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Review Article

Pitfalls in the Diagnosis of Celiac Disease: Bridging Gaps from Serology to Clinical Practice

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Abstract

Celiac disease is a chronic, immune-mediated enteropathy precipitated by gluten exposure in genetically predisposed individuals, with a global prevalence of approximately 1%. Though diagnostic workflows incorporate serologic techniques with both histologic and genetic evaluation, each approach carries key pitfalls that contribute to diagnostic inaccuracy. Serology testing is limited by selective immunoglobulin A deficiency and low-titer antibodies, in addition to interlaboratory variability of calibration standards and specimen concentrations. While duodenal biopsy is considered the gold standard for celiac diagnosis, patchy villous atrophy (e.g., ultrashort celiac disease) mimics other enteropathies, and the inherent subjectivity of histologic interpretation can compromise accuracy. Furthermore, celiac predisposition is highly correlated with two human leukocyte antigen (HLA) alleles, HLA-DQ2 and HLA-DQ8. However, nearly 30–40% of the general population expresses one of these alleles, thus introducing the risk of overdiagnosis and limiting the practical implications of genetic testing. There exist special celiac presentations, such as seronegative or potential celiac disease, overlap syndromes, and enteropathy-associated T-cell lymphoma, that introduce additional challenges to diagnostic success. The serologic-histologic discordance and nonspecific symptoms associated with these cases may require divergence from the traditional workflow, as well as supplemental investigations, such as a gluten challenge or breath testing, to confirm a celiac diagnosis. These challenges in celiac diagnosis have driven research into novel biomarkers and molecular assays that can not only enable earlier, more accurate detection but also provide longitudinal disease monitoring. Such markers include intestinal fatty acid-binding proteins, specific microRNA expression, and microbiome signatures that are strongly linked to celiac disease, which may one day serve as adjunctive screening tools to optimize diagnostic yield. This narrative review identifies the key pitfalls in adult celiac disease diagnosis — from pre-analytic serology issues to patchy histology and overinterpretation of HLA — and proposes a guideline-aligned, stepwise algorithm (with emerging biomarkers) to enhance accuracy and reduce missed or delayed cases. Ultimately, continued refinement of a comprehensive, multimodal diagnostic strategy that can integrate with emerging molecular tools is necessary for overcoming the current limitations of individual approaches to celiac diagnosis.

Introduction

Celiac disease is an immune-mediated enteropathy triggered by ingestion of dietary gluten—primarily gliadins and glutenin—in genetically predisposed individuals carrying human leukocyte antigen (HLA)-DQ2 and/or DQ8 alleles.[1,2] The pathogenesis involves an interplay of gluten peptides, tissue transglutaminase (tTG) modification, and activation of gliadin-specific $CD4^+$ T cells, culminating in villous atrophy, crypt hyperplasia, and inflammation of the small intestinal mucosa.[1]

Global seroprevalence approximates 1.4% (immunoglobulin A (IgA) anti–tTG positivity), yet only one in four cases is clinically recognized, reflecting significant underdiagnosis.[3,4] Delays from symptom onset to diagnosis often exceed five to ten years, during which continued gluten exposure perpetuates mucosal injury and systemic sequelae.[5,6]

While classic presentations—diarrhea, weight loss, and malabsorption—facilitate detection, up to 50% of adults exhibit non-classical or extraintestinal manifestations.[7] These include osteoporosis (fracture risk increased two- to sixfold), iron-deficiency anemia unresponsive to supplementation, dermatitis herpetiformis, neuro-

Keywords: Celiac disease; Serology; Duodenal biopsy; IgA deficiency; HLA-DQ2; HLA-DQ8; Capsule endoscopy; Seronegative celiac disease; Potential celiac disease; Intestinal biopsy; Emerging biomarkers.

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logic symptoms (ataxia, peripheral neuropathy), and reproductive issues such as infertility and recurrent miscarriage.[7–9] Moreover, untreated celiac disease carries a small but serious risk of enteropathy-associated T-cell lymphoma (EATL), with risk increased—particularly in refractory type 2 celiac disease—but remaining low in absolute terms compared to the general population.[10]

Diagnostic evaluation relies on serologic testing (IgA anti-tTG, IgA endomysial antibodies (EMA)) followed by confirmatory duodenal biopsy demonstrating characteristic histopathology.[11] However, selective IgA deficiency (present in 2–3% of patients), patchy villous atrophy, and histologic mimicry contribute to false-negative results, while reliance on serology alone may miss up to 10% of cases.[12–14] In adults, even very high titers (tTG-IgA ≥ 10× ULN with EMA positivity) should still prompt biopsy confirmation to assess for mimics and complications.[15] This differs from pediatric ESPGHAN no-biopsy pathways and should not be generalized to adults.[16]

Given the protean manifestations, genetic heterogeneity, and limitations of current assays, celiac disease remains a diagnostic challenge. Pre-analytic laboratory factors, particularly hemolysis, can artifactually suppress tTG-IgA signal and produce false-negative results.[15] Other complications, such as small intestinal bacterial overgrowth (SIBO), introduce further variability in overall antibody titers.[17] Additionally, ultrashort (bulb-only) celiac disease can be missed if D1 is not sampled; bulb-inclusive biopsies are therefore essential in adults.[18] This review examines key pitfalls—from serologic obscurity to focal histopathology—to enhance detection and improve patient outcomes. Importantly, diagnostic accuracy depends on testing while consuming gluten; premature gluten restriction reduces the sensitivity of serology and histology.[19,20]

Search strategy

We conducted a narrative review (PubMed, Embase, Cochrane Library) without language restrictions through July 2025, using MeSH/keywords ('celiac disease,' 'diagnosis,' 'seronegative,' 'duodenal biopsy,' 'HLA-DQ2,' 'HLA-DQ8,' 'capsule endoscopy,' 'microscopic colitis,' 'SIBO'). We prioritized adult guidelines and consensus documents (from the American College of Gastroenterology (hereinafter referred to as ACG) 2023 and the American Gastroenterological Association (AGA) Clinical Practice Update 2019), systematic reviews, and large cohort studies published between 2015 and 2025; pediatric-only data were included only when informative for adult practice. Searches used PubMed/Embase/Cochrane; guideline and consensus items were dual-reviewer screened; preference was given to studies with on-gluten testing and standardized biopsy protocols.

Serologic pitfalls

Serologic testing is a cornerstone of the initial evaluation of suspected celiac disease, offering a noninvasive means to detect disease-specific antibodies.[21] However, reliance on serology alone carries notable diagnostic pitfalls, particularly in patients with atypical presentations, confounding enteropathies, or altered immune profiles.[22–24] Additionally, there is no universal laboratory standardization for antibody testing, leading to discrepancies in sensitivity and specificity between platforms. Common variable immunodeficiency (CVID) may blunt serologic responses and mimic celiac histology; immunoglobulin profiling and clinical context are essential in such cases.[4,19] Key decision points, including IgA deficiency, biopsy triggers, and discordant results, are depicted in Figure 1.[4,17,20–22,25–27] Major serologic failure modes and mitigations are summarized in Table 1.

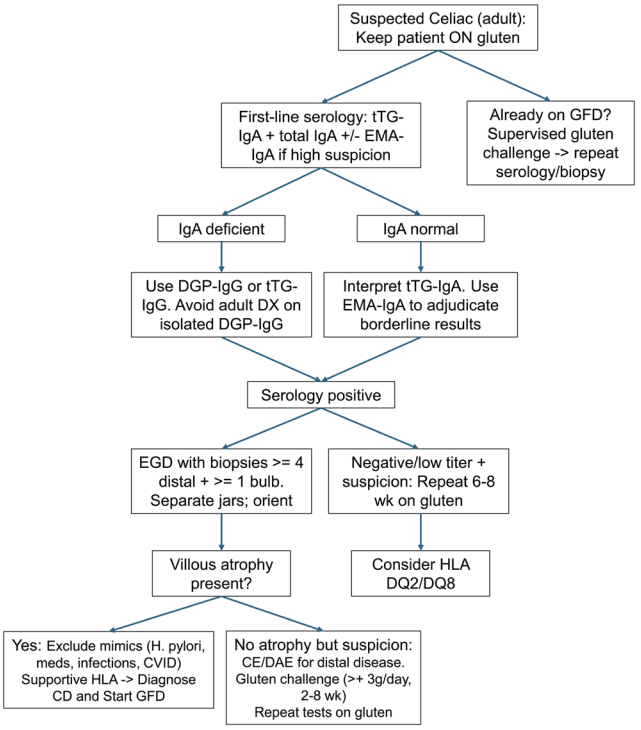

Fig. 1. Adult diagnostic algorithm for suspected celiac disease. Stepwise pathway integrating on-gluten serology (tTG-IgA with total IgA; IgG-based assays when IgA-deficient), indications for endoscopy with bulb-inclusive biopsies (≥4 distal D2/D3 + ≥1 bulb, separate jars, proper orientation), and management of discordant/seronegative or already-on-GFD scenarios; includes checkpoints for pre-analytic specimen quality (e.g., hemolysis) and complicated disease evaluation (splenic atrophy, cavitating mesenteric nodes) with capsule/device-assisted enteroscopy-guided biopsy.[4,17,21,25–27] CD, celiac disease; CE, capsule endoscopy; CVID, common variable immunodeficiency; DAE, device-assisted enteroscopy; DGP, deamidated gliadin peptide; DX, diagnosis; EMA, endomysial antibodies; GFD, gluten-free diet; HLA, human leukocyte antigen; IEL, intraepithelial lymphocytes; IgA, immunoglobulin A; tTG, tissue transglutaminase.

IgA deficiency and false negatives

One notable limitation in the serologic diagnosis of celiac disease is selective IgA deficiency, which is an often asymptomatic primary immunodeficiency characterized by relatively low or absent IgA levels, while other antibodies remain normal. Importantly, selective IgA deficiency occurs in approximately 2–3% of celiac patients, markedly higher than in the general population.[4] Since standard serologic assays for celiac diagnosis require an adequate IgA response (anti-tTG-IgA and anti-EMA-IgA), such individuals often yield false-negative results.[4] To mitigate this diagnostic shortcoming, measurement of total serum IgA should be performed in all patients undergoing serologic evaluation for celiac disease.[28] If IgA deficiency is identified, alternative IgG-based assays, such as IgG deamidated gliadin peptide (DGP-IgG) or tTG-IgG, should be employed.[13] However, IgG-based assays can produce false-positive results in patients with other inflammatory or autoimmune conditions, highlighting the importance of correlating serologic reports with histologic findings and clinical presentations.[28] In clini-

Table 1. Common sources of false negatives (missed or delayed celiac diagnosis)

Workflow step	Pitfall	Likely error	Mechanism/clue	Mitigation
Serology	Gluten restriction before testing	FN	Low antigen exposure → low/normal titers; biopsies may normalize	Keep patient on gluten during the work-up
	Selective IgA deficiency	FN	tTG-IgA/EMA-IgA negative despite disease	Check total IgA; switch to tTG-IgG/DGP-IgG
	CVID/ hypogammaglobulinemia	FN	Blunted antibody response, histology may mimic CD	Immunoglobulin profile; integrate clinicopathologic context
	Low-titer/borderline tTG-IgA	FN	Early/low-grade disease; dietary fluctuation	Repeat in 6–8 wk while on gluten; add EMA-IgA
	Assay & inter-lab variability	FN	Platform/calibration differences reclassify weak positives as negative	Use the same lab/assay serially; favor labs in EQA
	Using legacy anti-gliadin IgA/IgG assays/isolated DGP-IgG (adults)	FN/ Misstep	Low PPV; may divert from appropriate testing	Avoid anti-gliadin IgA/IgG assays; don't diagnose on isolated DGP-IgG in adults
Histology	Patchy villous atrophy	FN	Disease limited to bulb/distal segments	≥5 biopsies (≥4 distal, 1 bulb), separate jars
	Insufficient samples/ wrong sites	FN	Missed bulb; limited sampling	Follow sampling protocol; re-biopsy if suspicion is high
	Marsh interobserver variability	FN	Early lesions under-called	Report Marsh grade + IEL counts (≥25/100 EC); CD3 stain PRN
	Negative duodenal biopsies with distal disease	FN	Lesions in jejunum/ileum	CE → targeted enteroscopy for distal biopsies
Integration/ Algorithm	No biopsy in adults despite high serology	FN/ delay	Missed mimics/complications; loss of diagnostic certainty	In adults, confirm by EGD biopsies even at high titers
	High suspicion but single negative test	FN	Under-testing in high-risk phenotypes	Repeat serology and/or repeat biopsies on gluten

CD, celiac disease; CD3, cluster of differentiation 3; CE, capsule endoscopy; CVID, common variable immune deficiency; DGP, deaminated gliadin peptide; EC, epithelial cell; EGD, esophagogastroduodenoscopy; EMA, endomysial antibodies; EQA, external quality assessment; FN, false negative; IEL, intraepithelial lymphocytes; IgA, immunoglobulin A; PPV, positive predictive value; PRN, Pro re nata; tTG, tissue transglutaminase.

cal practice, the transition to IgG testing in IgA-deficient patients should be immediate upon recognition of the immunodeficiency to avoid diagnostic delay.[28] CVID may blunt serologic responses and mimic celiac histology; immunoglobulin profiling and clinical context are essential in such cases.[29]

Low-titer and fluctuating antibodies

Another challenge in serologic testing for celiac disease is the presence and interpretation of low-titer or borderline antibody levels. Many guidelines dictate a positivity threshold of 10 U/mL for tTG-IgA, but values near or just below this cut-off can occur in early disease or in patients on a gluten-free diet (GFD).[28] Moreover, transient seropositivity of tTG-IgA has been reported in non-celiac autoimmune diseases such as type 1 diabetes, autoimmune thyroiditis, and inflammatory bowel disease; this overlap may complicate lab interpretation, particularly when symptoms are nonspecific.[28] In adults, isolated DGP-IgG positivity has a low positive predictive value (PPV) and should not establish the diagnosis in the absence of supportive findings.[25] Antibody titers may also fluctuate due to dietary changes, illness, or immune modulation, rendering a single low-positive value insufficient to confirm diagnosis.[28] When serology is unequivocal, endoscopic evaluation and sampling of both the duodenal bulb and distal duodenum increase diagnostic yield and may help to evaluate borderline results.[30] In such cases, repeat testing after six to eight weeks, while ensuring consistent gluten consumption, can determine if elevated titers are sustained or transient, ultimately improving diagnostic yield.[13] Serial, longitudinal testing can be especially valuable in patients being screened due to family history rather than overt symptoms.[28] Anti-gliadin IgA/IgG assays are not recommended for diagnosis.[5]

Assay variability

Beyond patient-specific factors, the efficacy of celiac disease serologic testing is closely associated with technical variability between different assays and laboratories. For instance, enzyme-linked immunosorbent assay-based tTG tests can differ in both sensitivity and specificity depending on antigen source, degree of antigen purity, and the assay's calibration process.[4] Prior studies comparing commercial kits have reported inter-assay and inter-laboratory differences in measured antibody performance and concentrations that meaningfully affect clinical classification, even when analyzing identical samples.[4] As such, this variability can produce inconsistent results for the same patient if specimens are processed by different laboratories or at different time points.[5] Furthermore, without universal calibration standards, borderline and/or low-positive results may be classified differently depending on

the testing method and platform.[5] For patients requiring longitudinal monitoring of antibody levels, such as those being followed for dietary adherence, this inconsistency can undermine clinical decision-making and management.[4] To minimize these discrepancies, the same laboratory and assay platform should be utilized for serial measurements whenever possible.[4] Participation in external quality assessment (EQA) can serve as a critical quality control measure to address this variability in serologic testing; EQA and harmonization initiatives aim to identify outliers, promote best practices, and standardize interpretation thresholds across kits.[9] From a clinical standpoint, partnerships with laboratories engaged in regular EQA participation increase the reliability of results, subsequently strengthening the clinician's capacity to confidently interpret findings.[29] As serology often guides the decision to proceed with invasive biopsy for celiac diagnosis, ensuring the highest test quality is paramount to avoiding both over- and under-diagnosis.[4]

The AGA emphasizes a stepwise, serology-first strategy performed while the patient consumes gluten, followed by confirmatory histology and judicious use of genetics in equivocal scenarios.[13] Chronic liver disease may yield false-positive tTG-IgA; EMA confirmation and histology help adjudicate.[13]

Technical (pre-analytic) pitfalls

Hemolysis can artifactually lower tTG-IgA immunoassay signals, producing false-negative results; repeat testing on a non-hemolyzed specimen is warranted when clinical suspicion remains high.[29] Pre-analytical factors—including specimen mishandling or delayed processing—can compromise the accuracy of celiac serologic tests; consequently, the ACG advises using the same validated laboratory/assay for longitudinal testing to minimize between-assay variability and misclassification.[5,16]

Key elements

Workflow steps are collated in Figure 1 and Table 1.

1. *Test on gluten; avoid pre-test restriction:* Reduction or avoidance of gluten before testing lowers the sensitivity of both serology and biopsy; patients should remain on a normal diet during the diagnostic work-up.
2. *First-line serology:* Order tTG-IgA with total IgA for all adults; use EMA-IgA as a highly specific confirmatory test when results are equivocal or clinical suspicion is high.
3. *Handle IgA deficiency explicitly*: If total IgA is low, use DGP-IgG or tTG-IgG (recognizing lower specificity outside the IgA-deficient setting).
4. *Strongly positive serology:* In adults, even very high titers (tTG-IgA ≥ 10× ULN with EMA positivity) should trigger biopsy confirmation, consistent with ACG 2023; pediatric no-biopsy pathways (ESPGHAN) are not automatically generalizable to adults.[28,31] *Note:* "No-biopsy" diagnosis at very high serologic titers is a pediatric ESPGHAN pathway; in adults, biopsy confirmation remains recommended.
5. *Biopsy confirmation and technique:* Obtain multiple biopsies with careful morphologic assessment (Marsh grading, IEL counts). To maximize sensitivity, sample both the bulb and the distal duodenum.
6. *Discordant pathways:* Biopsy-first diagnosis: If villous atrophy is found before serology is sent, obtain celiac-specific serology before starting a GFD. *High suspicion but negative biopsies:* Send tTG-IgA; if positive, consider repeat biopsies (either immediately or later) while maintaining gluten exposure.
7. *Gluten challenge when already on GFD:* If a patient started a GFD before testing, the AGA suggests returning to a normal diet with approximately three slices of wheat bread daily for one to three months, then repeating tTG-IgA (±EMA) and biopsies as indicated. (Typical adult practice approximates ≥3 g gluten/day for two to eight weeks, balancing yield and tolerability; optimal dose and duration remain unsettled). Figure 1 summarizes decision points for HLA testing, supervised gluten challenge, and timing of repeat serology/biopsy in already-on-GFD presentations.[29]
8. *Role of HLA:* HLA-DQ2/DQ8 testing has a high negative predictive value (NPV; >99%) and is most useful to exclude celiac disease in equivocal or historical cases (not for routine screening given 30–40% carriage in the general population).

Histopathologic challenges

Duodenal biopsy is largely considered the gold standard for celiac diagnosis, though this approach contains several limitations that may compromise diagnostic accuracy.[10] The Marsh-Oberhuber system is the most referenced classification technique to analyze celiac-related alterations in mucosal histology. However, this approach is not only inherently subjective but also requires precise sampling of tissue that characteristically exhibits a patchy, variable distribution.[19] Even with adequate sampling, many histologic findings in celiac disease are not pathognomonic.[29]

Patchy villous atrophy

One challenge in histopathologic evaluation is patchy villous atrophy, a histologic finding that characterizes regions of the small bowel with blunting or flattening of the villi, while other regions appear normal, even in the same bowel segment. In other words, lesions may be confined to discrete mucosal areas, particularly within the duodenal bulb or extending into the more distal duodenum, leaving intervening segments with normal villous architecture.[32] This variability in histologic presentation naturally increases the risk of sampling error, which is compounded if biopsy sites are limited.[15] Current guidelines, including those from the American College of Gastroenterology and the British Society of Gastroenterology, recommend a minimum of five biopsy specimens—four from the distal duodenum and one from the duodenal bulb—to maximize diagnostic accuracy.[10] This approach is supported by studies demonstrating that duodenal bulb sampling increases diagnostic sensitivity by detecting early or localized disease that would otherwise be missed if only distal biopsies were obtained.[10] Endoscopic markers (mucosal scalloping, mosaic pattern, fissuring) are suggestive but insufficiently sensitive; biopsy is required irrespective of visual appearance.[15,26] Additionally, recognition of hyposplenism (splenic atrophy or Howell–Jolly bodies), a known complication of celiac disease, should heighten suspicion for complicated disease and support a low threshold for comprehensive duodenal sampling.[27] The inability to fully follow this protocol may increase the risk of false-negative histologic findings, especially in patients with mild disease or those who consume gluten occasionally.[9,16]

Ultrashort celiac disease is characterized by villous atrophy confined to the duodenal bulb (D1) with positive celiac serology.[33–36] Adult series, including a 2024 multicenter study, show that omitting bulb biopsies risks missed diagnoses, whereas adding ≥1 dedicated bulb specimen increases yield. See Figure 1 for recommended sampling.

Marsh-Oberhuber subjectivity

Histologic interpretation in celiac disease often relies on the

Table 2. Common sources of false positives/misclassification

Workflow step	Pitfall	Likely error	Mechanism/clue	Mitigation
Serology	Chronic liver disease, other autoimmunity	FP (tTG-IgA)	Non-celiac tTG elevations	Confirm with EMA-IgA; require histology on gluten
	Isolated DGP-IgG (adults)	FP	Low PPV without supportive findings	Do not diagnose CD on isolated DGP-IgG
	Assay/calibration drift	FP/FN	Borderline values flip across platforms	Same lab/assay longitudinally; lab EQA participation
Histology	Orientation artifact	FP (atrophy)	Tangential cuts flatten villi	Proper orientation; experienced GI path review
	Peptic/duodenitis, *H. pylori*-related lymphocytosis	FP (Marsh I)	IEL↑ without villous atrophy	Test/treat *H. pylori*; correlate with serology
	Drug-induced enteropathy (e.g., olmesartan)	FP	Villous blunting ± crypt hyperplasia	Review meds; consider withdrawal/re-challenge
	Infections (e.g., Giardia), tropical sprue	FP	CD-like histology	Stool O&P travel history; treat & reassess
	Autoimmune enteropathy	FP	Overlapping histology, different immunophenotype	Autoimmune work-up; expert pathology consult
	Diagnosing by endoscopic appearance alone	FP	Scalloping/mosaic is not diagnostic	Always biopsy irrespective of the endoscopic look
Genetics	Over-calling HLA-DQ2/DQ8 positivity	FP (labeling)	30–40% carriage in the general population	Use HLA to exclude CD; not for routine screening

CD, celiac disease; DGP, deaminated gliadin peptide; EMA, endomysial antibodies; EQA, external quality assessment; FP, false positive; GI, gastrointestinal; HLA, human leukocyte antigen; IEL, intraepithelial lymphocytes; IgA, immunoglobulin A; O&P, ova and parasites; PPV, positive predictive value; tTG, tissue transglutaminase.

Marsh-Oberhuber classification system, which grades the degree of mucosal metaplasia and atrophy. Though widely accepted, this approach is inherently subjective, and studies have reported only moderate interobserver agreement, often in the range of 60–70%.[26] These discrepancies are most pronounced when distinguishing early lesions that do not demonstrate overt villous atrophy, such as the isolated intraepithelial lymphocytosis of Marsh I versus the intraepithelial lymphocytosis and crypt hyperplasia of Marsh II. To remedy diagnostic subjectivity, quantitative intraepithelial lymphocyte (IEL) counts have been integrated into practice, with a threshold of 25 or more IELs per 100 enterocytes serving as an objective measure.[10] However, even IEL quantification requires careful sampling and standardized counting protocols, as counts may vary depending on imaging resolution, section thickness, and staining technique.[37]

Histologic mimics

Histologic patterns commonly utilized in celiac diagnosis are not pathognomonic and can be observed in numerous enteropathies. Conditions such as *Giardia lamblia* (hereinafter referred to as *G. lamblia*) infection, tropical sprue, and chronic bacterial overgrowth can produce villous blunting and crypt hyperplasia similar to that seen in celiac disease. Autoimmune enteropathy can also mimic this histology, as can drug-induced enteropathy from agents like olmesartan.[17,19,38] In such cases, reliance on histopathological findings alone may lead to misdiagnosis. To that end, stool microscopy for parasitic infections (e.g., ova and parasite testing for *G. lamblia*), small bowel aspirates for bacterial overgrowth, and serologic markers of autoimmunity can assist in distinguishing these pathologies.[17,19,38] *Helicobacter pylori* (hereinafter referred to as *H. pylori*) infection, nonsteroidal anti-inflammatory drug, and proton-pump inhibitors can produce duodenal lymphocytosis without villous atrophy and should be considered before labeling potential or seronegative celiac disease.[18] This overlap of biopsy results among mimics underscores the necessity of integrating histologic findings with serologic testing, genetic risk assessment, and clinical presentation to best optimize diagnostic accuracy.[4] Common histologic mimics and mitigation steps are summarized in Table 2.

Capsule endoscopy (CE) and biopsy sites

While upper endoscopy with duodenal biopsy remains the gold standard for histologic confirmation of celiac disease, CE offers a valuable complementary role in identifying disease beyond the reach of a standard gastroscope.[39] Celiac disease can sometimes involve segments distal to the duodenum, such as the proximal jejunum, that may not be sampled during routine biopsies. CE enables noninvasive imaging of these regions, allowing for the detection of characteristic celiac features like mucosal scalloping and villous atrophy in segments that would otherwise be inaccessible. In patients with persistent symptoms but negative duodenal biopsies, CE may serve an important role in informing targeted enteroscopy to sample abnormal jejunal or ileal mucosa.[20] Given the patchy and potentially distal distribution of histologic lesions in celiac disease, optimal site selection for biopsy is critical for proper diagnosis. Standard practice recommends sampling from both the duodenal bulb and the second or third portions of the duodenum, as these sites offer the highest yield in most patients.[10,40] In select cases, particularly when CE suggests distal small bowel involvement, targeted biopsies from the jejunum may be warranted using techniques such as enteroscopy.[41] This approach can assist in uncovering disease missed by standard duodenal sampling, especially in seronegative or treatment-refractory patients.[20] CE and

device-assisted enteroscopy are particularly useful when evaluating suspected ulcerative jejunoileitis or EATL in nonresponsive or refractory disease.[20] Ultimately, incorporating targeted sampling into diagnostic algorithms, alongside careful histologic assessment and correlation with both clinical and serologic findings, remains essential for accurate and timely diagnosis.[42]

Genetic testing limitations

Genetic testing for disease-associated alleles has emerged as a valuable adjunct in the diagnostic workup of celiac disease, though their high prevalence in the general population limits its utility and introduces the risk of overdiagnosis. Furthermore, though genotyping can confirm genetic susceptibility, this approach does not reveal active disease or the severity of symptoms.[2]

HLA-DQ2/DQ8 predictive values

The genetic predisposition to celiac disease is strongly associated with two specific HLA class II alleles: HLA-DQ2 and HLA-DQ8. The NPV of HLA-DQ2/DQ8 testing exceeds 99%, and nearly all patients with biopsy-confirmed celiac disease express at least one of these alleles. In other words, if an individual lacks both alleles, their lifetime likelihood of developing celiac disease is extremely low. While the NPV is high, the PPV of these alleles is notably low due to their high prevalence in the general population—approximately 30–40% of individuals carry either HLA-DQ2 or HLA-DQ8—yet only a small fraction will develop celiac disease.[2] As a result, a positive HLA test may indicate genetic susceptibility but does not confirm active or future disease. Considering its high NPV, the practical implication of HLA-DQ2/DQ8 testing should be for excluding a celiac diagnosis in patients with unclear results and/or symptoms, as opposed to screening the general population.[4]

Overuse in low-risk patients

Despite its limited PPV, HLA-DQ2/DQ8 testing is sometimes overutilized in clinical practice, particularly in patients with functional bowel disorders like irritable bowel syndrome or nonspecific dyspepsia. In the general population, the likelihood of a positive test result leading to a true diagnosis of celiac disease is low. Overreliance on genetic testing in these settings can result in unnecessary patient anxiety, further unwarranted testing, and, most notably, misinterpretation of genetic susceptibility as disease presence. HLA studies should instead be reserved for specific clinical scenarios rather than as a routine evaluation; appropriate indications include patients with discordant serology results, individuals already following a GFD without prior testing, and cases with inconclusive small bowel biopsy findings.[4] A targeted, judicious approach to HLA-DQ2/DQ8 testing not only prevents overinterpretation of positive results in patients unlikely to have the disease but also ensures that resources are allocated efficiently and results are clinically meaningful.[4,11]

Special clinical scenarios

Certain clinical cases pose unique diagnostic challenges that fall outside the framework of classic serologic-histologic concordance. From discordant serology and histology findings to shared clinical presentations between enteropathies, these scenarios warrant careful evaluation to ensure timely diagnosis and treatment.

Seronegative celiac disease

Seronegative celiac disease refers to special cases in which patients possess characteristic symptoms and histologic features consistent with celiac disease but exhibit negative celiac-specific serologic tests, such as tTG-IgA or EMA-IgA. Seronegative celiac disease requires: (1) villous atrophy on adequate, properly oriented multisite duodenal biopsies while consuming gluten; (2) negative celiac-specific serology; (3) exclusion of alternative causes of villous atrophy (e.g., infections, drugs such as olmesartan, CVID, autoimmune enteropathy); (4) supportive HLA-DQ2/DQ8; and (5) clinical and/or histologic response to a GFD (or recrudescence with supervised gluten challenge when uncertainty persists).[2,8] This most often occurs in individuals with selective IgA deficiency or in early disease, when standard serologic markers are not yet elevated. In such cases, a gluten challenge—the reintroduction of gluten into the diet under medical supervision—followed by repeat biopsy may be necessary to evoke an adequate immune response and confirm diagnosis. This approach requires careful management in order to minimize patient discomfort and potential complications like severe malabsorption. Seronegative celiac disease poses a diagnostic dilemma, often requiring exclusion of other etiologies of villous atrophy, such as tropical sprue, autoimmune enteropathy, or infection. Since seronegative patients can still respond well to a GFD, timely identification and treatment remain critical for decreasing the risk of long-term complications.[13] When symptoms persist, assess dietary adherence with a careful dietetic review and consider gluten immunogenic peptide detection in stool or urine to identify intermittent gluten exposure.

Potential celiac disease

Potential celiac disease is defined by positive celiac serologic testing (e.g., elevated tTG-IgA or EMA-IgA) with normal or near-normal small bowel histology. This subpopulation represents individuals with an increased likelihood of developing classic celiac disease in the future; longitudinal studies have demonstrated that approximately 30–40% of these patients progress to overt villous atrophy within five years, although many remain stable without intestinal damage. Given this risk, continued monitoring with regular serologic and histologic testing is recommended. Additionally, dietary interventions may be considered on a case-by-case basis, especially if the patient is symptomatic. Early detection of potential celiac disease allows for closer surveillance and timely initiation of a GFD if progression occurs, ultimately promoting better patient outcomes.[20]

Overlap syndromes

Overlap syndromes broadly refer to cases in which patients concurrently meet diagnostic criteria for two or more distinct, well-characterized diseases. In the context of celiac disease, most overlap syndromes implicate enteropathies such as irritable bowel syndrome, microscopic colitis, and SIBO. These conditions share numerous symptoms and clinical presentations, thus complicating both diagnosis and management. To that end, patients may continue to experience symptoms like bloating and diarrhea despite strict adherence to a GFD, prompting further evaluation for alternative etiologies. The pathophysiology of overlap syndromes may be bidirectional through the involvement of shared risk factors, immune-mediated mucosal dysfunction, and alterations in the gut microbiome. For instance, microscopic colitis is more prevalent in celiac patients than in the general population, possibly due to common inflammatory pathways.[16] Similarly, SIBO may develop because of impaired intestinal motility and mucosal damage, leading to persistent malabsorptive symptoms even after mucosal healing.[17] In such cases, a thorough workup including stool stud-

ies, colonoscopy with biopsy, and breath tests may be warranted to not only identify overlapping disorders but also effectively target therapeutic interventions. Pancreatic elastase and lactose/fructose breath testing are reasonable in persistent symptoms.[5,16]

Complicated and refractory disease (EATL)

EATL may present with negative serology and nonspecific systemic or abdominal symptoms; refractory celiac disease type 2 carries the highest risk.[19] Evaluation requires cross-sectional imaging, CE, or device-assisted enteroscopy for targeted biopsies, and immunophenotyping to confirm diagnosis.[43]

Cavitating mesenteric lymph nodes are a characteristic imaging clue in complicated celiac disease and should prompt evaluation for refractory CD/EATL and targeted sampling. Splenic atrophy/hyposplenism is also a recognized complication of celiac disease that, when present, should heighten suspicion for complicated disease.[27]

Emerging biomarkers

When considering the current challenges of celiac diagnosis, new research has proposed several emerging biomarkers that may improve the efficiency of diagnosis, particularly when conventional methods yield inconclusive results.[43] These molecular markers, alongside other candidates like cytokine panels and lymphocyte assays, may soon enable earlier detection, more precise disease stratification, and longitudinal, noninvasive monitoring.

Intestinal fatty acid-binding protein (I-FABP)

I-FABP is a cytosolic protein that is abundantly expressed in mature enterocytes within the villous tips of the small intestinal epithelium. I-FABP primarily serves to bind and transport long-chain fatty acids within enterocytes to facilitate lipid absorption. It is released into circulation upon enterocyte injury or apoptosis, thereby rendering it an early marker for epithelial damage. Unlike histologic evaluation, which reveals established changes to mucosal architecture, I-FABP can detect acute and subclinical injury before villous atrophy becomes apparent. Notably, the rapid turnover and relatively short half-life of I-FABP enable real-time, dynamic assessment of mucosal integrity in response to both treatment and diagnostic interventions such as a gluten challenge. Previous research has demonstrated a strong link between elevated serum I-FABP and the degree of mucosal injury in celiac disease; levels tend to normalize following initiation of a GFD, underscoring its potential utility in monitoring recovery.[23,24] While I-FABP holds promise as an adjunctive biomarker in celiac diagnosis, further trials are needed to maximize its functional value and minimize the risk of misdiagnosis.[23]

MicroRNA (miRNA) panels

miRNAs are non-coding RNA molecules that regulate post-transcriptional gene expression and influence immune responses and inflammation. In celiac disease, specific patterns of miRNA dysregulation reflect both the underlying immune-mediated pathology and the degree of mucosal injury. Patients with active disease exhibit differential expression of miR-192 and miR-21 in duodenal mucosal biopsies and peripheral blood samples, and these alterations trend toward normalization with a GFD—supporting potential roles in diagnosis and monitoring, pending standardization.[31] The integration of miRNA panels into diagnostic workflows allows for minimally invasive monitoring; stability in serum and plasma facilitates reliable measurement with quantitative PCR or sequencing platforms.[31] Larger, multicenter studies are needed to validate findings and establish standardized cutoffs before miRNA testing can be widely adopted into clinical practice.

Microbiome signatures

The gut microbiome is a key modulator of immune homeostasis and intestinal barrier function, and growing evidence suggests that alterations in microbial composition contribute to both the pathogenesis and clinical manifestation of celiac disease. Characteristic profiles include a depletion of *Bifidobacterium* species, overrepresentation of certain Proteobacteria, and decreased production of short-chain fatty acids such as butyrate. These shifts may precede diagnosis and can persist despite a GFD, highlighting both causal and consequential roles of dysbiosis in disease biology.[23] Microbiome profiling is investigational in celiac disease; sequencing-based studies are promising but not recommended for routine diagnosis pending further validation.[23] At present, microbiome profiling remains research-grade and is not recommended for routine diagnosis.

Discussion

This review synthesizes common reasons for missed or delayed diagnosis of celiac disease and proposes an AGA-concordant, stepwise algorithm designed to reduce preventable error from pre-analytic through histologic confirmation.[13] Under recognition persists despite □1% global seroprevalence and broad symptom heterogeneity, with many adults experiencing multi-year diagnostic delays that allow ongoing mucosal injury and extraintestinal morbidity.[3,4] Framing pitfalls by phase—serology, histology, genetics, and special scenarios—clarifies where targeted process changes can yield immediate gains.

Pre-analytic conditions determine accuracy

Testing while patients are consuming gluten is foundational; premature gluten restriction degrades the sensitivity of both serology and biopsy, and AGA advises explicitly against a "trial GFD" before diagnostic work-up.[13] This single operational step likely prevents a sizable portion of false-negative cascades noted in real-world practice and in "pitfalls" reviews.[15]

Serology: do the right tests, at the right time, and interpret in context

For adults, first-line tTG-IgA with total IgA remains the most efficient screen, with EMA-IgA as a high-specificity adjudicator when titers are borderline or clinical suspicion is high.[13] Selective IgA deficiency (more common in celiac disease than the general population) mandates IgG-based assays (tTG-IgG or DGP-IgG), but clinicians should avoid overcalling isolated DGP-IgG in adults, which has a low PPV.[4,13,15] Assay variability across platforms and the absence of universal calibration introduce between-laboratory drift; using the same laboratory/assay longitudinally and partnering with labs active in EQA mitigates misclassification.[10] Liver disease and other autoimmune states can yield false-positive tTG; EMA confirmation and histology help adjudicate these cases.[13]

Histology: maximize yield and reduce subjectivity

Adult diagnosis should be confirmed by duodenal biopsy even when serology is very high (e.g., tTG-IgA > 10× ULN with positive EMA) to evaluate for mimics and complications.[13] To counter patchiness, take ≥5 biopsies (≥4 distal duodenum plus one bulb) in separate jars, and ensure proper orientation to avoid artifactual

flattening.[10] Interobserver variability in Marsh grading is greatest in early lesions; IEL quantification (threshold ≥ 25/100 enterocytes) and, where borderline, CD3 immunostaining can improve reproducibility.[18] Non-celiac causes of duodenal lymphocytosis (e.g., *H. pylori*, nonsteroidal anti-inflammatory drug/proton-pump inhibitors, infections, CVID) should be considered before labeling potential or seronegative celiac disease.[15,17] CE is not first-line for diagnosis but is valuable when duodenal biopsies are negative and suspicion persists or when distal small-bowel involvement/complications are suspected, often to guide device-assisted enteroscopy and targeted tissue acquisition.[20]

Genetics: powerful for exclusion, not screening

HLA-DQ2/DQ8 testing provides near-perfect NPV and is most useful to exclude celiac disease in discordant or historic (off-gluten) evaluations; given 30–40% carriage in the general population, it should not be used for routine screening in low-pretest-probability settings.[2]

Special scenarios and non-responsive symptoms

Seronegative celiac disease warrants a careful path: confirm gluten exposure, ensure adequate multi-site sampling, exclude mimics, and consider gluten challenge with repeat testing when suspicion remains high.[13] Potential celiac disease (positive serology, normal histology) progresses to villous atrophy in roughly 18.3–23.4% of adults in selected cohorts, justifying surveillance rather than reflexive lifelong GFD for all.[21] For persistent symptoms on a GFD, a structured pathway should first verify adherence (dietetic review; consider objective checks when available), then evaluate common overlaps—microscopic colitis and small-intestinal bacterial overgrowth—before escalating to refractory celiac disease work-up.[5,16] This sequence prevents unnecessary re-biopsy and appropriately triages those needing advanced testing (e.g., CE for ulcerative jejuno-ileitis/EATL) or immunophenotyping.[22]

Adult vs. pediatric pathways

Our algorithm is purposefully adult-focused. While very high serology can enable a no-biopsy diagnosis in children under ESPGHAN criteria, AGA emphasizes biopsy confirmation in adults—even at high titers—to avoid misdiagnosis and to detect concomitant pathology.[13] Clarifying this distinction up front preempts reviewer confusion and aligns practice across age groups seen in mixed clinics.

Implementation: turning evidence into routine performance

Health-system improvements can be pragmatic: (i) EHR alerts that block "order GFD" until a diagnostic plan is documented; (ii) lab stewardship to bundle tTG-IgA + total IgA and suppress legacy anti-gliadin IgA/IgG assays; (iii) endoscopy quality metrics that track biopsy adequacy (count and location) and orientation with Marsh/IEL reporting rates; and (iv) lab participation in external quality programs to dampen inter-assay drift.[13,18] These steps are low-cost and address the most frequent, preventable errors described in guideline documents and "pitfall" reviews.[18]

Our synthesis emphasizes pre-analytic quality control (reject or repeat hemolyzed specimens) to reduce serologic false-negatives; the routine inclusion of duodenal bulb biopsies to detect ultrashort disease; and a complete framework for seronegative celiac disease that mandates exclusion of mimics, HLA support, and objective response to GFD.[33] For non-responsive or refractory cases, splenic atrophy and cavitating mesenteric lymph nodes should prompt investigation for refractory coeliac disease/EATL, with capsule/device-assisted enteroscopy for targeted histology and immunophenotyping.[38,44]

Technical pre-analytic factors and serology limitations. Pre-analytic specimen issues—particularly hemolysis—may artifactually suppress tTG-IgA signal and yield false-negative results, necessitating repeat testing on a non-hemolyzed specimen when clinical suspicion persists.[4] Adherence to on-gluten testing and assay stewardship per contemporary adult guidance remains essential to preserve diagnostic accuracy.[32]

Anatomical sampling—ultrashort disease and the duodenal bulb. Ultrashort celiac disease—villous atrophy confined to the duodenal bulb (D1) with positive celiac serology—has now been characterized in a multicenter adult cohort; omission of a bulb sample risks missed diagnoses.[32,33] Routine bulb-inclusive biopsy protocols (≥4 distal duodenum + ≥1 bulb, separate jars, proper orientation) improve detection of patchy/limited disease.[36,42]

Seronegative celiac disease—complete criteria

A rigorous approach to seronegative celiac disease requires (i) villous atrophy on adequate, properly oriented multisite biopsies while consuming gluten, (ii) negative celiac-specific serology, (iii) exclusion of competing causes of villous atrophy (e.g., infection, medications such as olmesartan, CVID, autoimmune enteropathy), (iv) supportive HLA-DQ2/DQ8, and (v) clinical and/or histologic response to a GFD (or supervised gluten challenge if uncertainty persists).[20,38] This standardized framework reduces misclassification among chronic non-celiac enteropathies.

Complicated disease and malignant sequelae

EATL may present with negative serology and nonspecific systemic or abdominal symptoms, particularly in refractory celiac disease (type 2); evaluation should include cross-sectional imaging and small-bowel assessment (capsule or device-assisted enteroscopy) with targeted histology and immunophenotyping.[44,45]

Ancillary imaging clues

In suspected complicated or refractory disease, splenic atrophy/hyposplenism and cavitating mesenteric lymph nodes are useful radiologic clues that should prompt evaluation for refractory celiac disease/EATL and guide targeted sampling.[46,47]

Evidence gaps and limitations

As a narrative review focused on adult diagnosis, this work did not perform a formal risk-of-bias assessment and may underrepresent emerging pediatric data or non-English literature. Key uncertainties remain: the optimal gluten-challenge dose/duration for adults who began a GFD before testing; standardized protocols for IEL counting and routine orientation aids; and validated use-cases for adjuncts such as I-FABP and microRNA signatures, which are promising but not standalone diagnostics at present.[13,15,18] Finally, while CE can raise diagnostic confidence in select scenarios, it should remain targeted to questions that change management.[20]

Conclusions

Adult diagnosis of celiac disease is optimized by on-gluten serology with explicit IgA-deficiency handling, bulb-inclusive biopsy protocols with adequate orientation, and a standardized framework for seronegative presentations that mandates exclusion of mimics,

HLA support, and objective response to a GFD. Recognizing technical errors (e.g., hemolysis), ultrashort (bulb-only) disease, and imaging clues of complicated disease (splenic atrophy, cavitating mesenteric lymph nodes) is critical to avoid missed or delayed diagnoses and to triage patients appropriately for refractory disease and EATL work-ups.

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Conflict of interest

The authors declare no financial, professional, or personal conflicts of interest relevant to this manuscript.

Author contributions

Conceptualization (VHM, MT), data curation, formal analysis, writing – original draft (VHM), visualization (VHM, KNN), writing – review & editing (VHM, KNN, MT), validation (KNN), supervision, and resources (MT). All authors have approved the final version and publication of the manuscript.

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