AmeriHealth Caritas Northeast

Clinical Policy Title: Diagnostic testing for celiac disease

Clinical Policy Number: 02.07.01

Effective Date: December 1, 2013
Initial Review Date: August 21, 2013
Most Recent Review Date: August 17, 2016
Next Review Date: August 2017

Related policies:
None.

ABOUT THIS POLICY: AmeriHealth Caritas Northeast has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Northeast’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas Northeast when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Northeast’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Northeast’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Northeast will update its clinical policies as necessary. AmeriHealth Caritas Northeast’s clinical policies are not guarantees of payment.

Coverage policy
AmeriHealth Caritas Northeast considers the use of diagnostic testing for celiac disease (CD) to be clinically proven and, therefore, medically necessary when any of the following criteria are met:

A. Serologic measurement of IgA-antiendomysial antibodies (EMA) or tissue transglutaminase (TTG) antibodies in patients with signs or symptoms (e.g., diarrhea, abdominal pain and bloating) suggestive of CD while patient is on a gluten-containing diet.

Repeat serologic testing for patients diagnosed with CD is considered medically necessary for those patients who remain symptomatic despite strict adherence to a gluten-free diet. In such a circumstance, serologic testing for CD should not be repeated more than once a year for each patient.

B. Testing of total serum IgA for patients with symptoms suggestive of CD and indeterminate serology results.

C. Testing of IgG-TTG or IgG-EMA in patients with an IgA deficiency who exhibit symptoms suggestive of CD.
D. HLA-DQ2 and HLA-DQ8 testing to rule out CD if either of the following medical necessity criteria is met:

- The individual has discordant serologic and histologic (biopsy) findings.
- The individual has persistent symptoms that warrant testing despite negative serology and histology.

For Medicare members only: For AmeriHealth Caritas Northeast Medicare members, coverage is consistent with the list of services provided by the Medicare Claims Processing Manual, Chapter 12 Physician, Non-physician Practitioners Section 190

Limitations:

All other uses of diagnostic testing for CD are not medically necessary, including any of the following:

- Screening individuals for asymptomatic CD using serologic testing.
- Screening individuals for asymptomatic CD using self-tests and/or point-of-care (POC) tests as a substitute for serologic testing.
- Using serologic testing as an alternative to biopsy.
- Using sequential measurement of EMA or TTG antibodies.
- Using anti-deamidated gliadin peptide antibody (DGP) tests as serologic markers for CD.
- Using human leukocyte antigen (HLA) DQ2/DQ8 testing in the initial diagnosis of CD. However, its high negative predictive value may be of use to gastrointestinal specialists in specific clinical situations.

Note: The following CPT/HCPCS code is not listed in the Pennsylvania Medicaid fee schedule:

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

Alternative covered services:

Clinical evaluation by physicians, and appropriate standard diagnostic procedures.

Background

CD is a chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals (Ludvigsson, 2012). Gluten is the commonly used term for the complex of water insoluble proteins from wheat, rye and barley that are poorly digested in the human intestine with or without CD but are particularly harmful to patients with CD. The immune reaction to gluten triggers an inflammatory response in the small intestine that impedes absorption of nutrients from ingested food. As CD is one of the most common causes of chronic malabsorption, the National Institutes of Health (NIH) developed a consensus statement on CD to raise awareness and diagnosis of the disease (NIH, 2004).
Estimates of the prevalence of CD in the general population vary widely because of serological test strategies, biopsy definitions and patient sampling. A recent study placed the U.S. prevalence at 0.71% (1.01% for white non-Hispanics), or 1 in 141 persons (Rubio-Tapia, 2012).

Patients with autoimmune thyroid disease, dermatitis herpetiformis, irritable bowel syndrome or type 1 diabetes, or with first-degree relatives (parents, siblings or children) with biopsy-confirmed CD, have a higher prevalence of CD than the general population. One report documented prevalence for not-at-risk persons to be 1 in 113, far lower than those with first- and second-degree relatives with CD (1 in 22 and 1 in 39), along with 1 in 56 for symptomatic persons (Fasano, 2003). The current rate of CD in the U.S. is estimated at 4 to 4.5 times greater than in the 1950s (Rubio-Tapia, 2009).

There are those who fail to meet the diagnostic criteria for CD, but still who exhibit the same symptoms and are sensitive to gluten. In recent years, persons categorized as non-celiac gluten sensitive are far more prevalent than CD; one study of symptomatic gluten-sensitive patients showed just 7% to be diagnosed with CD (Aziz, 2014).

Other evidence suggests an increased prevalence of CD in persons with autoimmune myocarditis, chronic thrombocytopenic purpura, depression or bipolar disorder, Down syndrome, epilepsy, liver conditions, lymphoid malignancy, polynepathy, Sjögren's syndrome, sarcoidosis, Turner syndrome or unexplained subfertility (NICE, 2009).

Signs, symptoms and conditions associated with CD:

CD presents in both adults and children and can be diagnosed at any age, including in infants who have been introduced to gluten-containing foods. Recognition and assessment of CD can be difficult because of the variety of gastrointestinal and non-gastrointestinal signs and symptoms at presentation, and some patients may present with no symptoms at all. The most frequent features found in patients with CD are chronic or intermittent diarrhea; failure to thrive or faltering growth (in children); persistent or unexplained gastrointestinal symptoms, including nausea and vomiting; prolonged fatigue; recurrent abdominal pain; cramping or distension; sudden or unexpected weight loss; and unexplained iron-deficiency anemia or other unspecified anemia. Other non-gastrointestinal features and conditions that may be present when CD is diagnosed include alopecia; amenorrhea; aphthous stomatitis (mouth ulcers); constipation; dermatitis herpetiformis; epilepsy; microscopic colitis; osteoporosis; recurrent abortion; and type 1 diabetes (Rostom, 2004 and NICE, 2009).

The genetic predisposition to CD is attributed to the specific genetic markers known as human leukocyte antigen (HLA)-DQ2 and HLA-DQ8 (NICE 2009). In addition, there is an increased risk for the HLA DQ2- or DQ8-positive family members (particularly first-degree relatives) of patients with CD. Despite these associations, several studies confirm that not all patients with CD express HLA DQ2 or DQ8 markers, and up to 40 percent of healthy individuals in the general population are carriers of the HLA-DQ, DQ2 or DQ8 markers. These data suggest that specific HLA genotypes are necessary, but not sufficient, for the development of CD (Hayes, 2010).

Undiagnosed CD can have serious consequences. Undiagnosed maternal CD has a negative effect on intrauterine growth and birth weight, and is associated with increased preterm birth and cesarean section rates. Evidence suggests an association between undiagnosed CD and an increased risk of fractures, as well as an increased risk of non-Hodgkin’s and Hodgkin’s lymphoma and small bowel cancer, but overall cancer rates are low (NICE, 2009). Children with CD are at risk of developing
neurological complications, although the risk is lower than in adulthood (Lionetti, 2010). Evidence suggests a positive association between CD and serum hypertransaminasemia, or elevated levels of transaminase and aspartate (Sainsbury, 2011).

Diagnosis of CD:

Diagnosing CD is critical to its management because a gluten-free diet usually resolves symptoms and can prevent long-term consequences. Mass screening for CD is controversial mainly because of low compliance with a gluten-free diet in screen-detected patients (even when symptomatic), although targeted screening in populations at high risk for CD may be beneficial (NICE, 2009). However, diagnostic uncertainty is high, particularly in unselected populations in the primary care setting, because patients may present with a range of symptoms. Those who present with abdominal symptoms may not have CD, and diagnostic confirmation requires histological assessment of small-bowel biopsy material. Therefore, primary care physicians also aim to avoid unnecessary diagnostic testing (van der Windt, 2010). The main hurdle for treating CD is identifying which test or tests to use to make the appropriate diagnosis (NICE, 2009).

Typically, the inflammation in CD includes an increased intraepithelial lymphocyte (IEL) count, most often >25/100 cells and incorporates an adaptive T-cell-mediated response to gluten in people who are DQ2- or DQ8-positive. A number of serologic tests are available for detecting the presence of specific antibodies. Anti-reticulin antibodies (ARA) have historically been used in the evaluation of CD, but they lack optimal sensitivities and specificities for routine diagnostic use and are considered obsolete. EMA (also called AEA) antitissue transglutaminase antibodies (TTG, a-tTG, TTA), and/or deamidated antigliadin peptide (DGP) antibodies in blood serum are used more commonly (Ludvigsson, 2013).

Serologic tests are automated, enzyme-linked immunosorbent assay (ELISA)-based laboratory tests, except for the EMA test, which is determined by indirect immunofluorescence and is more time-consuming and operator-dependent than the others. For each serologic test, both immunoglobulin A (IgA) or G (IgG) can be measured; however, IgA measurement is the standard antibody measured in CD. The newest serologic tests, DGP antibody tests, are believed to be more specific to CD than native peptides. Some of the DGP antibody tests are able to assay both IgA and IgG, so they could be used potentially in individuals regardless of IgA deficiency status.

POC (point of care) tests are emerging as potential alternatives to conventional serologic tests. POC tests that require serum also require some sample preparation, whereas whole blood samples are better suited to POC testing. POC tests are reportedly quick, economical and easy to use, and can be performed on-site in the physician’s office and in primary care settings without the need for laboratory analysis. Active case finding using POC tests may help shorten diagnostic delays, particularly in populations where diagnostic uncertainty is high (Popp, 2013).

Other ancillary testing may be done to improve diagnosis. HLA-DQ genotyping is typically performed by polymerase chain reaction with sequence-specific primers (PCR-SSP) or PCR with hybridization of sequence-specific probes. The main limitation of HLA-DQ genotyping is the possibility of PCR failure. Since some patients with CD do not express DQ2 or DQ8 HLA markers, and HLA-DQ2 or DQ8 is present in up to 40 percent of the general population, a positive test would have no predictive value. Therefore, the presence of a DQ2 or DQ8 genotype is not sufficient to establish the diagnosis of CD (Hayes, 2010).
Patients maintained on a strict gluten-free diet without prior definitive diagnostic testing may yield negative serology and histology results. As HLA-DQ genotypes are not influenced by diet, a negative result may obviate the need for further work-up. In patients on a gluten-free diet with a positive HLA-DQ, DQ2 or DQ8 result, a gluten challenge remains the gold standard for CD diagnosis. A gluten challenge involves introducing a normal, gluten-rich diet under medical supervision to enable diagnostic testing (Rubio-Tapia, 2013).

Because no single test is 100 percent specific for CD and diagnostic accuracy varies considerably among laboratories, small bowel biopsy is required to confirm a diagnosis of CD and is also useful for the differential diagnosis of other malabsorptive disorders. Confirmation requires multiple duodenal biopsies when patients are on a gluten-containing diet; typically four to six biopsies are necessary for diagnosis, including one or two from the duodenal bulb (Ludvigsson, 2013).

**Searches**

AmeriHealth Caritas Northeast searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on August 8, 2014. Search terms were “celiac Disease” (MeSH).

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

A cost-effectiveness analysis guideline applied a decision model to a screening protocol for identifying CD in patients with irritable bowel syndrome (IBS) with bowel habits of either diarrhea or mixed diarrhea and constipation, but not bowel habits restricted to constipation (Mohseninejad, 2013). The screening protocol consisted of serologic tTG testing and IgA antibody testing followed by confirmatory endoscopy with biopsy when IgA was less than 0.7 or greater than 0.7 with a positive tTG. This protocol was cost-effective in the Netherlands context. These results and a new guideline by the British Society of Gastroenterology confirms are consistent with current preferred guidelines for active case-finding using serologic testing for CD in patients with symptoms or conditions closely associated with CD to increase detection of CD (Ludvigsson, 2014 and Rubio-Tapia, 2013). This new information would not change the current policy.
Table 1 summarizes the findings from four systematic reviews of the clinical validity of serologic testing.

**Serologic testing for CD:**

The results from available systematic reviews listed in Table 1 indicate that IgA-TTG and IgA-EMA serological tests show high sensitivity and specificity for diagnosing CD in populations with symptoms suggestive of CD (NICE, 2009 and MAS, 2010). Limited evidence from studies with targeted low prevalence populations in whom diagnostic uncertainty is higher suggests similar findings (van der Windt, 2010). Results were comparable in adults and children (NICE, 2009 and Giersiepen, 2012).

Additional limited evidence from systematic reviews revealed that:

- Combination or sequential testing with IgA-TTG and IgA-EMA does not appear to substantially improve accuracy in the diagnostic process (NICE, 2009 and MAS, 2010).
- IgA-TTG yields more false positive results in people with liver disease than in the general population (NICE, 2009).
- Limited evidence suggests gliadin antibody serological tests show comparable or lower sensitivity and specificity than TTG and EMA, but these tests require further evaluation (Giersiepen, 2012, NICE, 2009, and MAS, 2010).
- The presence of IgA deficiency may affect the sensitivity of the IgA-based serologic tests since total/severe IgA deficient subjects may not produce detectable levels of IgA antibodies (NICE, 2009).
- Targeted screening with IgA-EMA as the preferred serologic marker would be cost-effective in populations with a high prevalence of CD, but additional studies are needed to establish the generalizability of the findings before implementing this screening strategy (Shamir, 2006).
- Routine screening for CD in asymptomatic children with Down syndrome was not found to be cost-effectiveness in preventing lymphoma (Swigonski, 2006).

**POC testing:**

The evidence for POC testing for screening for CD is based on two systematic reviews (Gierspiesen, 2012 and NICE, 2009) and one horizon scan (Purins, 2008); see Table 1. The evidence for POC tests in pediatric and adult populations suggests high clinical validity for IgA-TTG antibody screening. With a high specificity, its clinical utility may be in ruling out CD, leaving additional diagnostic testing and biopsy confirmation for those who test positive and before starting a gluten-free diet. While the POC test may fulfill an unmet need for a simple and inexpensive case-finding biomarker for early detection and presumptive diagnosis of CD, confirmatory studies are warranted in case-finding in specialized outpatient clinics and in primary care.

**HLA-DQ genotyping:**

Data regarding the clinical validity of HLA-DQ genotyping for CD indicates that its clinical sensitivity and negative predictive value are high, ranging from 92.4 percent to 100 percent and 95.4 percent to 100 percent, respectively. The data also suggest that HLA-DQ genotyping may facilitate the diagnosis of CD.
in patients with indeterminate biopsy results. In addition, there is an increased risk for DQ2- or DQ8-positive family members (particularly first-degree relatives) of patients with confirmed CD. Despite these associations, several studies confirm that not all patients with CD express DQ2 or DQ8 HLA molecules. Therefore, the evidence does not support HLA-DQ genotyping as an initial test for detecting CD. No studies were identified that specifically examined the impact of HLA-DQ genotyping for CD on health outcomes (Hayes, 2010).

Table 1. Pooled estimates of sensitivity and specificity of serological tests for CD specificity

<table>
<thead>
<tr>
<th>Serological test</th>
<th>Systematic review</th>
<th>Sensitivity (Se) (%)</th>
<th>Specificity (Sp) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA AGA</td>
<td>NICE 2009</td>
<td>23 – 100</td>
<td>45 – 100</td>
</tr>
<tr>
<td></td>
<td>van der Windt 2010</td>
<td>46 – 87</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MAS 2010</td>
<td>74.9 (95% CI, 63.6 – 86.2)</td>
<td>90.1 – 98.7 depending on test</td>
</tr>
<tr>
<td>IgG AGA</td>
<td>NICE 2009</td>
<td>46 – 100</td>
<td>77 – 99</td>
</tr>
<tr>
<td></td>
<td>van der Windt 2010</td>
<td>25 – 93</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MAS 2010</td>
<td>69.1 (95% CI, 56.0 — 82.2)</td>
<td>90.1 – 98.7 depending on test</td>
</tr>
<tr>
<td>IgA EMA</td>
<td>NICE 2009</td>
<td>68 – 100</td>
<td>89 – 100</td>
</tr>
<tr>
<td></td>
<td>Giersiepen 2012</td>
<td>&gt; 90</td>
<td>98.2</td>
</tr>
<tr>
<td></td>
<td>van der Windt 2010</td>
<td>90 (95% CI, 80 – 95)</td>
<td>99 (95% CI, 98 -- 100)</td>
</tr>
<tr>
<td></td>
<td>LR+=171</td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>MAS 2010</td>
<td>85.1 (95% CI, 79.5 – 94.4)</td>
<td>90.1 – 98.7 depending on test</td>
</tr>
<tr>
<td>IgG EMA</td>
<td>NICE 2009</td>
<td>39</td>
<td>98</td>
</tr>
<tr>
<td>IgA TTG</td>
<td>NICE 2009</td>
<td>38 – 100</td>
<td>25 – 100</td>
</tr>
<tr>
<td></td>
<td>Giersiepen 2012</td>
<td>≥ 90</td>
<td>≥ 90</td>
</tr>
<tr>
<td></td>
<td>van der Windt 2010</td>
<td>89 (95% CI, 82 – 94)</td>
<td>98 (95% CI, 95 – 99)</td>
</tr>
<tr>
<td></td>
<td>LR+=37.7</td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>MAS 2010</td>
<td>92.1 (95% CI, 88.0 – 96.3)</td>
<td>90.1 – 98.7 depending on test</td>
</tr>
<tr>
<td>IgG TTG</td>
<td>NICE 2009</td>
<td>23 – 85</td>
<td>89 – 98</td>
</tr>
<tr>
<td></td>
<td>MAS 2010</td>
<td>44.7 (95% CI, 30.3 – 59.2)</td>
<td>90.1 – 98.7 depending on test</td>
</tr>
<tr>
<td>IgA-DGP</td>
<td>Giersiepen 2012</td>
<td>80.7 – 95.1</td>
<td>86.3 – 93.1</td>
</tr>
<tr>
<td></td>
<td>MAS 2010</td>
<td>89.2 (95% CI, 83.3 – 95.1)</td>
<td>90.1 – 98.7 depending on test</td>
</tr>
<tr>
<td>IgG-DGP</td>
<td>Giersiepen 2012</td>
<td>80.1 – 98.6</td>
<td>86.0 – 96.9</td>
</tr>
<tr>
<td></td>
<td>MAS 2010</td>
<td>88.4 (95% CI, 82.1 – 94.6)</td>
<td>90.1 – 98.7 depending on test</td>
</tr>
</tbody>
</table>

Note: Shaded rows indicate tests with high sensitivity and specificity.

Policy updates:

None.
### Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serologic testing</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Giersiepen (2012)      | Key Points:  
  - Meta-analysis of 16 studies with 3,110 patients (1,876 with CD, 1,234 without CD):  
  - IgA-EMA had the highest pooled DOR (554) and LR+ (31.8) for a laboratory test, followed by IgA-anti-TG2, IgG-DGP, IgA-DGP and IgA-AGA.  
  - IgA-EMA and IgA-anti-TG2 tests appear highly accurate to diagnose CD.  
  - With a high Sp, IgG-DGP tests may help in excluding CD.  
  - IgA-AGA and IgA-DGP tests show inferior accuracy. |
| van der Windt (2010)   | Key Points:  
  - Systematic review of 16 studies with 6,085 patients:  
  - One recent study using DGP showed good Sp (≥ 94%), but evidence is limited in this target population.  
  - IgA-T2A and IgA-EMA antibody tests have high Se and Sp for diagnosing CD. |
| OHTAS (2010)           | Key Points:  
  - Report of five systematic reviews and 17 individual studies, tests, or combinations of tests.  
  - Clinical validity and utility of serologic tests for CD was considered high in subjects with symptoms consistent with CD based on moderate- to very low-quality evidence using GRADE work group criteria.  
  - IgA tTG is the most accurate and the most cost-effective test (moderate-quality evidence).  
  - Serologic test combinations appear to be more costly with little gain in accuracy.  
  - IgA deficiency seems to be uncommon in patients diagnosed with CD. |
| NICE (2009)            | Key Points:  
  - Systematic review of 102 studies with 21,202 total patients with suspected CD and biopsy confirmation.  
  - ROC analysis showed a lower level of accuracy for the IgA AGA than the other tests.  
  - IgA-AGA showed higher Se and Sp than the IgG-AGA tests.  
  - For IgG tTG and IgG EMA there were insufficient data available to draw reasonable conclusions.  
  - Combination testing with IgA tTG and IgA EMA does not appear to improve diagnostic accuracy.  
  - There is limited evidence that IgA tTG yields more false positive results in people with liver disease  
  - Serological tests have comparable accuracy in children and in adults. |
| **POC testing**        |                                                                                                                                                                |
| Giersiepen (2012)      | Key Points:  
  - Meta-analysis; IgA-TG2 pooled Se=96.4%, Sp=97.7%.  
  - POC tests may achieve high accuracy in the hands of experienced readers, but IgA-anti-TG2/EmA serologic tests were superior. |
| NICE (2009)            | Key Points:  
  - Based on one study that considered the use of immunochromatographic sticks for tTG and AGA antibody screening in 286 children and 49 adults.  
  - Limited evidence suggests that POC tests and self-tests may be accurate but require further evaluation. |
<table>
<thead>
<tr>
<th>Purins (2008)</th>
<th>Key Points:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods of diagnosing or screening for CD</td>
<td>• Horizon scanning report of three studies of POC tests used to diagnose or screen for CD:</td>
</tr>
<tr>
<td></td>
<td>• Stick CD1 (Operon S.A., Saragoza, Spain), which detects IgA-IgG tTA in serum.</td>
</tr>
<tr>
<td></td>
<td>• Biocard™ Celiac Disease Stick (Ani Biotech Oy, Vantaa, Finland), which detects IgA-tTA in blood.</td>
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<tr>
<td></td>
<td>• % Positive Sensitivity (Se) and % Negative Specificity (Sp) for</td>
</tr>
<tr>
<td></td>
<td>o Stick CD1 (100% pos. Se, 94.9% neg. Sp)</td>
</tr>
<tr>
<td></td>
<td>o Biocard (90.2% pos Se, 100% neg. Sp)</td>
</tr>
<tr>
<td></td>
<td>o Biocard accounting for IgA deficiency (95.8% pos Se, 100% neg Sp)</td>
</tr>
<tr>
<td></td>
<td>• The application of the Biocard test to a diverse population showed a high Sp. This may allow the confident application of more invasive investigations as the subjects who test positive are very likely to have CD and therefore require further testing.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HLA-DQ genotyping</th>
<th>Key Points:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayes (2010)</td>
<td>• Sufficient reproducibility, with intra-assay and inter-assay coefficients of variation 13% to 41%.</td>
</tr>
<tr>
<td>Accuracy of diagnosing CD</td>
<td>• High clinical Se (92.4 – 100%) and negative predictive value (95.4% – 100%).</td>
</tr>
<tr>
<td></td>
<td>• HLA-DQ genotyping may facilitate the diagnosis of CD in patients with indeterminate biopsy results.</td>
</tr>
<tr>
<td></td>
<td>• Increased risk for DQ2- or CD DQ8-pos. family members, especially 1st-degree relatives of CD patients.</td>
</tr>
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<td></td>
<td>• Several studies confirm that not all CD patients express DQ2 or DQ8 HLA molecules.</td>
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</table>

**Glossary**

**Asymptomatic celiac disease (CD)** — CD is present, but without noticeable symptoms; formerly called “silent” CD.

**Celiac disease (CD)** — A chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed people.

**IgA** — Immunoglobulin A, one of the most common antibodies produced by the human body to fight threats from viruses, bacteria and environmental toxins.

**IgG** — Immunoglobulin G, generalized antibody molecules.

**Malabsorption** — Difficulty digesting or absorbing nutrients from food.

**Non-celiac gluten sensitivity** — One or more immunological, morphological or symptomatic manifestations precipitated by ingestion of gluten in people in whom CD has been excluded.

**Serology (for CD)** — Testing of blood serum for the presence of endomysium, transglutaminase, gliadin or deamidated gliadin antibodies.

**References**

**Professional society guidelines/other:**


**Peer-reviewed references:**


Medical Advisory Secretariat (MAS). *Clinical utility of serologic testing for celiac disease in asymptomatic patients: an evidence-based analysis.* Toronto: Medical Advisory Secretariat Ontario Ministry of Health and Long-Term Care (MAS); 2011.

Medical Advisory Secretariat (MAS). Clinical utility of serologic testing for celiac disease in Ontario: an evidence-based analysis. Ontario Health Technol Assess Ser [Internet].


**Clinical trials:**

Searched clinicaltrials.gov on July 21, 2016, using terms “celiac disease.” | Open Studies | 78 trials found, two (2) relevant.


**CMS National Coverage Determinations (NCDs):**
No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

No LCDs identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

<table>
<thead>
<tr>
<th>CPT codes</th>
<th>Description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>81376</td>
<td>HLA Class II typing, low resolution; HLA-DRB1/3/4/5 and DQB1</td>
<td></td>
</tr>
<tr>
<td>81383</td>
<td>HLA Class II typing, high resolution: one allele or allele group (eg, HLA-DQB1*06:02P), each</td>
<td></td>
</tr>
<tr>
<td>82784</td>
<td>Gammaglobulin (immunoglobulin): IgA, IgD, IgG, IgM, each</td>
<td></td>
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<tr>
<td>83516</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method</td>
<td></td>
</tr>
<tr>
<td>86255</td>
<td>Fluorescent noninfectious agent antibody; screen, each antibody</td>
<td></td>
</tr>
<tr>
<td>86256</td>
<td>Fluorescent noninfectious agent antibody; titer, each antibody</td>
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<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>K90.0</td>
<td>Celiac disease</td>
<td></td>
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<tr>
<td>Z13.2</td>
<td>Encounter for screening for nutritional, metabolic, and other endocrine disorders</td>
<td></td>
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<thead>
<tr>
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<th>Description</th>
<th>Comment</th>
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