deficiencies of essential micronutrient, e.g. iron, folic acid, vitamin D and vitamin B12. (Strong recommendation, moderate level of evidence)

CD diagnosis may be made without duodenal biopsy in symptomatic children with high TG2 levels (>10 times ULN) and EMA in the presence of HLA-DQ2/8. The diagnosis is confirmed by an antibody decline and preferably a clinical response to a GFD. (Conditional recommendation, moderate level of evidence)

The ESSCD also lists recommendations for HLA-DQ2/8 typing, which are as follows:

A negative HLA test is helpful to exclude the possibility of CD. This is especially helpful in those already on a GFD before testing.

When diagnosis of CD is uncertain, e.g., negative serology, but histology suggestive of CD.

To distinguish siblings who can be reassured that it is unlikely that they will develop CD from those who need to be monitored. Furthermore, the data on the quality of life on a GFD in those patients detected by screening are conflicting, but there is a trend towards improvement. Also, the lack of understanding of the natural history of undiagnosed CD may justify screening asymptomatic persons.

In subjects with other autoimmune diseases and some genetic disorders who should be investigated for CD.

HLA-DQ2/DQ8 testing should not be used routinely in the initial diagnosis of CD. It is recommended that the results of such testing should be included along with a caution that patients at risk should be serologically tested for CD without changing their diet. (Strong recommendation, moderate level of evidence). (Al-Toma et al., 2019)

State and Federal Regulations, as applicable

The Quanta Lite Celiac Screen ELISA test for tissue transglutaminase/gliadin and the Quanta Lite Celiac DGP Screen by Inova Diagnostics, Inc. were approved by the FDA on 01/28/1999 and 12/13/2006, respectively. Quanta Plex Celiac IgA and IgG profiles by Inova Diagnostics, Inc. were approved on 03/14/2007 and 06/20/2007.

EliA Celikey IgG for use with the EliA Celikey IgG Immunoassay by Phadia US, Inc. was approved by the FDA on 12/26/2006.
The FIDIS Celiac on the FIDS Analyser and FIDIS CELIAC kit by Biomedical Diagnostics S.A. were approved by the FDA on 09/24/2004 and 03/29/2006, respectively.

The IMMULISA CELIAC ELISA testing systems for gliadin IgA/IgG and TTG IgA/IgG by IMMCO Diagnostics, Inc. were approved on 02/04/2010 and 03/10/2010. IMMCO’s IMMULISA enhanced celiac fusion (TTG/DGP) IgA/IgG antibody ELISA system was approved on 10/25/2013.

Bio-Rad Laboratories’ Bioplex 2200 Celiac IgA IgG kits were approved on 09/19/2013. The IgX Plex Celiac qualitative assay and Ig Plex Celiac DG panel by SQI diagnostics systems, Inc. were approved by the FDA on 06/02/2011 and 11/06/2014, respectively.

No nucleic acid-based test solely for celiac disease has been approved by the FDA as of July 2019. The FDA has approved the direct-to-consumer panel test by 23andme that includes a single nucleotide polymorphism in HLA-DQA1 (FDA, 2017).

Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ‘88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

### Applicable CPT/HCPCS Procedure Codes

<table>
<thead>
<tr>
<th>Code Number</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81376</td>
<td>HLA Class II typing, low resolution (eg, antigen equivalents); one locus (eg, HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each</td>
</tr>
<tr>
<td>81377</td>
<td>HLA Class II typing, low resolution (eg, antigen equivalents); one antigen equivalent, each</td>
</tr>
<tr>
<td>81382</td>
<td>HLA Class II typing, high resolution (ie, alleles or allele groups); one locus (eg, HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each</td>
</tr>
<tr>
<td>81383</td>
<td>HLA Class I typing, high resolution (i.e., alleles or allele groups); one allele or allele group (e.g., HLA-DBQ1*06:02P), each</td>
</tr>
<tr>
<td>82784</td>
<td>Gammaglobulin (immunoglobulin); IgA, IgD, IgG, IgM, each</td>
</tr>
<tr>
<td>83516</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple method</td>
</tr>
<tr>
<td>86255</td>
<td>Fluorescent noninfectious agent antobody, screen, each antibody</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>86256</td>
<td>Titer, each antibody (fluorescent technique for antigen identification in tissue, use 88346, for indirect fluorescence, use 88347) (FTA, use 86780) (Gel [agar] diffusion tests, use 86331)</td>
</tr>
<tr>
<td>86828</td>
<td>Antibody to human leukocyte antigens (HLA), solid phase assays (eg, microspheres or beads, ELISA, flow cytometry); qualitative assessment of the presence or absence of antibody(ies) to HLA Class I and/or Class II HLA antigens</td>
</tr>
<tr>
<td>86829</td>
<td>Qualitative assessment of the presence or absence of antibody(ies) to HLA Class I or Class II HLA antigens (if solid phase testing is performed to assess presence or absence of antibody to both HLA classes, use 86828)</td>
</tr>
<tr>
<td>86831</td>
<td>Antibody identification by qualitative panel using complete HLA phenotypes, HLA Class II</td>
</tr>
<tr>
<td>86833</td>
<td>High definition qualitative panel for identification of antibody specificities (eg, individual antigen per bead methodology), HLA Class II</td>
</tr>
<tr>
<td>86835</td>
<td>semi-quantitative panel (eg, titer), HLA Class II</td>
</tr>
<tr>
<td>88305</td>
<td>Surgical pathology, gross and microscopic</td>
</tr>
<tr>
<td>88346</td>
<td>Immunofluorescence, per specimen; initial single antibody stain procedure</td>
</tr>
<tr>
<td>88350</td>
<td>Immunofluorescence, per specimen; each additional single antibody stain procedure</td>
</tr>
</tbody>
</table>


Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

**Evidence-based Scientific References**


systematic review with meta-analysis. *PLoS One, 14*(2), e0212329. doi:10.1371/journal.pone.0212329


**Policy Implementation/Update Information**

7/1/20   New Policy

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.