

Epidemiology, Presentation, and Diagnosis of Celiac Disease



Benjamin Lebwohl^{1,2} and Alberto Rubio-Tapia³

From the ¹Department of Medicine, Columbia University Irving Medical Center, New York, New York; ²Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York; and ³Department of Gastroenterology, Hepatology, and Nutrition, Digestive Diseases and Surgery Institute, Cleveland Clinic, Cleveland, Ohio

The incidence of celiac disease is increasing, partly because of improved recognition of, and testing for, the disease. The rise in incidence is also due to a real increase of this immune-based disorder, independent of disease detection. The reasons for this true rise in recent decades are unknown but may be related to environmental factors that may promote loss of tolerance to dietary gluten. Strategies to reduce the development of celiac disease have not been proven successful in randomized trials, but the quantity of early-life gluten exposure has been a major focus of prevention efforts. The criteria for the diagnosis of celiac disease are changing, but in adults, diagnosis still depends on the presence of duodenal villous atrophy while the patient is on a gluten-containing diet, along with findings from serology analysis. Although guidelines in the United States continue to mandate a biopsy at all ages, some children receive a diagnosis of celiac disease without a biopsy. If proven accurate and scalable, assays that detect gluten-HLA tetramer complexes might be used in diagnosis to be made in the context of a gluten-free diet without intestinal biopsy.

Keywords: Celiac Disease; Gluten; Epidemiology; Diagnosis.

Celiac disease is an immune-mediated condition characterized by small intestinal enteropathy, systemic symptoms related to malabsorption and/or immune activation, and autoantibodies to tissue transglutaminase (TTG). It is unique among the autoimmune diseases in that the trigger, dietary gluten, has been identified, and its removal results in resolution of symptoms and enteropathy in the majority of patients. Rising awareness and the development of serologic testing have resulted in a rise in disease incidence and a change in the distribution of clinical features. We review the epidemiology, presentation, and diagnosis of celiac disease, the latest research findings, and trends to follow in the coming decade.

Epidemiology

Incidence and Prevalence

Previously thought to occur only (or predominantly) in Northern and Western Europe, celiac disease is now recognized to be present worldwide. A systematic review of the global prevalence of celiac disease found a seroprevalence rate of 1.4%, with prevalence varying by continent from 1.3% (South America, 11 studies) to 1.8% (Asia, 20

studies).¹ This might be an overestimate of the true prevalence of celiac disease, given the imperfect specificity of celiac disease serologies (see section on Diagnosis: Serology Performance). The prevalence of biopsy-diagnosed celiac disease was also measured in this study and was 0.7%; this likewise varied by continent and region. Although seroprevalence may be an overestimate, biopsy-proven celiac disease may be an underestimate of the condition, because not all individuals tested via serology agree to undergo full endoscopic evaluation.

One consistent observation across geographic regions is that the incidence and prevalence of celiac disease are increasing over time. A systematic review and meta-analysis of celiac disease incidence found that in 33 studies that measured incidence at more than 1 timepoint, 24 (73%) showed significant increases in diagnosis rates over time.² In Olmsted County, Minnesota, diagnosis rates increased by 8.1% per year from 1950 through 2010.^{2–4} Discrete rises in diagnosis rates have been documented in relation to the availability of serologic tests in the 1990s³ and have also been seen in response to incentives. For example, in Finland, after a policy was introduced requiring patients to have a physician-confirmed diagnosis of celiac disease to qualify for a government-subsidized dietary provision, diagnosis rates increased.⁵

Nevertheless, there is accumulating evidence that, beyond increased awareness, the true incidence of celiac disease has increased, which is affecting the prevalence of celiac disease. This has been shown by cohort studies that included celiac disease screening, such as the Diabetes Autoimmunity Study in the Young study. In that study, 1339 infants born with a celiac disease-compatible HLA haplotype at a hospital in Denver, Colorado, from 1993 through 2004 were tested for celiac disease antibodies at 9, 15, and 24 months and then annually. Participants with persistent increases in antibodies were offered duodenal biopsy analysis. Celiac disease was diagnosed in 66 children (4.9%); using population HLA distribution data, the researchers extrapolated the prevalence of celiac disease in the greater Denver area, by age 15 years, to be 3.1%.⁶

Celiac disease can develop at any age, including in geriatric populations.⁷ Such diagnoses do not necessarily

Abbreviations used in this paper: NHANES, National Health and Nutrition Examination Survey; TTG, tissue transglutaminase.

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indicate late discovery of longstanding celiac disease—they could result from de novo loss of tolerance of gluten. Studies of serial serum samples have reported loss of gluten tolerance in adulthood.⁸ Nevertheless, recent prospective cohort studies have found that most patients develop celiac disease before age 10 years.^{6,9} The incidence of celiac disease is higher in women than men (17.0 vs 7.8 per 100,000 person-years in a pooled analysis²), but this might be because men are more likely to remain undiagnosed. A systematic review and meta-analysis found a slight increase in seropositivity among female participants in screening studies,¹⁰ although some studies of adults found that men and women have similar seroprevalences.^{11,12} Men are less likely to undergo duodenal biopsy examination during upper endoscopy for indications such as diarrhea and weight loss, which might contribute to underdiagnosis.¹³

The risk of celiac disease varies within countries. In India, the prevalence of celiac disease is greater in the Punjab region (1.2%) and elsewhere in the north compared with the south (0.1%), despite similar prevalences of the HLA-permissive haplotypes DQ2 and DQ8.¹⁴ Celiac disease did not vary by urban vs rural areas or with socioeconomic status in that study. Similarly, an analysis of duodenal biopsy specimens submitted during upper endoscopy to pathology laboratories throughout the United States showed that persons of Punjab ethnicity had the highest prevalence of villous atrophy—far higher than from persons of Indian ethnicity from outside of that region.¹⁵ The reasons for these regional and ethnic differences are unknown, but they might be related to mean daily wheat intake, which is greater in the Punjab region.¹⁴ It is also possible that more than 1 environmental factor can account for regional differences.

There are also racial and ethnic differences in celiac disease prevalence, even in screening studies, independent of differences in testing rates. In the United States, celiac disease was less common in non-Hispanic black and Hispanic vs white individuals. Based on data from the National Health and Nutrition Examination Survey (NHANES), seroprevalence was 0.2% in non-Hispanic black and 0.3% Hispanic individuals, compared with 1.0% in white individuals.¹⁶

Likewise, the prevalence of celiac disease can vary widely among countries despite geographic proximity. A screening study found serologic evidence of celiac disease in 1.4% of individuals in Finland, but only 0.6% of people in the adjacent Russian Karelia, again without significant differences in compatible HLA haplotypes.¹⁷ Such differences have led investigators to test environmental exposures as possible risk factors for the development of celiac disease.

Diagnosis Rates

A feature of celiac disease that affects epidemiology studies is that a substantial proportion of individuals remains undiagnosed. There are many reasons for this. Some patients are minimally symptomatic or asymptomatic.¹⁸ Others may have longstanding symptoms attributed to irritable bowel syndrome and are not tested for celiac

disease.¹⁹ Patients may even undergo upper endoscopy to evaluate symptoms, but duodenal biopsy samples are not collected and analyzed, because of a normal-appearing duodenum—the endoscopic appearance may be normal, but there is microscopic evidence of villous atrophy.^{13,20,21} Prior low estimates of celiac disease, dating to the 1960s (based on diagnosis rates), have led some clinicians to believe that celiac disease is a rare condition. This results in the testing of only patients with characteristics such as chronic diarrhea and a family history of celiac disease.²²

Regardless of the reasons, celiac disease has remained largely hidden in the United States. In a screening study in 2001, 95% of individuals in Olmsted County were undiagnosed.³ With the publication of prevalence data indicating that almost 1% of individuals have celiac disease,²³ together with the widespread availability of serologic tests, the proportion of undiagnosed individuals began to decrease, from 95% in 2001³ and 90% in Wyoming in 2003¹² to 83% in 2009 to 2010, based on data from NHANES.²⁴ The most recent analysis of celiac disease prevalence in the United States, based on NHANES, found that the prevalence of celiac disease remained stable from 2009 to 2014, at 0.7%, but that the proportion of patients with celiac disease who remain undiagnosed has decreased over time.²⁵

This might be due to increased awareness of the clinical manifestations of celiac disease, but it might also be related to widespread interest in, and adoption of, the gluten-free diet in the general population. Interest in a gluten-free diet has indirectly increased testing for celiac disease. The prevalence of the gluten-free diet, based on data from NHANES, increased from 0.5% in 2009 to 1.7% in 2014, whereas the prevalence of celiac disease remained stable during that same period.²⁵ Reasons for the avoidance of gluten in the absence of celiac disease vary, but they include symptoms that improve on this diet (nonceliac wheat or gluten sensitivity),²⁶ and the belief, based on unproven notions, that gluten avoidance carries cardiovascular or neurologic health benefits.²⁷ Gluten avoidance in the absence of celiac disease is associated with higher socioeconomic status²⁸ and appears more common in higher-income countries.²⁹ Regardless of the reason, widespread adoption of a gluten-free diet can affect efforts to measure celiac disease prevalence, because serologic assays do not detect celiac disease with high levels of sensitivity in groups with gluten avoidance. The prevalence of undiagnosed celiac disease might be more difficult to quantify if substantial proportions of the population are avoiding gluten at the time of testing.

Risk Factors and Prevention Strategies

The enteropathy associated with celiac disease results from the presentation of gliadin peptide fragments, deamidated by TTG, by antigen-presenting cells via HLA proteins. HLA proteins are encoded by genes in the major histocompatibility complex locus on chromosome 6 and are expressed on the surface of antigen-presenting cells.³⁰ Specific haplotypes encode proteins with affinities for specific antigens. The haplotypes DQ2 and DQ8 allow for the

presentation of gluten antigens by antigen-presenting cells, which can result in activation of an immune response and development of celiac disease.

The presence of at least 1 of these haplotypes is necessary but insufficient for development of celiac disease. Approximately 35% of people in the United States population are carriers of a DQ2 or DQ8 haplotype, yet most never develop celiac disease.³⁰ Genome-wide association studies have identified additional (relatively minor) genetic risk factors for celiac disease, but DQ2 and DQ8 are the genetic features most strongly associated with celiac disease development.^{31–33}

Two twin studies have found concordance rates of only 49%–83% among monozygotic twins, indicating the existence of environmental risk factors.^{34,35} Also, in multiple countries, the seroprevalence of celiac disease has increased in recent decades. A comparison of serum samples collected at the Warren Air Force Base in 1950 with samples collected from age-matched individuals in 2006 found the prevalence of celiac disease serologies to increase from 0.2% to 0.9%.¹¹ A similar study in Finland, with a higher baseline prevalence of celiac disease, reported an increase from 1.05% in 1978 to 1.99% in 2000.³⁶ This rapid increase in prevalence would be due to environmental, rather than genetic, risk factors.

Infant feeding practices, particularly regarding the introduction of gluten, have been the focus of prevention strategies. Studies of the acute increase of celiac disease incidence in Sweden in the 1980s led to the hypothesis that early introduction of high quantities of gluten, without concurrent breastfeeding, were responsible for the epidemic observed in that country.³⁷ An analysis of the Diabetes Auto Immunity Study in the Young (DAISY) study found celiac disease-associated antibodies in a higher proportion of infants whose introduction to gluten occurred before age 3 months or beyond age 6 months.³⁸

These observational studies led to trials to test strategies to prevent celiac disease in infants at increased risk—such as those with a family history and a compatible HLA haplotype. In a multicenter trial conducted throughout Italy, 533 infants were randomly assigned to groups that were introduced to gluten at age 12 months or at age 6 months. By age 10 years, 16.8% developed celiac disease, with no significant difference between groups in disease development, apart from a slightly delayed risk of celiac disease in the 12-month group.³⁹ In a multicenter randomized trial, 944 infants were randomly assigned to groups given low-dose daily gluten or placebo at age 4 months, followed by full introduction of gluten at age 6 months in both groups. The prevalence of celiac disease was 12.1% at 5 years, with no significant difference between groups.⁴⁰ The results of these trials overturned longstanding beliefs, based on observational studies, that the timing of gluten exposure affected the risk of celiac disease development. These results led to liberalization of feeding recommendations by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition, which issued guidelines that advised introducing gluten any time between 4 months and 12 months.⁴¹

Despite the negative results from these studies, there is still interest in the effects of gluten exposure early in life and

its effects on celiac disease risk. It is possible that the interventions that were tested in this high-risk population have beneficial effects in lower-risk populations, although this would be difficult to study because of the low numbers of reported outcomes. The prevalence of celiac disease correlates with the amount of consumed gluten,¹⁴ so quantity, rather than timing, might affect risk of celiac disease. This hypothesis has recently gained support—3 cohort studies concluded that children consuming higher quantities of gluten had an increased risk of celiac disease.^{9,42,43} These studies were performed in different countries (Norway⁴²; the United States⁴³; and an international cohort including Finland, Germany, Sweden, and the United States⁹) with prevalences of celiac disease ranging from 1.1%⁴² to 7%.⁹ The studies included screen-detected celiac disease^{9,43} and clinically detected celiac disease.⁴² Their consistent findings, of a gradient between gluten quantity in early childhood and subsequent celiac disease, indicates that modifying the quantity of gluten intake should be assessed in intervention studies.⁴⁴

Environmental risk factors for celiac disease, apart from gluten intake, have also been proposed (Table 1). Perinatal factors, including being small for gestational age⁴⁵ and elective (but not emergent) cesarian birth,⁴⁵ have been

Table 1. Potential Risk Factors for Celiac Disease

Risk factor	Comment	References
HLA DQ2 and DQ8	Monozygotic twin concordance: 49%–83%	130
Quantity of gluten consumed in childhood	Higher quantity associated with higher risk	9,42,43
Elective cesarian birth	—	45
Small for gestational age	—	45
Shorter breastfeeding duration	—	131
Rotavirus infection	Interaction between infection and season of birth	47,50
Reovirus infection	—	49
Lack of <i>Helicobacter pylori</i> colonization	—	51
Summer birth	—	132,133
Northern latitude (in the United States)	—	134
Southern latitude (in Sweden)	—	133
Acid suppression drugs	Concern for protopathic bias	52
Antibiotics	—	56
Higher maternal education	—	54
Nonsmoking status	—	53

associated with modest increases in risk of celiac disease, although data for the effects of cesarian birth are mixed.⁴⁶ Infections with microbes such as rotavirus,⁴⁷ *Campylobacter* species,⁴⁸ or reovirus⁴⁹ might trigger celiac disease, and vaccination against rotavirus might be protective.⁵⁰ Aspects of the gastric environment, including lack of *Helicobacter pylori* colonization and the use of proton pump inhibitors, are associated with an increased risk of subsequent celiac disease diagnosis, although these associations may be related to socioeconomic factors and protopathic bias, respectively.^{51,52} Nonsmoking status⁵³ and socioeconomic factors including higher maternal education⁵⁴ have been associated with an increased risk of celiac disease, although the mechanism for this association is unknown. Most studies investigating risk factors are limited by the fact that the outcome is diagnosis (vs no diagnosis) of celiac disease, which can be confounded by increased encounters with health care. In such studies, the temporal lag between the loss of tolerance to gluten and the diagnosis of celiac disease may lead to spurious associations between proposed exposures (such as infections) that lead to the uncovering of longstanding celiac disease, even if they do not have a causal role. It is likely that some risk factors (such as those related to gluten introduction) are operative in early childhood, whereas others (such as smoking) contribute to risk later in life. The mechanism by which loss of tolerance to gluten occurs during adulthood remains poorly understood.

There is interest in identifying aspects of the microbiome associated with the development of celiac disease, because this may be a modifiable risk factor.⁵⁵ Epidemiology studies found associations between antibiotic use⁵⁶ and elective cesarian birth⁴⁵ with celiac disease, so the increase in celiac disease incidence might involve changes in the microbiome caused by these practices. The hypothesis that the microbiome serves as the mediator between other risk factors (genetic and environmental) and celiac disease was supported in a study⁵⁷ that analyzed the microbiomes of stool samples from infants who were exclusively breastfed. That study found that infants with the HLA DQ2 haplotype had distinct microbiota (characterized by higher proportions of Firmicutes and Proteobacteria and lower proportions of Actinobacteria) compared to infants negative for DQ2 or DQ8. This finding raises the possibility that HLA haplotype increases risk of celiac disease, in part, through the microbiome.⁵⁷ The mechanism by which the microbiome affects the risk of celiac disease is unknown. Studies of the proteolytic activity of *Pseudomonas* species in the duodenum⁵⁸ and of microbially derived mimickers of gluten⁵⁹ point to possible mediators. Despite the lack of certainty, there is significant interest in intervening along this pathway; early probiotic supplementation in the first year of life was not associated with a decreased risk of celiac disease in the TEDDY (The Environmental Determinants of Diabetes in the Young) cohort.⁶⁰

Presentation

When serologic testing began in the 1990s, there was broadening of the clinical presentations that lead to diagnoses of celiac disease. Before this time, most patients

presented with diarrhea. The proportion of patients with celiac disease presenting with diarrhea decreased from 73% before 1993 (the year that serologic testing became available at the site of the study) to 43% thereafter.⁶¹ Although diarrhea continued to be the most common symptom at presentation, most patients received their diagnosis based on other signs or symptoms, such as osteoporosis, anemia, bloating, or irregular bowel habits; some had less common symptoms, including infertility,⁶² migraines,⁶³ neuropsychiatric symptoms,⁶⁴ and abnormal liver enzyme levels.⁶⁵ These signs and symptoms collectively outnumber diarrhea, so it is no longer applicable to refer to presentation with diarrhea as typical and presentation without diarrhea as atypical. As such, a 2013 consensus statement renamed diarrhea and nondiarrhea presentations as classical and nonclassical celiac disease, respectively (see Table 2).⁶⁶ Regardless of the type of symptoms, there is often a prolonged delay between symptom onset and celiac disease diagnosis. A national survey of patients with celiac disease in the United States found a mean symptom duration of 11 years before diagnosis,⁶⁷ and a study in the United Kingdom found a median duration of 4.9 years.⁶⁸

Liver biochemistry abnormalities are present in 40% of patients with newly diagnosed celiac disease, according to 1 series; incidentally noted mild increases in aspartate and

Table 2. Presentations of Celiac Disease

Presentation	Comment
Classical presentation	—
Diarrhea with or without steatorrhea	Occurs in a plurality (but not a majority) of patients
Weight loss	—
Growth failure	—
Nonclassical presentation ^a	—
Iron deficiency anemia	May improve with gluten-free diet alone, but iron supplementation sometimes necessary
Constipation	—
Abdominal pain	—
Bloating	—
Neurologic symptoms (migraine, ataxia)	—
Abnormal liver biochemistry	Predominantly aspartate and alanine transaminases
Infertility	—
Metabolic bone disease	—
Delayed puberty	—
Fatigue	—
Asymptomatic (screen-detected) presentation	—
Family history of celiac disease	Screening asymptomatic relatives is controversial
Associated conditions (type 1 diabetes mellitus, autoimmune thyroid disease, Down syndrome)	—

^aTo be classified as a nonclassical presentation, the signs or symptoms of a classical presentation must be absent.

alanine transaminases are the most common abnormality.⁶⁵ A study of individuals with chronic liver disease found that the prevalence of celiac disease, confirmed by villous atrophy, was 2.4%, which is higher than that of the general population.⁶⁹ As such, testing for celiac disease is incorporated into algorithms for the evaluation of abnormal liver chemistries.⁷⁰

Patients with celiac disease have an increased prevalence of psoriasis⁷¹ and eczema,⁷² but the dermatologic condition most frequently associated with celiac disease is dermatitis herpetiformis. This condition is characterized by an intensely pruritic, vesicular rash, and biopsy of adjacent noninvolved skin shows granular deposits of IgA at the dermal-epidermal junction.⁷³ Most, but not all, patients with dermatitis herpetiformis have circulating antibodies against TTG and duodenal villous atrophy. Unlike celiac disease, the incidence of dermatitis herpetiformis appears to have decreased in recent years.⁷⁴

Patients with untreated celiac disease can have osteoporosis, due to chronic inflammation and malabsorption of calcium and/or vitamin D—these patients are at increased risk for fracture.⁷⁵ Despite this association, it is not clear whether the prevalence of celiac disease is increased among patients with osteoporosis. A systematic review and meta-analysis found that the prevalence of celiac disease among patients with osteoporosis is 1.6%, comparable to that of the general population.⁷⁶ Although the prevalence of celiac disease was higher in persons younger than 60 years (1.8%) vs persons 60 years and older (1.0%), metaregression did not find an association between age at testing and prevalence of celiac disease.⁷⁶

An increasing proportion of patients with celiac disease receive their diagnosis from screening, due to a family history or associated disorder, such as type 1 diabetes or autoimmune thyroid disease.¹⁸ The prevalence of celiac disease is increased among persons with these features, so positive results from serologic tests have higher positive predictive values in this population. In these individuals, a gluten-free diet can improve not only symptoms of celiac disease but also the related disorder, such as glycemic control in patients with type 1 diabetes. Although a gluten-free diet has not been empirically shown to benefit patients with type 1 diabetes, a trial is underway in children.

Pediatric patients with type 1 diabetes also found to have celiac disease have been randomly assigned to a gluten-free vs a gluten-containing diet—the primary outcome is level of glycosylated hemoglobin.⁷⁷ Some patients with so-called asymptomatic celiac disease⁶⁶ realize that they had symptoms in retrospect, after they improve on a gluten-free diet.⁷⁸ Nevertheless, compared to patients with antecedent symptoms, patients with screening-detected celiac disease are less likely to report that they are glad to have received a diagnosis.⁷⁹

The diverse clinical manifestations of celiac disease make it a challenge to determine whom to test. Arguments for and against widespread screening are listed in Table 3. Population-based screening for celiac disease has not been tested in a randomized trial, and there are concerns about the low positive predictive value of serologic tests in low-prevalence populations. It is not clear whether identifying and treating all patients with celiac disease will increase life expectancy, and little is known about the long-term progression of undiagnosed celiac disease—some studies have reported increased mortality,^{11,80} and others have not.^{81–84}

Given this uncertainty, the United States Preventive Services Task Force concluded that “the current evidence is insufficient to assess the balance of benefits and harms of screening for celiac disease in asymptomatic persons,” even among high-risk groups such as first-degree relatives of patients with celiac disease.⁸⁵ The scope of this guideline was limited to asymptomatic individuals. Some patients could have symptoms that were overlooked before their diagnosis, so screening apparently asymptomatic populations might reduce morbidity and increase quality of life. However, there are practical challenges to proving these outcomes. For asymptomatic individuals in high-prevalence populations, other guidelines offer more latitude on this question. The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommends that children in high-risk groups (including first-degree relatives and those with type 1 diabetes, autoimmune thyroiditis, Down syndrome, Turner syndrome, Williams syndrome, and selective IgA deficiency) be screened for celiac disease even if they do not have symptoms of this disease.⁸⁶ Guidelines for adult patients issued by the American College of Gastroenterology acknowledge that screening asymptomatic

Table 3. Pros and Cons of Widespread Screening for Celiac Disease

Supporting Screening	Against Screening
Suggestion of increased mortality in undiagnosed celiac disease	Data on mortality in undiagnosed celiac disease are inconclusive
Consequences of long-term untreated silent celiac disease (bone health, infertility)	Imperfect specificities/low positive predictive value if the population prevalence is 1%
Improved quality of life after adoption of a gluten-free diet among first-degree relatives with screening-detected celiac disease	Lack of randomized trial data evaluating screening strategies
Failure of case-finding approaches to adequately discern celiac disease	Difficulty of the gluten-free diet among previously asymptomatic individuals

relatives for celiac disease is “reasonable but controversial.”⁸⁷

The alternative to screening the general or enriched populations is to test persons with signs or symptoms of celiac disease. This poses a challenge, given the manifold clinical manifestations that can present, but it is logical to test persons with disorders associated with celiac disease, such as those with chronic diarrhea,⁸⁸ anemia,⁸⁹ or osteoporosis.⁹⁰ Aggressive case finding has increased rates of diagnosis in some settings,⁹¹ but the precise clinical criteria to prompt testing have not been established. Moreover, with the increased awareness and more widespread testing for celiac disease, it is possible that the remaining population of undiagnosed patients does not have a distinct set of symptoms. This concept is supported by findings from a case-control study in Olmsted County, Minnesota, which found that persons with undiagnosed celiac disease actually had lower prevalences of diarrhea and dyspepsia than control individuals.⁹² As such, applying a case-finding algorithm might not yield an enriched population. Nevertheless, despite the uncertainty regarding yield, it is reasonable to test persons with these symptoms for celiac disease. For example, even though the prevalence of celiac disease is not necessarily increased among persons with osteoporosis, compared with the general population,⁷⁶ persons with osteoporosis who are found to have celiac disease are likely to benefit from a gluten-free diet.

Diagnosis

Serology Performance

There is considerable evidence to support the use of the TTG-IgA assays as the first-line test for diagnosis of celiac disease.⁹³ This assay identifies persons with celiac disease (not on a gluten-free diet) with 95% sensitivity and specificity, provided that the patient is on a gluten-containing diet at the time of testing.⁹⁴ When the titer of TTG-IgA is more than 5-fold the upper limit of normal, the test has a low false positive rate.⁹⁵ However, there is lack of standardization among TTG-IgA assays, and test performance varies among laboratories.^{95–97} In fact, a large international study found that the sensitivity of TTG assays ranged from 63% to 93% and that specificity ranged from 96% to 100%.⁹⁵

Serologic testing is important in the detection of celiac disease.⁹⁸ Assays for antigliadin antibodies have been used for decades but are no longer recommended because of inferior performance compared to other available tests.⁹⁹ The discovery that TTG is the target of IgA endomysial antibodies (EMA) was key to the development of modern serologic tests for celiac disease.¹⁰⁰ Widespread availability of the assay for TTG-IgA has facilitated timely diagnosis. Measurement of total IgA to determine whether levels are sufficient and, if IgA levels are low or deficient, incorporation of IgG-based tests can reduce false negative results.^{87,101} Assays for IgG against deamidated gliadin peptides and/or the TTG-IgG assay are best for this scenario.¹⁰²

The assay for EMA-IgA is an immunofluorescence-based test using primate esophagus or human umbilical cord samples. It is operator dependent, and interpretation of the results requires significant experience. The specificity of the EMA-IgA assay is close to 100%, and it has been mainly used as a confirmatory test.¹⁰³ According to European guidelines, the EMA-IgA test is required for the diagnosis of celiac disease in children without a biopsy.¹⁰⁴ It might be necessary to analyze intestinal biopsies from patients suspected of having celiac disease despite negative results from serologic tests—serologic tests performed in clinical practice detect celiac disease with lower levels of sensitivity than tests performed in trials, which generally include high-prevalence populations.

The clinical performance of antibody tests depends on ingestion of gluten. Patients should be informed that reducing or stopping intake of gluten before the test is administered can result in false negative results.¹⁰⁵ After 6–12 months of adhering to a gluten-free diet, at least 80% of persons with celiac disease have a negative result from a serologic assay.¹⁰⁶ Production of the antibody depends on dietary intake of gluten, so the assays might be helpful for monitoring adherence to the gluten-free diet after diagnosis. An assay for HLA-DQ–gluten tetramers in blood samples can identify patients with gluten-specific T cells, even in patients on a gluten-free diet. This test identifies patients with celiac disease with 97% sensitivity and 95% specificity,¹⁰⁷ but it requires validation in a larger population before implementation in clinical practice. One practical diagnostic approach uses the total IgA assay as the initial test; subsequent tests are then performed for IgA deficiency (see the proposed algorithm in [Figure 1](#)).¹⁰⁸

Genetic Testing

Polymorphisms in HLA-DQB1 (variants A1*05 and B1*02) and HLA-DQA1 (variant alleles A1*03 and B1*0302) increase risk for celiac disease.^{30,109} Tests for these alleles are not required for the diagnosis of celiac disease in most patients. Approximately one third of the white population, but almost 100% of patients with celiac disease, carry the risk alleles.¹¹⁰ A negative result from a test for these variants can rule out celiac disease (negative predictive value, >99%),¹¹¹ but not all carriers of these variants develop celiac disease—the predictive value is only approximately 12%.¹¹² Genetic tests are used to rule out celiac disease in specific clinical situations, such as for patients with equivocal findings from small bowel histology, such as those with Marsh scores of I or II, which correspond to increased intraepithelial lymphocytosis and crypt hyperplasia but lack villous atrophy (Marsh score III). Genetic tests can be helpful for the evaluation of patients on a gluten-free diet who were not tested for celiac disease before they started the diet, for patients with discrepant results from serology or histology analyses, and for patients with suspected refractory celiac disease for whom a diagnosis of celiac disease remains in question. Although risk is highest in persons homozygous for the DQ2 haplotype and lowest in persons heterozygous for the DQ8 haplotype,¹¹³ this genetic

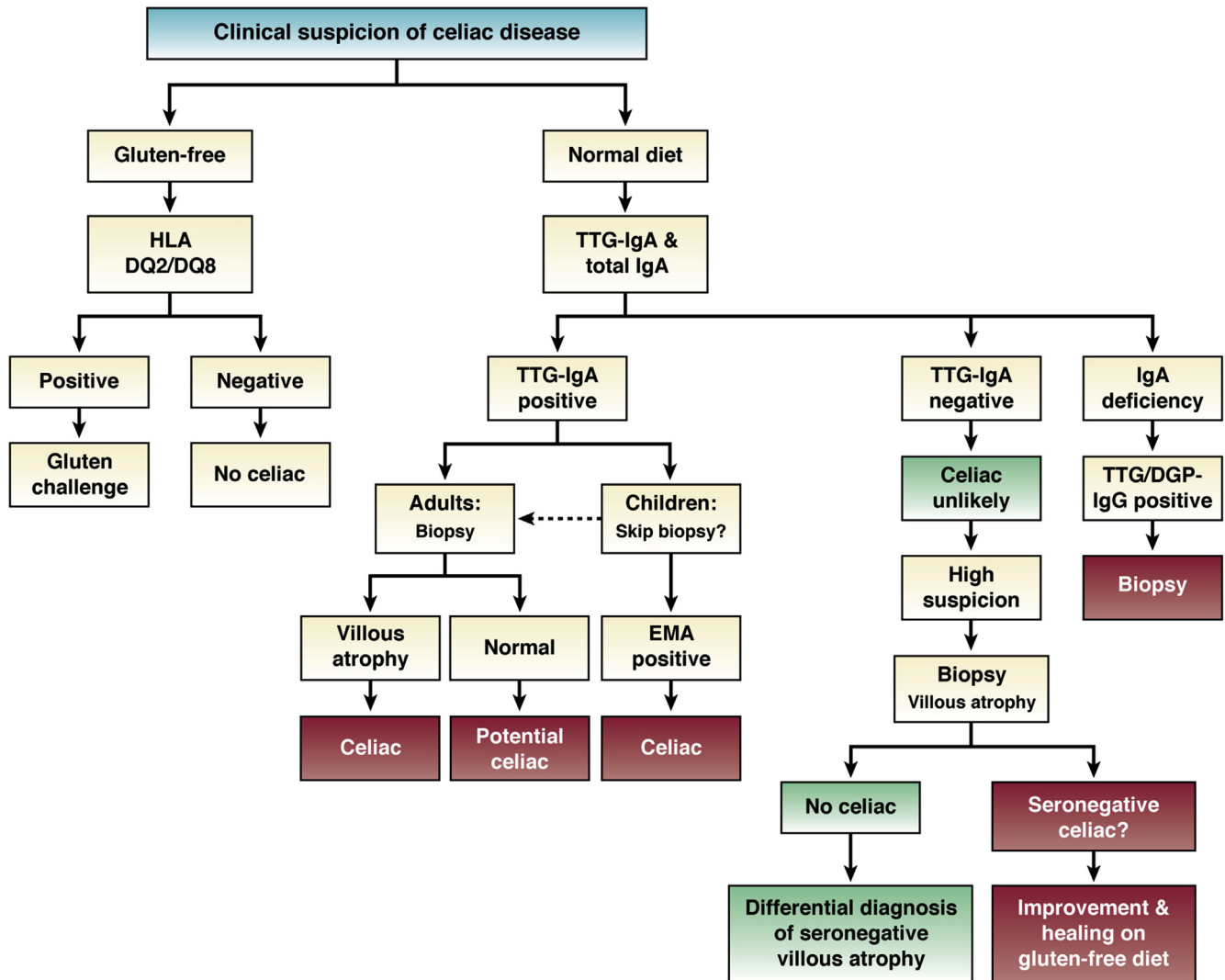


Figure 1. Diagnostic algorithm for celiac disease. Adapted from *Mayo Clin Proc* with permission.¹⁰⁸

information is less useful in clinical practice, because most patients, in even the highest-risk genetic category, still do not develop celiac disease. The major utility of a genetic test is its negative predictive value.

Duodenal Biopsies of Children and Adults

Abnormalities detected during upper endoscopy that are characteristic of celiac disease, but not specific to the disease, include scalloped folds and fissuring in the duodenum (Figure 2).¹¹⁴ Intestinal biopsy analysis is therefore used to confirm a diagnosis of celiac disease. Before serologic testing for celiac disease, a diagnosis required histologic analyses of biopsy samples collected while patients were on a gluten-containing diet (as a baseline for diagnosis), after a period on a gluten-free diet (to show improvement), and after medically supervised reintroduction of gluten into the diet (gluten challenge). An abnormal intestinal biopsy finding at the time of diagnosis in children without subsequent intestinal biopsies was able to correctly diagnose 95% of cases.¹¹⁵ Positive results from serologic tests can

support the diagnosis, but no single test is 100% specific for celiac disease.⁸⁷ Serologic tests perform less well in real-world clinical settings than in validation studies.¹¹² Confirmation of a diagnosis of celiac disease requires the demonstration of histologic changes associated with the disease, classified according Marsh, Marsh-modified, Corazza, or other classification systems, characterized by intraepithelial lymphocytosis with villous atrophy (Figure 3).^{116,117} Small-bowel biopsies might be useful in the differential diagnosis of celiac disease.

The European Society of Pediatric Gastroenterology, Hepatology, and Nutrition proposed in 2012 that it might be possible to avoid collection of intestinal biopsy samples from children who meet the following criteria: have characteristic symptoms of celiac disease, levels of TTG-IgA greater than 10-fold the upper limit of normal (confirmed with a positive result from a blood test for EMA), and homozygosity or heterozygosity for HLA-DQ2 or -DQ8.¹¹⁸ A large multinational validation study of 707 children estimated that this approach identified children with celiac disease with a positive predictive value of 99.75% (no

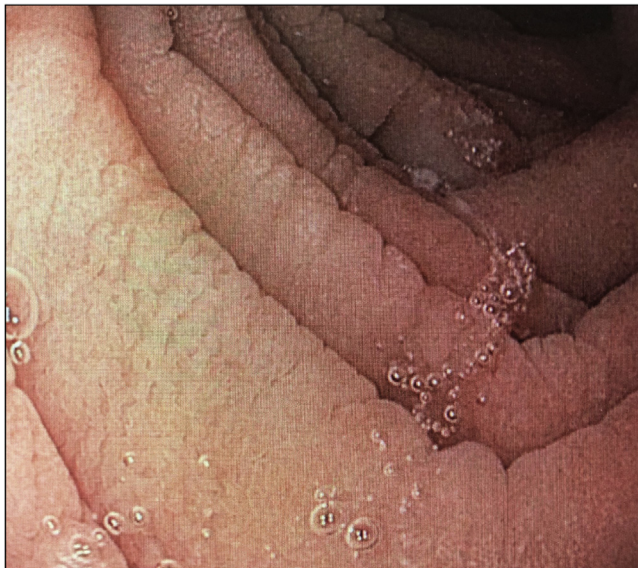


Figure 2. Water immersion endoscopic image of the distal duodenum in a patient with celiac disease. Fissuring and scalloping are seen in biopsy samples from patients with celiac disease.

biopsy but level of TTG-IgA 10-fold or more the upper limit of normal, a positive result from an EMA test, and at least 1 symptom).¹¹⁹ Genetic analysis for HLA-DQ2 or HLA-DQ8 haplotypes and symptoms are no longer required criteria in the revised European Society of Pediatric Gastroenterology, Hepatology, and Nutrition guidelines, updated in 2020.¹⁰⁴ There have been some studies to evaluate this strategy in adults,¹²⁰ but given the lack of multicenter validation and use of different serologic tests, it is premature to recommend a biopsy-free approach to diagnosis of adults.

Histologic abnormalities associated with celiac disease are not necessarily consistent throughout the duodenum.¹²¹ Multiple biopsy specimens of the duodenum should be submitted for analysis (1 or 2 specimens from the duodenal



Figure 3. Duodenal biopsy showing villous atrophy, intra-epithelial lymphocytosis, and crypt hyperplasia.

bulb and 4 from the distal duodenum), as recommended by different gastroenterology and pathology society guidelines.^{87,122,123} Submitting 1 specimen per pass of the biopsy forceps (instead of 2) can increase the likelihood of well-oriented specimens.¹²⁴ The probability of a new diagnosis of celiac disease is significantly increased when ≥ 4 specimens are submitted.¹²⁵ Adding biopsy samples of the duodenal bulb increases the diagnostic yield of celiac disease in high-risk groups.¹²⁶ In low pretest probability populations, separate sampling of the duodenal bulb has a minimal effect on celiac disease detection, so the advisability of routine bulb biopsies in low-prevalence settings has been questioned.¹²⁷ When indicated, targeted duodenal bulb biopsy from either the 9 o'clock or 12 o'clock position, in addition to biopsy samples from the distal duodenum, might increase sensitivity.¹²⁸ Care must be taken when interpreting the results from duodenal bulb biopsy analyses to avoid overdiagnosis.¹²² Overdiagnosis and underdiagnosis are concerns, particularly for patients with borderline histologic abnormalities—review by an expert pathologist can be helpful to confirm or rule out a diagnosis.¹²⁹

Future Directions

The incidence of celiac disease is increasing, with worldwide distribution. There is a trend toward increasing diagnoses of nonclassical presentations, and there is emerging evidence for accurate nonbiopsy diagnosis in selected children. Incidence might continue to increase if the data from the childhood cohort in Colorado (predicting a cumulative incidence of 3%) can be extrapolated to the general population.⁶ Recently developed diagnostic tools, such as the HLA-DQ–gluten tetramer-based blood assay, might change the way we diagnose celiac disease in the near future, pending validation and scalability. This technology, along with the validation of diagnostic algorithms based on serology, might lead to a change in diagnostic criteria in which it is no longer necessary to perform a small intestinal biopsy while patients continue a gluten-containing diet. These changes might shift the roles of gastroenterologists, from diagnosis to management and follow-up. If an evidence-based, biopsy-free strategy is developed for diagnosis, the incidence of celiac disease might increase further and spur interventional studies to prevent celiac disease in at-risk individuals.

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Correspondence

Address correspondence to: Benjamin Lebwohl, MD, MS, Celiac Disease Center, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York. e-mail: BL114@columbia.edu; fax: (212) 305-3738.

Conflicts of interest

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