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Celiac Disease Laboratory Testing

Clinical Policy Bulletins | Medical Clinical Policy Bulletins

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Table Of Contents

Policy History

Last Review
12/03/2024
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Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes

Policy

Scope of Policy

This Clinical Policy Bulletin addresses celiac disease laboratory testing.

I. Medical Necessity

Aetna considers the following interventions medically necessary:

A. Serological testing of IgA anti-human tissue transglutaminase (TTG) antibodies, IgG and IgA deamidated gliadin antibodies (DGP), and IgA anti-endomysial antibodies (EMA) for *any* of the following indications:

1. As a preliminary diagnostic test for persons with symptoms suggestive of celiac disease; *or*
2. To monitor response to a gluten-free diet; *or*
3. To screen first-degree relatives of individuals with celiac disease; *or*
4. To screen persons with type 1 diabetes for celiac disease.

B. Measurement of total serum IgA for the diagnosis of celiac disease;

C. Genetic testing for HLA-DQ2 and HLA-DQ8 haplotypes for evaluating persons with the following indications:

1. Seronegative persons with equivocal small bowel histology findings (Marsh I-II); *or*
2. Evaluation of persons on a gluten-free diet in whom no serologic testing was performed before starting a gluten-free diet; *or*
3. Persons with discrepant celiac-specific serology and histology; *or*
4. Persons with suspicion of refractory celiac disease where the original diagnosis of celiac remains in question; *or*
5. Persons with Down syndrome.

D. IgG-TTG and IgG-EMA for persons with symptoms suggestive of celiac disease and a low IgA or selective IgA deficiency.

II. **Experimental, Investigational, or Unproven**

Aetna considers the following interventions experimental, investigational, or unproven because the clinical value and effectiveness of these approaches has not been established:

A. HLA genotyping for screening of persons with type 1 diabetes mellitus for celiac disease;

B. Prometheus Celiac Plus Panel for assessing risk or diagnosing celiac disease and all other indications;

C. Serological testing of IgA or IgG anti-gliadin antibodies (AGA) and anti-reticulin antibodies (ARA) for diagnosis or monitoring of celiac disease;

D. Serological tests for celiac disease (IgA-TTG, IgG-TTG, IgA-EMA, IgG-EMA, IgA-DGP, IgG-DGP) as an alternative to biopsy for assessing mucosal damage in individuals with celiac disease, and for all other indications;

E. The following tests for the diagnosis and management of celiac disease (not an all-inclusive list):

- D-xylose and/or lactulose absorption test;
- Celiac disease testing for atrial fibrillation;
- Celiac disease testing for autism spectrum disorder;
- Gene expression profiling of peripheral blood monocytes;
- Intestinal permeability tests;
- Measurement of serum anti-phospholipid antibodies;
- Measurement of serum neurotensin levels;
- Mitochondrial antibody testing;
- Salivary tests (including salivary microbiomes);
- Screening for hepatitis B at diagnosis;
- Small-bowel follow-through (barium follow-through examination);
- Stool studies (e.g., fecal microbiomes, and fecal fat evaluation).

CPT Codes / HCPCS Codes / ICD-10 Codes

CPT codes covered if selection criteria are met:

Code	Code Description
81382	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
82784	Gammaglobulin; IgA, IgD, IgG, IgM, each

Code	Code Description
83516	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen, qualitative or semiquantitative; multiple step method [covered for IgG and IgA deamidated gliadin antibodies (DGP)] [not covered for IgA or IgG anti-gliadin antibodies (AGA)]
83520	Immunoassay, analyte, quantitative; not otherwise specified
86255	Fluorescent noninfectious agent antibody; screen, each antibody [covered for genetic testing for HLA-DQ2 and HLA-DQ8 haplotypes] [not covered for serological testing of antireticulin antibodies (ARA)]
86362	Myelin oligodendrocyte glycoprotein (MOG-IgG1) antibody; cell-based immunofluorescence assay (CBA), each
86363	flow cytometry (ie, fluorescence-activated cell sorting [FACS]), each
86828 - 86829	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
86830 - 86831	Antibody to human leukocyte antigens (HLA), solid phase assays (eg, microspheres or beads, ELISA, Flow cytometry); antibody identification by qualitative panel using complete HLA phenotypes, HLA Class I or II
86832 - 86833	Antibody to human leukocyte antigens (HLA), solid phase assays (eg, microspheres or beads, ELISA, Flow cytometry); high definition qualitative panel for identification of antibody specificities (eg, individual antigen per bead methodology), HLA Class I or Class II
86834 - 86835	Antibody to human leukocyte antigens (HLA), solid phase assays (eg, microspheres or beads, ELISA, Flow cytometry); semi-quantitative panel (eg, titer), HLA Class I or Class II
CPT codes not covered for indications listed in the CPB (not an all-inclusive list):	
Measurement of serum neurotensin, measurement of fecal and salivary microbiomes, prometheus celiac plus panel - no specific code	

Code	Code Description
81376	HLA Class II typing, low resolution (eg, antigen equivalents); one locus (eg, HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each
82705 - 82710	Fat or lipids, feces; quantitative or qualitative
84378 - 84379	Sugars (mono-, di-, and oligosaccharides); single or multiple; qualitative or quantitative each specimen [includes intestinal permeability tests] [blood and/or urine]
84620	Xylose absorption test, blood and/or urine
86015	Actin (smooth muscle) antibody (ASMA), each
86036	Antineutrophil cytoplasmic antibody (ANCA); screen, each antibody
86037	titer, each antibody
86146	Beta 2 Glycoprotein I antibody, each
86147	Cardiolipin (phospholipid) antibody, each IG class
86148	Anti- phosphatidlserine (phospholipid) antibody
86258	Gliadin (deamidated) (DGP) antibody, each immunoglobulin (Ig) class
86364	Tissue transglutaminase, each immunoglobulin (Ig) class
86381	Mitochondrial antibody (eg, M2), each
86596	Voltage-gated calcium channel antibody, each
86704	Hepatitis B core antibody (HBcAb); total
86705	IgM antibody
86706	Hepatitis B surface antibody (HBsAb)
86707	Hepatitis Be antibody (HBeAb)
87340	Infectious agent antigen detection by immunoassay technique (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]), qualitative or semiquantitative; hepatitis B surface antigen (HBsAg)
87341	hepatitis B surface antigen (HBsAg) neutralization
87350	hepatitis Be antigen (HBeAg)

Code	Code Description
Other CPT codes related to the CPB:	
86021	Antibody identification; leukocyte antibodies
86256	titer, each antibody
86671	Antibody; fungus, not elsewhere specified
88271 - 88275	Molecular cytogenetics
ICD-10 codes covered if selection criteria are met:	
E10.10 - E10.9	Type 1 diabetes mellitus
K59.00 – K59.09	Constipation
K90.0	Celiac disease
Q90.0 - Q90.9	Down syndrome
R10.0 – R10.9	Abdominal and pelvic pain
R14.0	Abdominal distension (gaseous)
R19.7	Diarrhea, unspecified
R63.4	Abnormal weight loss
R63.8	Other symptoms and signs concerning food and fluid intake [decreased appetite]
Z83.79	Family history of other diseases of the digestive system [first-degree relatives]
ICD-10 codes not covered for indications listed in the CPB:	
F84.0 – F84.9	Pervasive developmental disorders
I48.0 – I48.21	Atrial fibrillation
I48.91	Unspecified atrial fibrillation
Z11.59	Encounter for screening for other viral diseases [Hepatitis B]
Z13.811	Encounter for screening for lower gastrointestinal disorder [celiac disease]

Background

Celiac disease (CD) is an immune disorder in which an individual is unable to tolerate gluten, a protein found in wheat, rye and barley and sometimes in products such as vitamin supplements and some medications. The diagnosis of celiac disease is based on the biopsy and histopathologic examination of the small intestine. Blood tests may be used to choose individuals for biopsy and to aid in diagnosis. Genetic testing, which may also be referred to as human leukocyte antigen (HLA) typing for celiac disease, may be ordered if results from these tests are inconclusive.

CD is characterized by an abnormal proximal small intestinal mucosa, and it is associated with a permanent intolerance to gluten. Removal of gluten from the diet leads to a full clinical remission and restoration of the small intestinal mucosa to normality. It is a lifelong disorder and affects both children and adults. It may present for the first time in either childhood or adult life.

Gluten, which is the protein responsible for CD, is found in the grain of wheat, rye, oats, and barley. The toxic effects of gluten most likely result from an immunologic mechanism. Circulating antibodies to wheat fractions and other dietary proteins have been detected in the sera of patients with CD. Increased density of the intraepithelial lymphocytes in the small intestinal mucosa is a hallmark of the disease.

The hallmark of CD is permanent gluten intolerance, requiring a lifelong, gluten-free diet. Spontaneous recovery in children has been reported, but it is not yet known whether these children will eventually relapse. A disorder of transient gluten intolerance has been described in early infancy, with clinical features that are indistinguishable from CD. This is rare, but this syndrome has made it necessary to demonstrate that gluten intolerance persists by means of gluten challenge in children presenting before 2 years of age.

Age at onset of symptoms varies, but most children present between 1 and 2 years of age. Recently, symptoms seem to be appearing at a later age, possibly because gluten is being introduced into the diet in most Western countries at an older age.

Diarrhea, which may be acute or insidious in onset, is the most common presenting symptom. The stool characteristically is pale, loose, and very offensive. The child may have 2 or 3 such stools a day but often passes just 1 large, bulky stool. Recurrent attacks of more severe diarrhea with watery stools may occur. However, a few children present with constipation and may have a dilated colon or, occasionally, rectal prolapse. Failure-to-thrive is common, and children may present with short stature alone. Celiac disease must be considered in every child with failure-to-thrive and short stature regardless of whether diarrhea is present.

Emotional symptoms are common, although they are not often the mode of presentation. Anorexia classically is said to be present, but sometimes appetite is increased. In countries such as Finland, where the disease is presenting at a later age, anorexia, delayed puberty, or unexplained nutritional deficiencies such as iron deficiency may be the earliest symptom. Although the classic appearance of a miserable child with a distended abdomen, wasted buttocks, and shoulder girdles still occurs, physical examination may show little abnormality apart from abdominal protuberance. Muscle wasting, hypotonia, and a delay in motor milestones may be present in severe cases. Height and weight at the time of diagnosis often are below the 10th percentile, and weight is sometimes below the 3rd percentile.

Diagnosis of CD is based on the demonstration of characteristic features on small intestinal biopsy and on a clinical response to withdrawal of gluten from the diet. Accepted guidelines indicate that a gluten-free-diet trial should not be initiated before obtaining a small bowel biopsy. Strict adherence to this diet is generally viewed as difficult and more stressful than undergoing a diagnostic biopsy. Clinical response is demonstrated by significant weight gain and relief of all symptoms.

Circulating TTG, DGP, and anti-endomysial antibodies have a high degree of sensitivity and specificity for the diagnosis of CD. The presence of these antibodies at the time of diagnosis, with a typical small intestinal mucosa and their disappearance with a clinical response to a gluten-free diet and return on challenge, establishes the diagnosis. Although anti-endomysial antibodies have a high degree of specificity, particularly in adult patients, false-positive results may occur in children.

Accepted guidelines indicate that antibody estimations on their own should not be relied on for the final diagnosis of CD. Accepted guidelines indicate that small intestinal biopsy is still mandatory.

Treatment of CD consists of excluding wheat, rye, barley, and oats from the diet for life. In the short-term, clinical studies have shown that this will permit normal growth, with achievement of the child's full growth potential. There is evidence that, in the long-term, a gluten-free diet may prevent complicating malignancy. Available literature suggests that patients with CD who receive a reduced-gluten or a normal diet have increased risk for lymphoma and for cancers of the mouth, pharynx, and esophagus. However, available evidence suggests that strict adherence to a gluten-free diet for 5 years or more decreases the risk of these malignancies in adults to rates similar to that of the unaffected population.

Celiac disease guidelines from the American College of Gastroenterology (Rubio-Tapia, et al., 2013) state that IgA anti-TTG antibody is the preferred single test for detection of CD in individuals over the age of 2 years. When there exists a high probability of CD wherein the possibility of IgA deficiency is considered, total IgA should be measured. An alternative approach is to include both IgA and IgG-based testing, such as IgG DGPs, in these high-probability patients. The guidelines state that, in patients in whom low IgA or selective IgA deficiency is identified, IgG-based testing (IgG DGPs and IgG TTG) should be performed. If the suspicion of CD is high, intestinal biopsy should be pursued even if serologies are negative. Antibodies directed against native gliadin are not recommended for the primary detection of CD. AGA guidelines state that, combining several tests for CD in lieu of TTG IgA alone may marginally increase the sensitivity for CD but reduces specificity and therefore are not recommended in low-risk populations. When screening children younger than 2 years of age for CD, the IgA TTG test should be combined with DGPs (IgA and IgG).

AGA guidelines state that the confirmation of a diagnosis of CD should be based on a combination of findings from the medical history, physical examination, serology, and upper endoscopy with histological analysis of multiple biopsies of the duodenum (Rubio-Tapia, et al.,, 2013). Upper

endoscopy with small-bowel biopsy is a critical component of the diagnostic evaluation for persons with suspected CD and is recommended to confirm the diagnosis.

The European Society of Pediatric Gastroenterology and Nutrition has established criteria for definitive diagnosis of CD. In children younger than 2 years of age, the criteria state diagnosis would be made only when reintroduction of gluten into the diet, after the intestinal mucosa has become normal, causes the mucosa again to become abnormal, with or without symptoms. In children older than 2 years of age, the criteria state a second challenge with gluten is not required if the initial biopsy is positive.

It has also been suggested that these serological tests can be used to screen first-degree relatives of affected individuals to diagnose subclinical (latent) CD. These tests have also been shown to be useful in determining compliance with a gluten-free diet.

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

According to the NIH Consensus Statement (2004), if an individual has suggestive symptoms and negative serologies, it may be necessary to measure serum IgA to detect a selective IgA deficiency. If an IgA deficiency is identified, an IgG-TTG or IgG-EMA test should be performed.

An assessment by the Ontario Ministry of Health Medical Advisory Secretariat (MAS, 2010) on the use of serologic testing for CD in symptomatic persons found that the clinical validity and clinical utility of serologic tests for CD was considered high in subjects with symptoms consistent with the disease as they aid in the diagnosis of CD and some tests present a high accuracy, and a CD diagnosis leads to treatment with a gluten-free diet. The assessment found that study findings suggest that

IgA TTG is the most accurate and the most cost-effective test, and that IgA AGA has a lower accuracy compared to other IgA-based serologic celiac disease tests. Serologic test combinations appear to be more costly with little gain in accuracy. The assessment found that IgA deficiency seems to be uncommon in patients diagnosed with CD. The assessment stated that the generalizability of study results is contingent on performing both the serologic test and biopsy in subjects on a gluten-containing diet, since the avoidance of gluten may affect test results.

An assessment by the Ontario Ministry of Health Medical Advisory Secretariat (MAS, 2011) of the use of serologic testing for CD found that, based on a review of the literature, there is an increased risk of asymptomatic CD in patients with type 1 diabetes. The assessment found, based on low quality evidence, in patients with idiopathic short stature and asymptomatic celiac disease there is an acceleration in growth once a gluten-free diet is introduced. With the exception of idiopathic short stature, there was no published evidence of clinical utility of CD testing in asymptomatic patients with respect to a gluten-free diet intervention in the other conditions evaluated. The report also found, based on low to very low quality evidence, asymptomatic CD does not confer an increased risk of lymphoma or mortality. Similarly, in patients with lymphoma there is no increased risk of asymptomatic celiac disease.

There is strong evidence for an increased occurrence of celiac disease in children with type 1 diabetes (Hill et al, 2005; Dretzke et al, 2004). It has been estimated that 6 to 8 % of children with type 1 diabetes have concomitant CD (American Gastroenterological Association, 2001). Guidelines from the American Diabetes Association (Silverstein et al, 2005) recommend that children and adolescents with type 1 diabetes should be screened for celiac CD. The ADA recommends celiac disease testing soon after the diagnosis of diabetes and subsequently if growth failure, failure to gain weight, weight loss, or gastroenterologic symptoms occur. The ADA also states that consideration should be given to periodic re-screening of children and adolescents with negative antibody levels. Guidelines from the National Collaborating Centre for Women's and Children's Health (2004) recommend screening children and adolescents with type 1 diabetes for CD at diagnosis and at least every 3 years thereafter.

The CeliaGENE test (Prometheus Laboratories, Inc., San Diego, CA) is a genetic test for HLA-DQ2 and HLA-DQ8. Kaukinen and associates (2002) investigated whether HLA-DQ2 and HLA-DQ8 typing is helpful when diagnosis of CD is uncertain because of the absence of unequivocal small bowel villous atrophy. The authors concluded that HLA-DQ2 and HLA-DQ8 determination is useful in exclusion, probably lifelong, of CD in individuals with an equivocal small bowel histological finding.

According to the NIH Consensus Statement, when the diagnosis of CD is uncertain because of indeterminate results, testing for certain genetic markers (HLA haplotypes) can stratify individuals to high or low risk for CD. The Consensus Statement noted that greater than 97 % of patients with CD have the DQ2 and/or DQ8 marker, compared to about 40 % of the general population. Therefore, an individual negative for DQ2 or DQ8 is extremely unlikely to have CD (high negative-predictive value).

Guidelines on celiac disease from the American Gastroenterological Association (Rubio-Tapia et al, 2013) state that HLA-DQ2/DQ8 testing should not be used routinely in the initial diagnosis of CD. HLA-DQ2/DQ8 genotyping testing should be used to effectively rule out the disease in selected clinical situations: 1) Equivocal small-bowel histological finding (Marsh I-II) in seronegative patients; 2) Evaluation of patients on a gluten-free diet (GFD) in whom no testing for CD was done before GFD; 3) Patients with discrepant celiac-specific serology and histology; 4) Patients with suspicion of refractory CD where the original diagnosis of celiac remains in question; 5) Patients with Down's syndrome.

The addition of HLA-DQ typing to TGA and EMA testing, and the addition of serologic testing to HLA-DQ typing, provided the same measures of test performance as either testing strategy alone (Hadithi et al, 2007). Hadithi et al (2007) prospectively examined the performance of serologic testing and HLA-DQ typing. Patients referred for small-bowel biopsy for the diagnosis of CD underwent celiac serologic testing (AGA, TGA, and EMA) and HLA-DQ typing. Diagnostic performance of serologic testing and HLA-DQ typing compared with a reference standard of abnormal histologic findings and clinical resolution after a gluten-free diet were

carried out. Sixteen of 463 participants had celiac disease (prevalence, 3.46 % [95 % confidence interval [CI]: 1.99 % to 5.55 %). A positive result on both TGA and EMA testing had a sensitivity of 81 % (CI: 54 % to 95.9 %), specificity of 99.3 % (CI: 98.0 % to 99.9 %), and negative-predictive value of 99.3 % (CI: 98.0 % to 99.9 %). Testing positive for either HLA-DQ type maximized sensitivity (100 % [CI: 79 % to 100 %]) and negative-predictive value (100 % [CI: 98.6 % to 100 %]), whereas testing negative for both minimized the negative likelihood ratio (0.00 [CI: 0.00 to 0.40]) and post-test probability (0 % [CI: 0 % to 1.4 %]). The addition of HLA-DQ typing to TGA and EMA testing, and the addition of serologic testing to HLA-DQ typing, did not change test performance compared with either testing strategy alone. The authors concluded that a patient population referred for symptoms and signs of CD with a prevalence of CD of 3.46 %, TGA and EMA testing were the most sensitive serum antibody tests and a negative HLA-DQ type excluded the diagnosis. However, the addition of HLA-DQ typing to TGA and EMA testing, and the addition of serologic testing to HLA-DQ typing, provided the same measures of test performance as either testing strategy alone.

In an editorial that accompanied the afore-mentioned paper, Rashtak and Murray (2007) stated that "Hadithi and colleagues' study illustrate the importance of considering the pretest probability of celiac disease and the performance and limitations of each test when deciding which diagnostic tests to use for celiac disease. In most circumstances, physicians should use TGA-IgA but not AGA as the initial diagnostic test, referring patients who test positive and those with reasons to suspect other diagnoses for duodenal biopsies. The principal role of HLA testing is trying to rule out celiac disease in diagnostically challenging circumstance, such as discrepant serologic and histopathologic findings and refractory symptoms despite a gluten-free diet, or when patients with an uncertain diagnosis have already begun a gluten-free diet".

In a review on diagnosis, monitoring, and risk assessment of celiac disease, Setty et al (2008) stated that "[c]urrently, serological screening tests are utilized primarily to identify those individuals in need of a diagnostic endoscopic biopsy. The serum levels of immunoglobulin (Ig)A anti-tissue transglutaminase (or TG2) are the first choice in screening for celiac disease, displaying the highest levels of sensitivity (up to 98 %) and specificity (around 96 %). Anti-endomysium antibodies-IgA (EMA),

on the other hand, have close to 100 % specificity and a sensitivity of greater than 90 %. The interplay between gliadin peptides and TG2 is responsible for the generation of novel antigenic epitopes, the TG2-generated deamidated gliadin peptides. Such peptides represent much more celiac disease-specific epitopes than native peptides, and deamidated gliadin peptide antibodies (DGP) have shown promising results as serological markers for celiac disease".

A systematic review of the evidence for DGP for celiac disease conducted by the Institute for Clinical Effectiveness and Health Policy (Pichon-Rivere et al, 2009) found the evidence supporting its use to be controversial. Of the 11 studies of sufficient quality to be included in the review, 10 were of case-control design, and only 1 study of a consecutive series of patients. Using biopsy results as a gold standard, the sensitivity values reported for the IgA DGP ranged from 74 % to 98.3 % while the specificity values ranged from 90 % to 99.1 %. For IgG DGP tests, sensitivity values ranged from 65 % to 96.7 % and specificity values ranged from 95 % to 100 %. The assessment concluded that whether DGP is superior to ATG antibodies in the diagnosis of CD is controversial, with studies reporting conflicting results. The assessment also noted that, given the case-control nature of most of the studies, the patients included in these studies may not be representative, in terms of clinical presentation and stage of disease, of the patients for whom the test would be used in clinical practice.

Prause and colleagues (2009) examined investigated the performance of new assays for antibodies against deamidated gliadin (anti-dGli) in childhood CD. These investigators retrospectively compared children (142 with active CD and 160 without CD, diagnosis confirmed or excluded by intestinal biopsy) concerning (immunoglobulin [Ig] G and IgA) anti-nGli, anti-tissue transglutaminase (tTG), and 2 different anti-dGli assays. IgG-anti-dGli1, IgG-anti-dGli2, and IgA-tTG antibodies performed similarly. Area under the receiver-operating characteristic curve (AUC) was 98.6 %, 98.9 %, and 97.9 %; accuracy was 94.7 %, 95.7 %, and 96.7 %. Anti-dGli1 and anti-dGli2 (IgG and IgA) and IgA-anti-tTG performed significantly better than IgA-anti-nGli and IgG-anti-nGli. Both IgG-anti-dGli showed higher AUC and accuracy than IgA-anti-dGli and IgG-anti-tTG. Combined evaluation of IgA-anti-tTG with one of the IgG-anti-dGli tests reduced the rate of falsely classified patients. At enhanced cut-off

(specificity greater than 99 %), sensitivity was above 67 % for both IgG-anti-dGli and IgA-anti-tTG. If IgA-anti-tTG assay was combined with one of the IgG-anti-dGli tests, then the fraction of patients identified with more than 99 % specificity as celiacs increased significantly above 84.5 %. Combined evaluation of the 2 IgG-anti-dGli tests did not improve the performance. The authors concluded that the new IgA and IgG-anti-dGli tests out-perform conventional anti-nGli assays. The validity of IgG-anti-dGli can not be distinguished from IgA-anti-tTG. They stated that whether antibody assays could replace biopsy in diagnosis of CD in a substantial segment of children should be studied prospectively.

Lewis and Scott (2010) compared the performance of the DGP antibody test with the current standard, the TTG antibody test, through a meta-analysis of published studies. Databases from 1998 to 2008 were searched for relevant studies. These were assessed for methodological quality and standard statistical tests were applied to compare particularly the sensitivity and specificity of the 2 tests for the diagnosis of CD. Most studies had methodological flaws, especially ascertainment bias. The pooled sensitivities for the DGP antibody and TTG antibody tests were 87.8 % (95 % CI: 85.6 to 89.9) and 93.0 % (95 % CI: 91.2 to 94.5), respectively and the pooled specificities were 94.1 % (95 % CI: 92.5 to 95.5) and 96.5 % (95 % CI: 95.2 to 97.5), respectively. The authors concluded that although both tests performed well, the TTG antibody test out-performed the DGP antibody test and remains the preferred serological test for the diagnosis and/or exclusion of CD.

Parizade and Shainberg (2010) noted that reports from their clinical laboratory database show that 75 % of children less than 2 years old tested for celiac serology who were found positive for DGP antibodies had negative results for IgA-TTG. Levels of DGP were shown to decline and disappear without a gluten-free diet. This observation questions DGP's specificity for diagnosis of CD.

Vecsei et al (2009) ascertained which non-invasive follow-up investigation -- serological tests or intestinal permeability test (IPT) -- correlated best with histology and whether the interval between diagnosis and follow-up affects the accuracy of these tests. Data from adult patients with CD (followed up with biopsy, IPT, and serological tests [IgG anti-gliadin antibodies (AGA-IgG), AGA-IgA, and endomysial antibodies (EMA)] were

retrieved from a computerized database. Results of non-invasive tests were compared with the persistence of villous atrophy on biopsy. Patients were divided into 2 groups: Group A (comprised patients followed-up within 2 years after diagnosis), and Group B (comprising patients followed-up later than 2 years). A total of 47 patients were evaluable. The lactulose/mannitol (L/M) ratio had a sensitivity of 85 % and a specificity of 46.2 % for mucosal atrophy, whereas saccharose excretion showed a sensitivity of 60 % and a specificity of 52.6 %. The sensitivities of AGA-IgA and AGA-IgG were 15 % and 20 %, respectively, while specificity was 100 % for both. Validity of AGA was limited due to low number of positive results. Endomysial antibodies assay was 50 % sensitive and 77.8 % specific. In group A (n = 23) L/M ratio performed best in terms of sensitivity (88.9 %), whereas EMA achieved a higher specificity (71.4 %). In group B, the sensitivity of the L/M ratio decreased to 85.7 %, while the specificity of EMA increased to 91.7 %. The authors concluded that in this study, none of the non-invasive tests was an accurate substitute for follow-up biopsy in detecting severe mucosal damage.

Armstrong and colleagues (2011) stated that IgA-TTG is the single most efficient serological test for the diagnosis of CD. It is well-known that IgA-TTG levels correlate with the degree of intestinal damage, and that values can fluctuate in patients over time. Serological testing can be used to identify symptomatic individuals that need a confirmatory biopsy, to screen at-risk populations or to monitor diet compliance in patients previously diagnosed with CD. Thus, interpretation of serological testing requires consideration of the full clinical scenario. Anti-gliadin tests are no longer recommended for the diagnosis of classical CD. However, the understanding of the pathogenesis and spectrum of gluten sensitivity has improved, and gluten-sensitive irritable bowel syndrome patients are increasingly being recognized. The authors noted that studies are needed to determine the clinical utility of anti-gliadin serology in the diagnosis of gluten sensitivity.

Kurppa et al (2011) noted that the widely used serum endomysial (EmA) and transglutaminase 2 (TG2-ab) antibodies predict forthcoming villous damage and CD when the small-bowel mucosa structure is still normal. However, these autoantibodies may remain negative in this early stage of the disease. These researchers hypothesized that the antibodies

against DGP (DGP-AGA) might appear before the other antibodies and would thus be useful in the diagnosis and follow-up of patients with early-stage CD. Serum DGP-AGA, TG2-ab, and EmA were measured at baseline and after 1 year on a gluten-free diet in 42 adults proven to have early-stage CD despite normal small-bowel mucosal morphology (Marsh I-II), and in 20 celiac subjects evincing villous atrophy (Marsh III); 39 subjects with no signs of CD served as non-celiac controls. Sensitivity to detect early-stage CD was 79 % for DGP-AGA, 64 % for TG2-ab, and 81 % for EmA. Specificities were 95 %, 100 %, and 100 %, respectively. The corresponding efficiencies of the tests were 89 % for DGP-AGA, 81 % for TG2-ab, and 91 % for EmA. All 3 antibodies were significantly decreased on a gluten-free diet. The authors concluded that this study showed that the sensitivity of DGP-AGA was superior to TG2-ab and comparable to EmA in celiac patients having early-stage CD with normal villous morphology. They stated that, on the basis of these results, DGP-AGA would seem to offer a promising new method for case-finding and follow-up in this entity.

Sakly et al (2012) evaluated the usefulness of anti-DGP antibodies (a-DGP), in the diagnostic of celiac disease. A total of 103 untreated CD patients (67 children and 36 adults) and 36 CD patients under gluten-free diet were studied; and 274 subjects served as controls (114 healthy blood donors, 80 healthy children and 80 patients with primary biliary cirrhosis). Anti-DGP antibodies (IgG and IgA) and anti-tTG (AtTG) were detected by enzyme-linked immunosorbent assay (Elisa). Anti-endomysium antibodies (AEA) were detected by indirect immunofluorescence on human umbilical cord. The sensitivity of IgG and IgA a-DGP were 94 % and 97 % respectively, compared to 96 % for AEA and AtTG. The specificity of a-DGP was 93.6 % for IgG and 92 % for IgA. The specificity of AEA and AtTG were 100 %. The frequency of IgG and IgA a-DGP was significantly higher in patients with CD than in control group (94 % versus 4.4 %, $p < 10(-7)$; 97 % versus 8 %, $p < 10(-7)$). The frequency of IgG a-DGP was the same in children and adult (94 %). The frequency of IgA a-DGP were similar in children and adults (95.5 % versus 100 %). The authors concluded that the findings of this study showed that a-DGP increases neither the sensitivity nor the specificity of AEA and AtTG.

Hojsak et al (2012) compared the performance of 3 serological tests (IgA + IgG DGP, IgA TTG, and IgA + IgG EMA) for CD in young children younger than 3 years of age. These investigators identified all subjects younger than 3 years of age (n = 6,074) that were tested for CD serology and included those with biopsy data. Patients were classified as group 1 (n = 47): patients with confirmed CD, or group 2 (n = 12): patients with normal biopsy findings. There was statistically significant difference between group 1 and group 2 with regard to number of patients with positive IgA TTG (97.87 % versus 50 %, p < 0.001), IgA + IgG DGP (100 % versus 77.78 %, p = 0.007), and IgA + IgG EMA (95.65 % versus 9.09 %, p < 0.001). There was a significantly positive correlation between Marsh-Oberhuber score on the small duodenal biopsies and all tests. Analysis of sensitivity and specificity showed that manufacturer's levels had high sensitivity for all tests (IgA TTG 97 %, IgA + IgG DGP 100 %, IgA + IgG EMA 96 %), however specificity was low for IgA + IgG DGP (44 %) and IgA TTG (50%) but not for IgA + IgG EMA (91 %). The authors concluded that for children younger than 3 years of age, IgA + IgG EMA is highly sensitive and specific. Use of IgA + IgG DGP or IgA TTG as a single serological marker is insufficient for definite diagnosis of CD in this age group. Based on these findings, it might be reasonable to postpone the biopsy for asymptomatic children with negative EMA.

Olen et al (2012) evaluated diagnostic performance and actual costs in clinical practice of immunoglobulin (Ig)G/IgA DGP as a complement to IgA-TTG for the diagnosis of pediatric CD. All of the consecutive patients younger than 18 years tested for TTG and/or DGP, who underwent duodenal biopsy because of suspected CD in Stockholm and Gothenburg, Sweden, from 2008 to 2010, were included. Medical records were reviewed. Of 537 children who underwent duodenal biopsy, 278 (52 %) had CD. A total of 71 (13 %) were younger than 2 years and 16 (4 %) had IgA deficiency. Sensitivity and specificity for TTG were 94 % and 86 %, respectively. Corresponding values for DGP were 91 % and 26 %. Positive-predictive values (PPV) were 88 % for TTG and 51 % for DGP. There were 148 children who were TTG-negative and DGP-positive, of which only 5 % (8/148) had villous atrophy. Among children younger than 2 years with normal IgA, PPV was 96 % (25/26) for TTG and 48 % (24/50) for DGP. In 16 IgA-deficient children, 11 were DGP positive, of which 5 had CD (PPV 45 %). Eight of 278 cases of CD would possibly have been missed without DGP. The cost of adding DGP and

consequently more biopsies to be able to detect 8 extra cases of CD was Euro 399,520 or Euro 49,940 per case. 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.

Neves et al (2013) described the first electrochemical immunosensor (EI) for the detection of antibodies against DG. A disposable nano-hybrid screen-printed carbon electrode modified with DGP was employed as the transducer's sensing surface. Real serum samples were successfully assayed and the results were corroborated with an ELISA kit. The authors stated that the EI is a promising analytical tool for the diagnosis of CD.

Galatola et al (2013) analyzed the expression of CD-associated genes in small bowel biopsies of patients and controls in order to explore the multi-variate pathway of the expression profile of CD patients. Then, using multi-variant discriminant analysis, these researchers examined if the expression profiles of these genes in peripheral blood monocytes (PBMs) differed between patients and controls. A total of 37 patients with active and 11 with treated CD, 40 healthy controls and 9 disease controls (CD patients) were enrolled in this study. Several genes were differentially expressed in CD patients versus controls, but the analysis of each single gene did not provide a comprehensive picture. A multi-variate discriminant analysis showed that the expression of 5 genes in intestinal mucosa accounted for 93 % of the difference between CD patients and controls. These investigators then applied the same approach to PBMs, on a training set of 20 samples. The discriminant equation obtained was validated on a testing cohort of 10 additional cases and controls, and these researchers obtained a correct classification of all CD cases and of 91 % of the control samples. They applied this equation to treated CD patients and to disease controls and obtained a discrimination of 100 %. The authors concluded that the combined expression of 4 genes allows one to discriminate between CD patients and controls, and between CD patients on a gluten-free diet and disease controls. They stated that these findings contributed to the understanding of the complex interactions among CD-associated genes, and they may represent a starting point for the development of a molecular diagnosis of CD.

The American College of Gastroenterology's clinical guidelines on "Diagnosis and management of celiac disease" (Rubio-Tapia et al, 2013) stated the following:

- Intestinal permeability tests, D-xylose, and small-bowel follow-through are neither specific nor sensitive and are not recommended for CD diagnosis (Strong recommendation, moderate level of evidence).
- Stool studies or salivary tests are neither validated nor recommended for use in the diagnosis of CD (Strong recommendation, weak level of evidence).

An UpToDate review on "Diagnosis of celiac disease" (Kelly, 2014) states that "A variety of hematologic and biochemical abnormalities may be found in individuals with untreated celiac disease including iron deficiency, folic acid deficiency, and vitamin D deficiency. These abnormalities reflect nutritional deficiency states secondary to enteropathy-induced malabsorption. Although relevant to patient evaluation and management, none is sufficiently sensitive or specific to serve as useful screening or diagnostic tools. An oral xylose and/or lactulose absorption test, fecal fat evaluation, small bowel radiographic study, may also be abnormal in untreated celiac disease, but are not recommended for the diagnosis of celiac disease. Salivary and stool tests are also not recommended for screening, diagnosis, or monitoring of celiac disease".

HLA Genotyping for Celiac Disease Screening in Children with Type 1 Diabetes Mellitus

Elias and co-workers (2015) examined the clinical relevance and cost-effectiveness of HLA-genotyping in the Netherlands as a screening tool for the development of CD in children with type 1 diabetes mellitus (T1DM). These investigators performed a retrospective analysis in 110 children with T1DM diagnosed between January 1996 and January 2013. All children were screened for CD using coeliac disease-specific antibodies and HLA genotyping was performed in all children. Participants were screened for CD, and CD could be confirmed in 7; 86 % of the children with T1DM had one of the variants of HLA-DQ2.5 and DQ8. HLA genotypes observed in children with T1DM children and CD

were heterozygote DQ2.5, homozygote DQ2.5 and heterozygote DQ2.5/DQ8. HLA genotyping in CD screening in children with T1DM was more expensive than screening for CD with antibodies alone (€326 versus €182 per child). The authors concluded that the risk of CD development in children with T1DM was increased when they were heterozygote DQ2.5/DQ8, homozygote or heterozygote DQ2.5. They stated that the implementation of HLA genotyping as a first-line screening tool has to be reconsidered because it is not distinctive or cost-effective.

Mitchell and colleagues (2016) stated that children with T1DM are at increased risk of CD. Recent guidelines indicated celiac screening should include HLA typing for CD predisposing (DQ2/DQ8) alleles and those negative for these alleles require no further celiac screening. In this study, children (n = 176) with T1DM attending clinics across 2 Scottish regions were screened for HLA DQ2/DQ8 as part of routine screening. Data collected included the frequency of DQ2/DQ8 genotypes and the additional cost of HLA screening. Overall, DQ2/DQ8 alleles were identified in 94 % of patients. The additional cost of HLA typing was £3699.52 (£21.02 per patient). All patients with known CD (11/176) were positive for DQ2/DQ8 and all were diagnosed with CD within 5 years of T1DM diagnosis. The authors noted that the vast majority of children with T1DM have CD-predisposing HLA genotypes limiting the number of patients that can be excluded from further screening. They concluded that HLA genotyping is not currently indicated for CD screening in this population.

Binder and associates (2017) noted that due to a high linkage disequilibrium of diabetes and celiac-specific HLA genotypes, the prevalence of CD in children and adolescents with T1DM is much higher than in the general population. Recently, the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) revised new screening guidelines in which genotyping for celiac-specific HLA alleles is recommended for high-risk patients as patients with T1DM. These researchers examined the frequency and distribution of celiac-specific HLA genotypes in pediatric patients with T1DM. HLA genotyping was performed on pediatric patients with T1DM, recruited at the Medical University Hospital of Innsbruck and Graz. The test was done by PCR; statistical analysis was performed with IBM-SPSS V.20. In 121 pediatric patients with T1DM (52 % male), mean age of 13.3 (SD of

3.9) years, mean age at diabetes diagnosis was 7.4 (SD 3.8) years and mean diabetes duration of 5.9 (SD of 3.3) years, HLA genotyping was conducted. A total of 92 % showed positive HLA DQ2 and/or HLA DQ8 genotypes; 34 % carried HLA DQ2, 33 % were HLA DQ2+DQ8 positive and 25 % of the patients showed positive results for HLA DQ8 alone. Only 8 % had no celiac-specific HLA markers; 4 (3 %) patients were diagnosed with CD. The authors concluded that the majority of pediatric patients with T1DM had positive celiac-specific HLA genotypes DQ2 and/or DQ8. Therefore, genotyping for celiac-specific HLA alleles as a first-line test in patients with T1DM as recommended in the ESPGHAN guidelines did not seem reasonable. Screening for celiac-specific antibodies needs to be performed on a regular basis for patients with T1DM.

Paul and colleagues (2017) stated that the European guidelines for diagnosing CD in children were revised in 2012. The revised guidelines recommended that in symptomatic children, a diagnosis of CD can be made without small-bowel biopsies provided their anti-tissue transglutaminase (anti-tTG) titer is greater than 10 times of upper-limit-of-normal (greater than 10 × ULN) and anti-endomysial antibody is positive. In order to firm up the diagnosis in these children with very high anti-tTG titer, HLA-DQ2/DQ8 should be checked and be positive. Approximately 25 to 40 % of white Caucasian population has HLA-DQ2/DQ8 haplotype. However, only 0.1 to 1.0 % of the population will develop CD. Therefore, HLA-DQ2/DQ8 testing must not be done to “screen” or “diagnose” children with CD. Its use by pediatricians should be limited to children with anti-tTG greater than 10 × ULN, where the diagnosis of CD is being made on serology alone. A review of case referrals made to a tertiary pediatric gastroenterology center in Southwest England demonstrated that HLA-DQ2/DQ8 testing is being requested inappropriately both in primary and secondary care suggesting a poor understanding of its role in diagnosis of CD.

Deja and associates (2020) examined the usefulness of HLA DQ2/DQ8 genotyping in children with T1DM in various clinical situations: as a screening test at the diabetes onset, as a verification of the diagnosis in doubtful situations, and as a test estimating the risk of CD in the future. Three groups of patients with T1DM were included: newly diagnosed (n = 92), with CD and villous atrophy (n = 92), and with CD and villous atrophy

(n = 92). The results of genetic tests confirmed the presence of DQ2/DQ8 in 94 % of children with diabetes (group I) and in 100 % of children with diabetes and CD (groups II and III, respectively). Comparative analysis of the HLA DQ2/DQ8 distribution did not show any differences. Allele DRB1∗04 (linked with HLA DQ8) was significantly less common in children with diabetes and CD (group I versus groups II and III, 56.5 % versus 24.5 %; p = 0.001). The probability of developing CD in DRB1∗04-positive patients was 4 times lower (odds ratio [OR] 0.25; 95 % CI: 0.118 to 0.529; p = 0.001). The probability of developing CD in DRB1∗04-positive patients was 4 times lower (OR 0.25; 95 % CI: 0.118 to 0.529; p = 0.001). The probability of developing CD in DRB1∗04-positive patients was 4 times lower (OR 0.25; 95 % CI: 0.118 to 0.529). The authors concluded that genotyping HLA DQ2/DQ8 as a negative screening has limited use in evaluating the risk of CD at the diabetes onset and did not allow to verify the diagnosis of CD in doubtful situations. The presence of the DRB1∗04 allele modulated the risk of CD and significantly reduced it and could predict a potential form.

Measurement of Serum Anti-Phospholipid Antibodies

Laine and associates (2018) noted that an increased incidence of thrombosis is suggested in CD. These researchers examined serum levels of anti-phospholipid antibodies in untreated and treated adult CD patients. A cohort of 179 biopsy-proven CD patients (89 untreated, 90 on long-term GFD) and 91 non-celiac controls underwent clinical examination, assessment of celiac serology and enzyme immunoassay testing for anti-cardiolipin IgG and IgM, prothrombin IgG, and phosphatidylserine-prothrombin IgG and IgM. The level of anti-phospholipid antibodies was higher in CD patients compared with controls: anti-cardiolipin IgG 4.9 (0.7 to 33.8) versus 2.2 (0.4 to 9.6) U/ml, anti-prothrombin IgG 2.9 (0.3 to 87.8) versus 2.1 (0.5 to 187.0) U/ml, anti-phosphatidylserine-prothrombin IgG 6.9 (0.0 to 54.1) versus 2.3 (0.5 to 15.1) U/ml; $p < 0.05$ for all. Anti-cardiolipin IgG, anti-prothrombin IgG and anti-phosphatidylserine-prothrombin IgG were higher in treated compared with untreated patients. The phenotype of CD at presentation (gastro-intestinal [GI] symptoms, mal-absorption or anemia, and extra-intestinal symptoms or screen-detected disease) had no effect on the level of serum anti-phospholipid antibodies. The authors concluded that the serum level of anti-phospholipid antibodies is increased in adults with CD;

the higher level of antibodies in treated patients suggested that the increase is not gluten-dependent. They stated that the prothrombotic role of anti-phospholipid antibodies in CD warrants further investigation.

Measurement of Serum Neurotensin Levels as a Diagnostic Marker

Iorfida and colleagues (2020) stated that neurotensin (NT) is a gut hormone secreted by specific endocrine cells scattered throughout the epithelial layer of the small intestine, which has been identified as an important mediator in several GI functions and disease conditions. Its potential involvement in CD has been examined, however, there were contrasting findings. These researchers examined serum NT levels in children with CD at diagnosis, compared to a control group, and examined if NT correlated in CD patients with symptoms, antibody response, and intestinal mucosal damage. Children (age of 1 to 16 years) undergoing GI endoscopy for CD or for other clinical reasons were included in this study. Patients with CD diagnosed according to the 2012 European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines without biopsy were also recruited. Fasting serum samples were analyzed for NT levels using ELISA. Logistic regression, Wilcoxon rank sum, and Spearman's rank tests were used for statistical analysis. A total of 30 children (18 females, age of 2.2 to 15.9 years) were enrolled. Of 25 patients who underwent endoscopy, 9 were CD patients, 13 were controls, and 3 were excluded due to non-specific inflammation at duodenal biopsy. CD was diagnosed in 5 patients without biopsy. NT median was higher in CD patients compared to controls (13.25 (inter-quartile range [IQR] 9.4 to 17.5) pg/ml versus 7.8 (IQR 7.6 to 10) pg/ml; $p = 0.02$). No statistically significant association between NT and clinical, serological, or histological data of CD was observed in this CD cohort. The authors concluded that this was the first study that examined NT in CD children from Italy. Results showed that NT was higher in the serum of CD children at diagnosis compared to controls. Moreover, these researchers stated that larger-scale studies are needed to validate these findings, and to determine whether the increase in NT levels may represent an additional diagnostic marker for CD.

The authors concluded that a drawback of this study was the small number of patients enrolled (n = 30): this made the chances of finding statistically significant associations very low. Moreover, the relatively large number of patients who have received biopsy-sparing CD diagnosis limited further the ability to correlate NT with the severity of histological damage. Another drawback could be that the disease controls were children examined for various reasons. Access to reference levels for fasting NT levels in both young and older healthy children would be required, however, it is not feasible from an ethical point of view.

Furthermore, UpToDate reviews on “Diagnosis of celiac disease in children” (Hill, 2020) and “Diagnosis of celiac disease in adults” (Kelly, 2020) do not mention serum neurotensin as a diagnostic marker.

Celiac Disease and Atrial Fibrillation

Hidalgo and colleagues (2020) noted that several studies have found CD may be associated with various cardiac manifestations. Atrial fibrillation (AF) is one of the most common arrhythmias that can cause significant morbidity; however, the risk of AF in patients with CD remains unclear. In a meta-analysis, these researchers examined the risk of AF in patients diagnosed with CD compared to controls. They carried out a systematic literature review in Medline, Embase, Cochrane databases from inception through December 2017 to identify studies that examined the risk of AF in patients with CD. These investigators included randomized controlled trials (RCTs), cross sectional and cohort studies that reported the OR, relative risk (RR), hazard ratio (HR), and standardized incidence ratio comparing the risk of developing AF among patients with CD, versus patients without CD as control. The Newcastle-Ottawa scale was employed to determine the quality of the studies. Effect estimates from individual studies were extracted and combined using random-effect, generic inverse variance method of DerSimonian and Laird. Celiac disease is an autoimmune condition. This inflammatory state predisposes patients to develop AF. After a review of the literature, 4 observational studies with a total of 64,397 subjects were enrolled. The association between CD and increased risk of AF was significant, with a pooled OR of 1.38 (95 % CI: 1.01 to 1.88). No publication bias as evaluated by the funnel plots and Egger's regression asymmetry test with p = 0.54; however, the heterogeneity of the included studies was high (I2

= 96). The authors concluded that a significant association between CD and risk of AF was found in this analysis; there was a 38 % increased risk of AF. Moreover, these researchers stated that additional studies are needed to clarify the mechanistic link between AF and CD. A good understanding of the mechanisms behind it could let researchers work more on preventive measures to decrease risk factors. The authors concluded that the drawbacks of this meta-analysis were that all were observational studies, some with medical registry-based, only 4 articles were included and there was high heterogeneity between these studies.

Celiac Disease and Autism Spectrum Disorder

In a systematic review, Quan and colleagues (2021) examined the association between CD and autism spectrum disorder (ASD). These investigators carried out a literature search of Medline and Embase without limits placed on year or language. Observational studies reporting on the occurrence of CD among patients with ASD and/or the occurrence of ASD among patients with CD were included. Study design, characteristics, diagnostic criteria for ASD and CD, and the frequency of positive cases in the studied sample were recorded. Study quality was examined using an adapted Newcastle-Ottawa Quality Assessment Scale. Due to substantial heterogeneity between studies, a meta-analysis was not conducted. Of the 298 unique citations identified within the search strategy, 17 articles examining the association between CD and ASD were included. Of those articles, 13 observed samples of patients with ASD, and 6 observed samples of patients with CD. Overall, most studies had small sample sizes and reported no evidence for an association between the 2 conditions; however, a limited number of population-based studies of higher quality suggested a potential association between CD and ASD. The authors concluded that most studies evaluating an association between CD and ASD were at risk for systematic and/or random error; however, a potential link has been shown in a limited number of high-quality studies. Thus, this co-morbidity cannot be ruled out. These researchers stated that future studies should recruit larger sample sizes, include precise definitions of CD and ASD, and exclude patients with ASD on a gluten-free diet.

Celiac Care Index

Sparks and colleagues (2020) described quality improvement efforts to reduce variability in the care of children diagnosed with CD via the use of an institutional patient registry and a chronic care index. An institutional patient registry tracked rates of follow-up visits as well as repeat serologic testing. A Celiac Care Index that included anthropometrics, biopsy expectations, dietician consultation, and baseline laboratory evaluation was developed to standardize evaluation at diagnosis. Provider education sessions communicated expectations for this standard of care and order sets within the electronic medical record simplified test collection. Data were recorded and reviewed weekly and structured communications with providers were provided bi-weekly. Adherence with follow-up expectations (77 % to 89 %; $p = 0.03$) and repeat serologic testing (50 % to 90 %; $p < 0.0001$) significantly increased during the study period. Adherence with completion of the Celiac Care Index resulted in significant improvement in obtaining complete blood count ([CBC]; 80 % to 98 %; $p < 0.0001$), iron (25 % to 78 %; $p < 0.0001$), ferritin (34 % to 80 %; $p < 0.0001$), alanine aminotransferase/aspartate aminotransferase (74 % to 96 %; $p < 0.0001$), thyroid-stimulating hormone ([TSH]; 64 % to 90 %; $p < 0.0001$), vitamin D (36 % to 83 %; $p < 0.0001$), and hepatitis B immune status (30 % to 80 %; $p < 0.0001$). Iron deficiency demonstrated by low ferritin levels was common (41%) and a high rate of non-immunity to hepatitis B (70 %) was detected. The authors concluded that the Celiac Care Index improved adherence with published care recommendations and reduced variability in baseline evaluation at diagnosis. Moreover, these researchers stated that laboratory test results indicated that further studies are needed to evaluate these recommendations.

Fecal and Salivary Microbiomes

Bibbo and colleagues (2020) noted that to-date, reliable tests enabling the identification of CD patients at a greater risk of developing poly-autoimmune (PAI) diseases are not yet available. In a pilot study, these researchers identified non-invasive microbial biomarkers, useful to implement diagnosis of PAI. A total of 20 CD patients with PAI (cases) and 30 matched subjects affected exclusively by CD (controls) were selected. All patients followed a varied GFD for at least 1 year. Fecal

microbiota composition was characterized using bacterial 16S ribosomal RNA gene sequencing. Significant differences in gut microbiota composition between CD patients with and without PAI disease were found using the edgeR algorithm. Spearman correlations between gut microbiota and clinical, demographic, and anthropometric data were also examined. A significant reduction of Bacteroides, Ruminococcus, and Veillonella abundances was found in CD patients with PAI compared to the controls. Bifidobacterium was specifically reduced in CD patients with Hashimoto's thyroiditis and its abundance correlated negatively with abdominal circumference values in patients affected exclusively by CD. Furthermore, the duration of CD correlated with the abundance of Firmicutes (negatively) and Odoribacter (positively), whereas the abundance of Desulfovibrionaceae correlated positively with the duration of PAI. The authors concluded that they found evidence, for the 1st time, of an association between the gut microbiota and PAI in CD patients. According to the experimental evidences of this pilot study, certain variations of the gut microbiota composition might play a role in maintaining the gut homeostasis in GFD-treated CD individuals, while others might promote an increased risk of PAI. More specifically, gut microbiota species belonging to Bacteroides, Bifidobacterium, Veillonella, and Ruminococcus, as well as to Desulfovibrionaceae, warrant further investigation as their modulation might be a potential signature of association with PAI in genetically susceptible hosts. These researchers stated that these findings might be the basis for new studies designed with a wider number of individuals.

The authors stated that the small sample size (n = 20 CD patients) and the duration of PAI represented the main drawbacks of this study. Indeed, the lengthy duration of PAI (average duration 9.4 years) did not permit these researchers to examine about early biomarkers of autoimmunity, but only to hypothesize a signature of undiagnosed sub-clinical PAI. Instead, these findings (in particular regarding the abundance of Desulfovibrionaceae) may represent markers of PAI progression, although this hypothesis needs to be tested in an appropriately designed longitudinal study.

Sacchetti and Nardelli (2020) stated that the human body is inhabited by a variety of microbes (microbiota), mainly bacteria, that outnumber humans' own cells. Until recently, most of what is known regarding the

human microbiota was based on culture methods, whereas a large part of the microbiota is uncultivable, and consequently previous information was limited. The advent of culture-independent methods and, especially, of next-generation sequencing (NGS) methodology, marked a turning point in studies of the microbiota in terms of its composition and of the genes encoded by these microbes (microbiome). The microbiome is influenced mainly by environmental factors that cause a large inter-individual variability (approximately 20 %) being its heritability only 1.9 %. The gut microbiome plays an important role in human physiology, and its alteration ("dysbiosis") has been linked to a variety of inflammatory gut diseases, including CD. In recent years, a large body of experimental evidence suggested that the gut microbiome is an additional contributing factor to the pathogenesis of CD. These researchers examined the literature that has investigated the gut microbiome associated with CD, the methods and biological samples usually employed in CD microbiome investigations and the putative pathogenetic role of specific microbial alterations in CD. The authors concluded that both gluten-microbe and host-microbe interactions drive the gluten-mediated immune response; however, it remains to be established whether the CD-associated dysbiosis is the consequence of the disease, a simple concomitant association or a concurring causative factor.

Poddighe and Kushugulova (2021) noted that the human salivary microbiota includes hundreds of bacterial species. Alterations in gut microbiota have been examined in CD; however, fewer studies assessed the characteristics of salivary microbiome in these patients, despite the potential implications in its pathogenesis. Several recent studies suggested that the partial digestion of gluten proteins by some bacteria may affect the array of gluten peptides reaching the gut and the way by which those are presented to the intestinal immune system. The available clinical studies examining the salivary microbiota in children and adults, are insufficient to make any reliable conclusion, even though some bacterial species/phyla differences have been reported between patients with CD and healthy controls. However, the salivary microbiome could correlate better with the duodenal microbiota, than the fecal one. The authors concluded that further clinical studies on salivary microbiome by different and independent research groups and including different

populations, are advisable in order to examine the clinical value of the salivary microbiome analysis and understand some aspects of CD pathogenesis with potential clinical and practical implications.

Mitochondrial Antibody Testing

An UpToDate review on “Diagnosis of celiac disease in adults” (Kelly, 2022) does not mention mitochondrial antibody testing as a management tool.

Prometheus Celiac Plus Panel

The Prometheus Celiac Plus Panel includes both Celiac Genetics (HLA DQ2/DQ8) and Celiac Serology using both serum and whole blood specimens. The presence of these genes includes an estimate of patient’s risk, from extremely low to extremely high, according to individual genetic make-up. There are 2 DQ2 haplotypes, but only 1 DQ8 haplotype -- specific combinations may confer different risks for the development of CD. Although the Celiac Plus Panel includes genetic and serologic markers associated with CD, the panel tests for all of these markers simultaneously, rather than sequentially based upon baseline risk.

Pietzak et al (2009) noted that susceptibility to CD is related to HLA-DQ2 and DQ8 alleles and the heterodimers they encode. These investigators stratified risk for CD on the basis of HLA-DQ genotype. DNA from 10,191 subjects who were at risk for CD was analyzed for HLA-DQ haplotypes. Individuals with CD were identified as those who tested positive for anti-endomysial immunoglobulin A (EMA+) in an immunofluorescence assay. Samples homozygous for DQ2.5 (HLA-DQA1 05-DQB1 02) or DQ2.2/DQ2.5 (HLA-DQA1 05-DQB1 02 and HLA-DQA1 0201-DQB1 02) comprised 5.38 % of the total; 28.28 % of these were EMA+ (95 % CI: 24.55 to 32.26). Of the samples that were DQ2.5 heterozygous (HLA-DQA1 05-DQB1 02); 9.09 % were EMA+ (95 % CI: 7.82 to 10.51). Among samples in which HLA-DQ8 (HLA-DQA1 03-DQB1 0302) was detected, 8.42 % of homozygotes (95 % CI: 3.71 to 15.92) and 2.11 % of heterozygotes (95 % CI: 1.43 to 3.00) were EMA+. Samples with DQ2.2/DQ8 or DQ2.5/DQ8 comprised 5.08 % of the total, and 11.78 % of these were EMA+ (95 % CI: 9.13 to 14.87). HLA-DQ2 and HLA-DQ8

were absent in 4,283 samples (42.03 % of the total); 0.16 % of these samples were EMA+ (95 % CI: 0.07 to 0.34). The authors concluded that high-resolution, sequence-specific oligonucleotide probe typing with 35 DQA1-specific and 37 DQB1-specific probes of DNA from more than 10,000 subjects was used to stratify risk of CD in an at-risk U.S. population. DQ2 homozygosity (DQ2.5/DQ2.2+2.5) increased risk for CD, estimated by the rate of EMA positivity, compared with the entire sample population and other DQ genotypes. These data suggested a quantitative relationship between the type/proportion of DQ heterodimers and the risk of CD and identify potential immunotherapeutic targets.

Furthermore, these investigators stated that this analysis extended existing data to suggest a quantitative relationship between the type and proportion of DQ heterodimers and CD risk in an at-risk population. This information might further quantify the relationship between the expression of CD-associated heterodimers and the occurrence of CD, aid in characterizing previously indeterminate cases, and potentially avoid intestinal biopsies when used in combination with highly sensitive and specific serology. Targeting these high-risk alleles might aid the design of peptide immunotherapeutic strategies to augment the gluten-free diet (GFD).

GeneReviews' webpage on "Celiac disease" (Taylor et al, 2019) provided the following information – "Diagnosis without a duodenal biopsy. Pediatric guidelines from Europe present a pathway for the diagnosis of celiac disease in children that does not include a biopsy. Under these guidelines a diagnosis of celiac disease could be considered in a symptomatic child with a tTG IgA value of more than 10 times the upper level of normal, the presence of HLA haplotype DQ2 or DQ8, positive celiac serologic testing on 2 occasions, and evaluation by a pediatric gastroenterologist. There is ongoing debate regarding this approach to diagnosis".

Aboulaghras et al (2023) stated that although individuals with HLA DQ2 and/or DQ8 are more likely to develop CD, the condition could not be fully explained by this genetic predisposition alone. Multiple, as yet unidentified, factors contribute to the genesis of CD, including genetics, the environment, and the immune system. In order to provide insight into a prospective possibility and an expanded screening technique, these

researchers carried out a comprehensive and meta-analytical study of the assessment and distribution of HLA class II (HLA-DQ2/DQ8) in adult CD patients. They performed a systematic review using an electronic search of databases (PubMed, Google Scholar, Embase, and Direct Science) from January 2004 to February 2022. DQ2/DQ2 homozygotes have the highest risk of developing CD. DQ2/DQ8 typing was an effective test to exclude CD from the differential diagnosis of a patient with CD symptoms. Although other non-HLA genes have been associated with CD, they were rarely considered at diagnosis because they accounted for only a small proportion of the heritability of CD. This finding, together with the information gathered previously, may be useful in considering widely available and economically feasible screening options for CD in young individuals. The authors concluded that the findings of this study confirmed that the DQ2 allele is the primary one related to CD due to its high frequency in adult patients in all studies; the homozygous and heterozygous status of HLADQ2 is present with increased frequency in most adult patients. The high immunodominance and the pathogenic mechanisms of gluten peptide presentation by DQ2 contribute to the close connection between HLA haplotypes and CD. Although the classical DQ2/DQ8 associations with CD were confirmed in this meta-analysis, a minority of CD cases developed in the absence of predisposing HLA haplotypes. A detailed analysis of MHC in DQ2-negative CD should result in a better understanding of the susceptibility genes for CD. Recent data on microbiome studies in CD evidence the importance of a broader HLA screening, as some bacteria were associated with CD in the absence of the classical HLA risk alleles. At present, the real contribution of non-HLA genes is still unknown. In the future, the knowledge of the grade of the relevance of HLA associations could be included in algorithms for the evaluation of the risk in different populations, also considering a broader range of HLA haplotypes. These observations may contribute to the debate on the potential and cost-effective implementation of broader or mass screening strategies for CD in adults. Additionally, the determination of genetic risk for CD early in life may allow subsequent antibody monitoring in older adults.

Furthermore, an UpToDate review on “Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults” (Peppercorn and Kane, 2024) states that “The diagnosis of ulcerative colitis is based on the presence of chronic diarrhea for more than 4 weeks and evidence of active

inflammation on endoscopy and chronic changes on biopsy. Since these features are not specific for ulcerative colitis, establishing the diagnosis also requires the exclusion of other causes of colitis by history, laboratory studies, and by biopsies of the colon obtained on endoscopy". This UpToDate review does not mention genetic testing of HLA DQ2 and/or DQ8 for ascertaining the risk of development of CD.

Serological Laboratory Testing

Farmer et al (2023) analyzed laboratory testing results from pediatric patients newly diagnosed with CD to determine the usefulness of each test derived from recommended guidelines. These investigators examined serological testing at the time of diagnosis from patients enrolled in their CD registry from January 2018 through December 2021. The incidence of abnormal laboratory results, routinely obtained as per the recommendations of Snyder et al and the authors institution's Celiac Care Index, was assessed. Rates of abnormal laboratory values and estimated costs associated with these screening measures were analyzed. The data showed abnormalities in all serological testing obtained at celiac diagnosis. Hemoglobin (Hb), alanine aminotransferase (ALT), ferritin, iron, and vitamin D screening were found to be abnormal with notable frequency. Only 7 % of patients had an abnormal thyroid-stimulating hormone (TSH) and less than 0.1 % had an abnormal free thyroxine (T4). Non-response to hepatitis B vaccination was prominent, with 69 % of patients considered non-immune. Screening protocols as currently outlined in their Celiac Care Index resulted in an estimated cost of approximately $320,000 during the study. The authors concluded that review of screening laboratory results at their center demonstrated that abnormal values for several recommended measures were uncommon. Thyroid screening was infrequently abnormal and the usefulness of screening for hepatitis B at diagnosis is uncertain. Similarly, these findings suggested that iron deficiency screening may be condensed effectively into HB and ferritin testing, eliminating the need for initial iron studies. Decreasing baseline screening measures could safely decreased the burden of testing on patients and overall healthcare expenditures.

An UpToDate chapter on diagnosis of celiac disease in adults (Kelly, 2024) states that persons without other explanations for iron deficiency anemia should be tested for celiac disease. Autoimmune thyroiditis is one risk factor that places an individual at elevated risk of celiac disease.

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The above policy is based on the following references:

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