Gastroenterology 2024;■:1–11

Opportunities for Improving Biopsy and Non–Biopsy-Based Diagnosis of Celiac Disease



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The accumulating data regarding a non-biopsy diagnosis of celiac disease has led to its adoption in certain scenarios, although debate on whether and when to use non-biopsy criteria in clinical practice is ongoing. Despite the growing popularity and evidence basis for a biopsy-free approach to diagnosis in the context of highly elevated serologies, there will continue to be a role for a biopsy in some groups. This review summarizes the current evidence supporting a non-biopsy approach and arguments supporting continued reliance on biopsy, and focuses on opportunities to improve both approaches.

Keywords: Celiac Disease; Duodenal Biopsy; Tissue Transglutaminase; Intraepithelial Lymphocytes; Adults.

For more than a decade, there has been debate in the clinical and scientific community regarding the role of the duodenal biopsy as the basis of a celiac disease (CeD) diagnosis. This debate has played out at conferences and in the medical literature,[1–3] and consensus continues to evolve, with a gradual movement toward biopsy-sparing approaches in certain circumstances.[4,5]

There is a diversity of opinion regarding whether and how to adopt a non-biopsy approach, both in the CeD community at large, and among the authors of this article. Our purpose is not to recount the points of contention or the relative merits of a biopsy or non-biopsy approach. Rather, it is to describe areas where both approaches could improve in the years ahead. We describe current best practices in both approaches, as well as deviations from these standards in real-world settings. We also present promising avenues to improve the performance of both biopsy and non-biopsy–based diagnoses in the future. The focus of this article concerns adults primarily, given the emergence of more recent data on non-biopsy–based approaches in that population. However, these advances and opportunities may ultimately be applicable to children as well.

Emergence of the Non-Biopsy Approach and How to Improve it

Endoscopy to obtain duodenal biopsies is invasive, costly, carries some risk, and is losing widespread acceptance as universally necessary for the diagnosis of CeD.[6–8] The opportunity for a non-biopsy approach in diagnosing CeD derives from the accuracy of the anti-tissue transglutaminase (TTG) IgA test in predicting mucosal atrophy in patients on a regular gluten-containing diet.[9] Retrospective studies in adults found that, in different clinical settings, TTG IgA raised to 10 or more times the upper normal value predicts the presence of mucosal atrophy from 95.2% in low-risk populations to 100% in high-risk populations.[10–12] There is evidence that the magnitude of the TTG increase correlates with the risk of more severe damage at histology.[13] The literature increasingly shows that, among the available gluten-related biomarkers, TTG has a strong positive predictive value (PPV) in the diagnosis of CeD. To make a comparison, a 10-fold–elevated TTG has a PPV in the diagnosis of CeD stronger than the dynamic change in fasting blood glucose in 2 samples in the diagnosis of diabetes.[14]

Abbreviations used in this paper: CeD, celiac disease; GFD, gluten-free diet; IEL, intraepithelial lymphocyte; PCeD, potential celiac disease; PPV, positive predictive value; TTG, tissue transglutaminase; VH:CD, villous height to crypt depth ratio.

0016-5085
https://doi.org/10.1053/j.gastro.2024.01.031

An international, multicenter retrospective study published in 2021[11] aimed to report the PPV of CeD serologies in a variety of settings: consecutive patients (n = 740) referred to a CeD center in Sheffield, UK; patients (n = 778) undergoing duodenal biopsy for a variety of symptoms (with or without elevated CeD-related serologies); and patients (n = 145) with elevated TTG IgA undergoing duodenal biopsy in 11 endoscopy suites in 8 countries, including the United States (n = 40). In the first cohort, 380 of 740 (51%) had a TTG IgA with a >10-fold elevation, and among those patients 375 of 380 (98.7%) had a Marsh 3 lesion confirming the diagnosis of CeD. (They also noted that when stratifying by the 2 TTG assays used, the PPVs ranged from 98.1% to 100%.) In the second (low-risk) cohort, 9 of 532 (1.7%) patients had a >10-fold TTG elevation, and all 9 (100%) had a Marsh 3 lesion. In the multicenter cohort, 42 of 145 patients (29.0%) had a >10-fold TTG IgA elevation, of whom 40 (95.2%) had Marsh 3 histology.

A subsequent prospective multicenter, international study added further evidence for a non-biopsy approach. This study confirmed that a 5-fold and a 10-fold increase of TTG in a high-risk population predicted mucosal atrophy in 97.4% and 97.5%, respectively, when the biopsy was interpreted locally. However, after a central expert pathologist re-evaluated local histology, the PPV of a 10-fold TTG elevation was 99.4%, showing that the discordance was mainly due to misinterpretation of histology. The only case with a 10-fold increase of TTG without atrophy showed an increase in intraepithelial lymphocytes (IELs) and increased depth of crypts (Marsh grade 2 lesion); this patient was eventually diagnosed as having CeD on the basis of very high titer serology, symptoms, and improvement after adopting a gluten-free diet (GFD).[15]

Beyond the burden of an endoscopy, duodenal histology over the last few decades has not seen an improvement in its power to predict CeD. The practice of obtaining biopsies, orientation on appropriate filters, processing, staining, and immunostaining with anti-CD3 monoclonal antibodies are time-consuming and operator-dependent procedures, among other pitfalls.[16] Two studies conducted 10 years apart in the United States (2011) and United Kingdom (2021) reported that adherence of endoscopists to guidelines in obtaining a sufficient number of biopsies for the diagnosis of CeD was 35% and 40%, respectively.[17,18] Moreover, interobserver variability in the widely used Marsh histologic classification in pathology reports is a common phenomenon.[19]

The no-biopsy strategy requires highly elevated levels of TTG IgA, and this concept must be correctly conveyed to non–gastroenterologist physicians using these criteria. There is a risk that over-reliance on serologies by non-gastroenterologists could lead to a rise in uncertain diagnoses based on serologic values that are misinterpreted. A slight increase of the TTG should prompt assessing whether it is a false positive, potential CeD (PCeD), or whether the patient is already on a reduced-gluten diet at the time of the test. Starting the GFD before testing, for example, due to family history of CeD or as a self-prescribed diet to treat a variety of symptoms, may yield an elevation of TTG IgA in a true celiac patient that falls short of this non-biopsy threshold.

Another opportunity for improvement of the non-biopsy strategy is establishing a common standard for the range of normality of the several TTG laboratory tests available on the market worldwide. In the prospective international study addressing the non-biopsy strategy in adults.[15] TTG measurements showed high concordance between the local results and central laboratory testing ($\kappa = 0.952$), suggesting that overall reliability did not differ substantially among various laboratory tests. Still, the reliability of serum TTG IgA assessment could be improved by means of developing an international calibrator with a defined concentration of TTG IgA for assay standardization.[20]

In adults, the following 3 concerns support continued reliance on endoscopy and biopsy: the possibility of missing other CeD-unrelated diseases if endoscopy is skipped; detection of CeD complications; and occurrence of normal mucosa at histology, that is, PCeD, which may not require a GFD.

Patients with CeD have an increased risk of eosinophilic esophagitis[21,22] and lymphocytic gastritis,[23] and might benefit from identification and management of these conditions at the time of their CeD diagnosis. This concern about missed diagnosis is allayed by findings from retrospective and prospective studies that other diseases detectable with a gastroscopy at the time of CeD diagnosis are infrequent or already known.[15,24,25] Moreover, an international study analyzed the incidental findings of 1328 adults undergoing upper endoscopy for suspected CeD.[26] Although 10.1% had additional endoscopic findings, such as reflux esophagitis and gastric erosions, Barrett's esophagus was rare (0.2%) and no cases of eosinophilic esophagitis or cancer were identified. As such, the concern about missed endoscopic diagnoses in a biopsy-free approach appears to be a theoretical concern without empiric data.

Complications of CeD, such as ulcerative jejunitis and enteropathy-associated T cell lymphoma are rare and, generally, not detected by the initial endoscopy at the time of diagnosis, although they may develop in the first years after diagnosis.[27,28] Risk factors for complications are the classical presentation with diarrhea, advanced age at diagnosis, negative serology, and homozygosity for HLA-DQ2.[29] Including this information when assessing which strategy is best for individual patients may support a non-biopsy approach that assures that complications are not missed. In the only available prospective study on the non-biopsy strategy in adults,[15] only 1 major complication, a lymphoma, was detected 1 year after diagnosis. Its location in the mid-ileum would not have been detected if present at the time of the endoscopy for CeD diagnosis.

The third issue is the possibility of missing PCeD. PCeD is a condition that presents with or without gluten-induced symptoms, likely in the context of a peculiar genetic asset.[25] PCeD frequency was reported in 18% of adults referred to a CeD center,[30] and its progression toward overt CeD is unpredictable. Currently, aside from a general recommendation that these patients should be followed, there are no specific recommendations as to the necessity to

adhere to a GFD.[31] As patients with PCeD may be variably symptomatic, patients and physicians can decide on the adoption of a GFD on a case-by-case basis.[32] PCeD is rarely found in cases of very high levels of TTG. As noted above, in 162 participants with a >10-fold TTG elevation in a multicenter prospective study evaluating the non-biopsy strategy, only 1 patient had a centrally adjudicated duodenal biopsy indicating changes short of Marsh 3[15]; thus, this condition will be rare in patients who are diagnosed via a non-biopsy approach. Moreover, concern about the long-term implications of untreated PCeD may lead to a recommendation for a GFD, rendering moot the need for a biopsy; the uncertainty of the natural history of PCeD is an unmet need, and advances will lead to improvements in both the biopsy approach and non-biopsy approach to diagnosis (see below).

Evidence for Maintaining and Improving a Biopsy-Based Approach

The primary impetus for continuing to optimize a biopsy-based approach to CeD has been the imperfect PPV of serologies for villus atrophy. Close to 100% certainty in medicine is a high bar, but for the diagnosis of CeD, some aspire to this for a biopsy-free approach, given the potential downsides of a life-long prescription of a GFD. Costs of this diet include financial burden,[33] social challenges,[34] nutritional complications,[35] and the possibility of increasing clinical sensitivity to gluten exposure after it is excluded.[36]

Thus, despite the recognized economic and psychological burdens associated with endoscopy with anesthesia, pitfalls of histology, widespread use of the non-biopsy strategy in European children,[37,38] and reassuring follow-up studies on the quality of diagnoses,[39–41] most adult providers and some pediatricians believe that the biopsy would lend further credibility to the CeD diagnosis and the need for a life-long GFD.[5,42]

As noted above, the recent multicenter study found good concordance between local and central TTG IgA measurement.[15] Still, even in the face of improved laboratory standards or local validation, the intrinsically stable performance characteristics of a laboratory assay, that is, sensitivity and specificity, will yield varying PPVs on the basis of underlying prevalence of CeD in the population being studied. Although this is an intrinsic property of diagnostic testing related to Bayes' theorem,[43] this was borne out empirically in striking detail. In a study of patients undergoing endoscopy in 2 centers in Buenos Aires, Argentina, the cutoff of TTG IgA elevation yielding a PPV was calculated in 2 adult populations: a high-risk group with diarrhea, weight loss, iron deficiency anemia, or suspected malabsorption; and a low-risk group undergoing endoscopy with duodenal biopsy for evaluation of dyspepsia, heartburn, or regurgitation. Using a TTG IgA with an upper limit of normal of 20 units, the investigators found that a PPV of 100% could be achieved using a TTG IgA cutoff of 34 units for the high-risk group, but that a comparable PPV in the low-risk group would require a cutoff of 139 units.[44] Although setting a sufficiently high cutoff value would reduce the risk of a false diagnosis in low-risk populations, this would inevitably yield a large proportion of patients with TTG IgA elevations that fall short of this cutoff. Such patients would require a duodenal biopsy for clarification. Thus, any biopsy-sparing approach would inevitably apply only to a segment of patients with suspected CeD, with the remainder continuing to require a biopsy.

One dilemma that comes up in clinical practice is the adult presenting with symptoms or anemia and found to have elevated TTG, who had already undergone upper endoscopy (without a duodenal biopsy). In this situation, the benefit of a biopsy approach to diagnosis is uncertain, and there is not a clear evidence-based path. One approach to this scenario, in our opinion, is to advise a GFD if the TTG is 10 times higher than the normal value and perform the endoscopy only if signs and symptoms do not improve.

There is particular concern about relying on a serologic approach to diagnosis when considering certain populations that are candidates for CeD screening, such as those with a personal history of type 1 diabetes or a family history of CeD. Although the treatment of CeD with a GFD is advised regardless of symptoms, the diagnostic accuracy of a serology-based approach may vary in certain groups. The practice of testing high-risk groups is common, although it is not universally recommended to do so if the patient is asymptomatic. For instance, a 2017 analysis report by the US Preventive Services Task Force concluded that the evidence is insufficient to recommend for or against screening asymptomatic individuals, including those in high-risk groups.[45] Nevertheless, screening is often offered with the rationale that identifying and treating CeD in the asymptomatic phase may prevent downstream morbidity. One study found that the specificity of a highly elevated TTG IgA is lower in asymptomatic (85%) than symptomatic (99%) children,[46] raising the possibility that a non-biopsy approach could yield more false-positive results in asymptomatic children. Although the 2020 European Society for Paediatric Gastroenterology Hepatology and Nutrition guidelines no longer factor in the presence of symptoms for a biopsy-free diagnostic criteria,[38] rigorously testing this approach stratified by the presence of symptoms in adults remains a gap in our knowledge, Likewise, in asymptomatic individuals with type 1 diabetes, a group with an increased risk of CeD,[47] TTG IgA appears to have a lower specificity in children and adults, and thus this group may require a higher threshold for a serology-based diagnosis.[48] This is particularly relevant, given that screening for serum antibodies for type 1 diabetes and CeD in children is now recommended in Italy by law.[49] Future Q9 evaluations of this national recommendation will shed light on the long-term implications of such a policy, at least in children.

Reliance on a biopsy for the diagnosis of CeD implies that the results of the biopsy will change clinical management. Yet, as noted above, there remains uncertainty regarding the management of PCeD, wherein patients with

an elevated TTG IgA have duodenal biopsy that does not show villus atrophy. Penny et al[11] reported on the follow-up of the 5 patients in the high-risk cohort who fell into this category. All 5 were symptomatic with iron deficiency anemia, abdominal pain, or diarrhea. Only 1 of the 5 had a totally normal duodenal biopsy, and the other 4 had Marsh 1 or 2 lesions. All 5 were prescribed a GFD and subsequently had a substantial decline in TTG IgA level after commencing the diet. Therefore, in this case, relying on a biopsy for diagnosis did not ultimately change the management of CeD.

Still, in patients who are asymptomatic or only transiently symptomatic, it is likely that some will prefer to avoid the GFD if it is safe to do so; a proportion of such patients might also experience a decline in TTG IgA while maintaining a gluten-containing diet and might be spared the diagnosis and treatment.[50] Natural history studies in this population are lacking, and study of this scenario is complicated by the possibility that some patients in this gray diagnostic zone may reduce, but not eliminate, their gluten intake, a practice of uncertain (and unproven) benefit. Given this uncertainty, it is appropriate to engage in shared decision making with patients about their desire to know their CeD status with certainty and to proceed with a gluten-containing diet if their biopsy does not show villus atrophy.

At present, there is broad consensus that among individuals with an elevated TTG IgA that falls short of a 10-fold elevation, a biopsy-based approach is necessary. But this may also come to be questioned because a key maxim in medicine is that a test should not be performed if it will not change the treatment course. Indeed, among 16 asymptomatic patients with elevated serology (all <10-fold elevated), normal duodenal histology (ie, PCeD) and continued gluten ingestion, only 1 developed villus atrophy subsequently over the course of 3 years.[50] However, among symptomatic patients with the constellation of abnormal serology and normal histology (n = 61), adoption of the GFD led to symptom reduction and resolution in all cases.[50] This finding implies that, in a patient with elevated TTG IgA, the decision to proceed with a duodenal biopsy may one day depend on the presence of symptoms and the plan for a GFD. At present, the requirement for duodenal villus atrophy in adults implies that an asymptomatic patient with positive serologies and normal histology can continue to be monitored while maintaining a gluten-containing diet. The long-term natural history and safety of this approach needs further study. One population-based analysis found that patients with elevated CeD antibody levels and normal duodenal histology had an increased mortality risk compared with the general population, although this risk was no longer significantly elevated beyond 5 years.[51] A study of the National Health and Nutrition Examination Survey in a cohort of adults age ≥50 years found that those with an elevated TTG IgA (comprising 1.4% of the cohort) had an increased mortality risk for cardiovascular disease and respiratory diseases, even though most of these seropositive individuals had a negative endomysial antibody status, suggesting that they may not have had duodenal villus atrophy.[52] (The variability and quality of the endomysial antibody assay may have contributed to this serologic discrepancy.) As such, a key item on the research agenda should be the investigation of the implications of elevated CeD serologies in the presence of normal duodenal histology and whether adoption of a GFD is necessary for preventing downstream morbidity.

Current Best Practices and Challenges to Optimizing Utility of Duodenal Biopsies

Regardless of the acceptability of a non-biopsy approach to diagnosis, given that many patients' TTG IgA levels fall short of predefined thresholds, biopsy will remain a key component of CeD diagnosis in many scenarios. Challenges facing pathologists in rendering complete and accurate assessments of duodenal biopsies fall into the following 4 broad categories: (1) incomplete clinical information, (2) insufficient sampling, (3) suboptimal handling and orienting of mucosal biopsies, and (4) lack of uniformity of reporting terminology in pathology reports. Best practices for the use of the duodenal biopsy in CeD require collaboration among the gastroenterologist, endoscopy suite personnel, pathology laboratory, and surgical pathologist.[53]

With respect to the gastroenterologist, there is a minimal clinical data set to be communicated to the pathologist to maximize diagnostic utility of mucosal biopsies, including reason for endoscopy, designation as diagnostic or follow-up biopsy in an established patient with CeD, serology if available, status of gluten consumption, medications (especially sartans, nonsteroidal anti-inflammatory drugs, checkpoint inhibitors, and other chemotherapeutic agents), and site of biopsies. Symptoms and signs and endoscopic

Box 1. Clinical Data to be Provided to Pathologists in the Setting of Celiac Disease

Essential	Desirable
Reason for endoscopy	Symptoms
CeD status	Signs
Initial biopsy to investigate CeD	Endoscopic appearance
Established patient with CeD	
Serology results (if existing)	
Status of gluten consumption at time of biopsy	
Medications	
Sites of biopsies	

appearance are helpful, although the sensitivity and specificity of the endoscopic appearance has been shown to be limited[54,55] (Box 1). In centers with an electronic medical record, clinicians may assume pathologists will access the electronic chart, however, due to time constraints, most samples are evaluated with the clinical data immediately at hand (eg, pathology requisition form or endoscopy report).

The approach to duodenal sampling has been established by professional society guidelines, which recommend 2 biopsies from the first duodenum and 4 biopsies from the distal duodenum.[5,56–59] Sampling that does not include the recommended numbers and locations risks missing diagnostic changes, because patchy distribution of mucosal injury in CeD is well documented.[60–63] Despite these recommendations, adherence to biopsy guidelines in the United States appears to be low,[17] presenting an opportunity for improvement (Box 2). There are also data to suggest that obtaining just 1 biopsy per pass of the forceps better preserves duodenal mucosal integrity.[64]

Duodenal mucosal biopsies are delicate and should be handled as little as possible by endoscopy and pathology personnel. The most crucial step affecting quality of the pathology evaluation of duodenal biopsies is the embedding process, during which samples are oriented and stabilized into paraffin wax tissue blocks for sectioning. The goal is to achieve perpendicular orientation such that a continuous layer of epithelium can be traced from villous tip to crypt base. In busy laboratories, the success in orienting mucosal biopsies varies (Figure 1). Damage done during the preanalytical steps can be irretrievable (eg, villi shorn off during transfer or poor orientation in tissue blocks), except in rare laboratories that may tilt tissue blocks to achieve a better villus–crypt orientation in tissue sections.[65,66] Challenges in biopsy orientation in the pathology laboratory represent an important opportunity to improve biopsy reporting in CeD.

Best practices for the histologic assessment of duodenal mucosal biopsies require a holistic approach to detect abnormalities from any cause and are not limited to considering a single disease. The differential diagnosis for inflammation in the duodenum includes drug reactions; physiologic, so-called "peptic injury"; *Helicobacter pylori*–associated duodenal inflammation; immunodeficiency disorders; bacterial overgrowth; and infections. The histologic changes of active CeD are established and include increases in IELs >25/100 enterocytes, with varying degrees of villous blunting and crypt hyperplasia assessed by means of subjective categorical scoring classifications or, less likely, by means of exact measurement of the villus height to crypt depth (VH:CD) ratio.[67,68] Normal VH:CD beyond the duodenum bulb is at least 2.5:1 and increases from the proximal to the distal small intestine. The classic changes are reliably present at diagnosis in patients with CeD consuming gluten and ameliorate (partially or wholly) in most patients with CeD following a strict GFD. The most common cause of persistent mucosal inflammation in follow-up biopsies is ongoing gluten ingestion,[69] and the astute clinician

Box 2. Challenges and Solutions to Improving Duodenal Biopsy Diagnosis in Celiac Disease

Challenge	Solution
Inadequate clinical information	Endoscopist to include pertinent data set on pathology requisition form (see Box 1)
Pathologist workload prevents searching electronic medical record	Automatic uploading of endoscopic report and pertinent clinical data into pathology information system
Duodenal sampling not following guidelines	Education to increase awareness of importance of following sampling guidelines to assure diagnosis of patchy mucosal injury
Physical damage due to sample handling	
In endoscopy suite	1 biopsy per pass, minimize handling when transferring to formalin-filled specimen container (not on filter paper)
In pathology laboratory	Avoid grasping with forceps, use of appropriate tissue cassettes or mesh bags
Failure to embed biopsies "on edge" in busy laboratories, such that many villous–crypt units are inadequately oriented to allow for architectural assessment	Education for pathologists and laboratory directors to increase awareness of importance of proper biopsy orientation Goal is to achieve improvement while not significantly impeding laboratory flow
At microscopy, rendering assessment on poorly oriented villous–crypt units	Education for pathologists to limit architecture assessment to well-oriented regions, obtaining level sections as needed.
Uniformity and completeness of pathology report	Use of published best practices in reporting duodenal biopsy findings Future incorporation of digital pathology and software-assisted quantitative morphometry

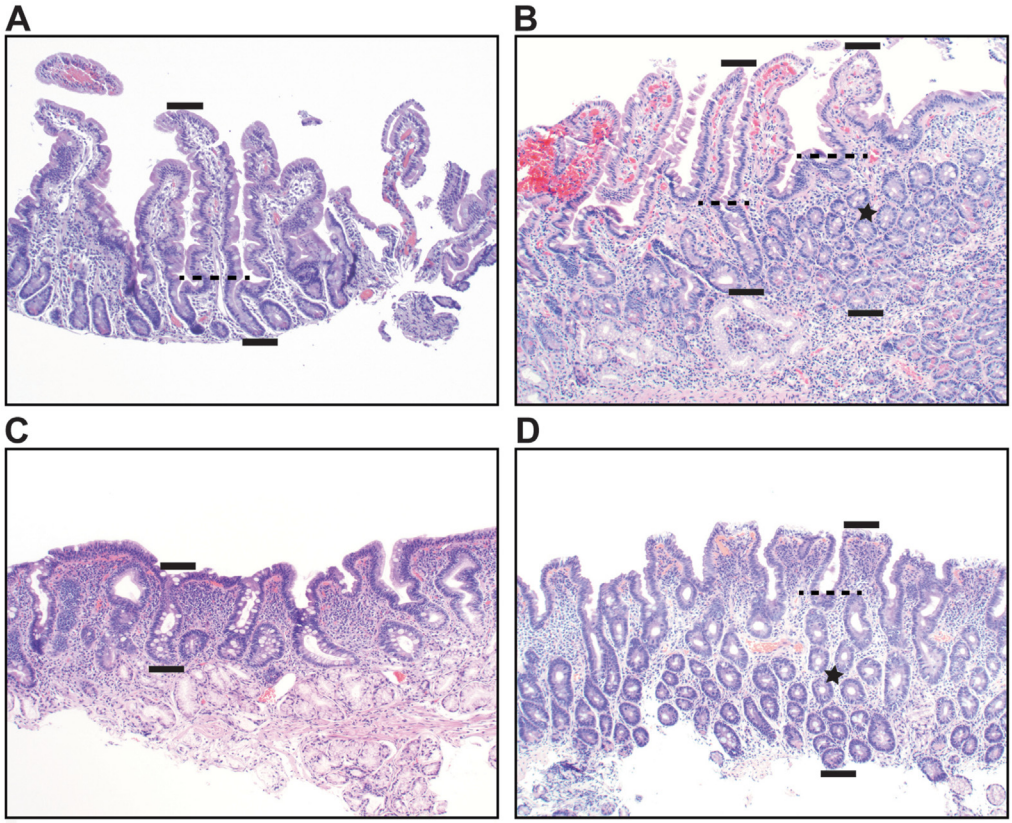

Figure 1. Examples of the impact of laboratory tissue embedding on microscopic interpretation of duodenal mucosal biopsies. Normal mucosa: (*A*) This sample shows desired perpendicular orientation of the mucosa in the middle of the sample, such that there is a continuous line of epithelium from the top of the villus to the crypt base (*bracketed by solid bars*). The villus–crypt junction is indicated by the *dashed line*. (*B*) Normal mucosa with suboptimal orientation. Although a continuous epithelial line can be seen for the villus on the left, much of the biopsy shows tangential sectioning with crypts appearing as multiple rings (*star*) on the *right*. This precludes assessment of the villus–crypt ratio. CeD: (*C*) In this well-oriented duodenal bulb biopsy taken at the time of diagnosis, there is a continuous line from the surface epithelium to the crypt base (*solid bars*), allowing for the accurate designation of complete villus blunting (Marsh-Oberhuber 3C). (*D*) Another biopsy fragment from the same endoscopic procedure with poor orientation (*star* indicates rings of crypts), giving the false appearance of preserved, although shortened, villi (*bars*).

considers the multiple causes of "apparent refractoriness" to the GFD before considering a diagnosis of refractory CeD.[69,70] The workup of suspected refractory CeD is often performed at specialized celiac centers, where flow cytometry on fresh samples and other advanced techniques can be applied.[70–72]

Table 1. Categorical Classifications for Pathologic Evaluation of Celiac Disease

	Marsh-Oberhuber, 1999			
Type[a]	Crypts	Appearance of villi	Corazza and Villanacci, 2005	Ensari, 2010
Infiltrative type 1	Normal	Normal	Grade A	Type 1
Hyperplastic type 2	Hypertrophic	Normal	Grade A	Type 1
Destructive type 3a	Hypertrophic	Mild blunting	Grade B1	Type 2
Destructive type 3b	Hypertrophic	Moderate blunting	Grade B1	Type 2
Destructive type 3c	Hypertrophic	Severe blunting (flat)	Grade B2	Type 3
Hypoplastic type 4	Atrophic	Severe blunting (flat)	Obsolete	Obsolete

NOTE. Modified from Oberhuber et al,[97] Corazza and Villanacci,[77] and Ensari.[78]
[a]All types/grades show increased IELs ≥25/100 enterocytes.

To consider whether changes consistent with CeD are present, the first rule of biopsy interpretation is to evaluate duodenal mucosa only in well-oriented villus–crypt units (Figure 1). This allows for a valid assessment of mucosal architecture to detect villous blunting and crypt elongation. Studies have established that assessing architecture in unoriented regions results in either over- or underestimating abnormalities.[19,73,74] Although orientation is less vital to assess IELs, it is still important because IELs are normally more numerous in the bases and lateral aspects of villi, whereas in CeD, IELs are increased in villous tips. Multiple subjective algorithms exist to classify villus architecture in CeD, including those of Marsh, Marsh-Oberhuber, Corazza and Villanacci, and Ensari,[75–78] and descriptive approaches (mild, moderate, or severe villus blunting[53]) (Table 1). Of these reporting approaches, Marsh-Oberhuber is used commonly in Europe, although descriptive language is used commonly in the United States. Provided clinicians and pathologists are in clear communication, no system has been found to be superior to the others. With respect to Marsh-Oberhuber, studies have reported both poor and good interobserver agreement among pathologists, with differences in results likely related to methodology.[79–81] Very few centers routinely provide numeric measurements of VH:CD ratios in clinical reports.

The Future

Digital Pathology, Machine Learning, and Artificial Intelligence

As an improvement over subjective, categorical approaches to histologic evaluation, digital pathology has the potential to allow software-assisted numeric measurements of both IELs and VH:CD ratios, with very little increased time commitment on the part of pathologists.[82,83] To date, digital measurements have been used primarily in the research and clinical trial settings,[84,85] with very limited application in daily clinical practice. High interobserver agreement (intraclass correlation coefficient or Cohen's κ) in VH:CD and IELs/100 enterocytes was demonstrated among pathologists from 3 centers after brief training using software on digital images.[86] Wider availability of digital evaluation will eliminate the need for painstaking IEL counting at the microscope and assigning categorical scores of villus architecture, with the advantage of providing numeric results that could be compared between biopsies on the same patient. However, the digital approach still relies on well-oriented sections, again highlighting the importance of this step as an opportunity for improvement.

As pathology laboratories continue to pivot to digital pathology, interest in artificial intelligence to generate diagnoses is an area of active engagement, primarily by commercial AI companies. The most significant barrier to artificial intelligence applications in pathology diagnosis is the high cost of developing reliable algorithms, which requires significant computing power, large training sets and subsequent validation sets.[87] It should be understood that US Food and Drug Administration approval of AI-assisted pathology diagnoses will be required before artificial intelligence can be used to render clinical diagnoses in the United States.

A "Molecular Microscope" for Celiac Disease

Histologic examination of duodenal biopsies provides a useful snapshot of mucosal injury but lacks dynamic information that allows for a complete assessment of disease activity, such as the degree of IEL cytotoxic activity, IgA anti-TTG deposits, or cytokine expression in epithelium and lamina propria inflammatory cells. The concept of a molecular microscope, introduced in solid organ transplantation to pair histology with transcriptomic/genomic expression, allows for the definition of immune signatures associated with rejection and other inflammatory states.[88] Similarly, in CeD, transcriptomic signatures in duodenal biopsies at diagnosis and follow-up are being defined.[89–95] These signatures could eventually translate into biomarkers in tissue and blood (with or without a gluten challenge step) providing a "disease activity index" to complement, or in some settings replace, histologic evaluations. To date, such analyses using fresh or fixed duodenal samples have identified potential biomarker genes showing differential expression among normal, untreated, and treated duodenal mucosa in CeD, including pre-disease changes in at-risk populations.[82,90–95] Such biomarkers can also play a role in measuring responses to therapeutic interventions in clinical trials.[96]

Conclusions

An increasing body of data supports the accuracy of a non-biopsy approach in the context of a highly elevated TTG IgA in diagnosing CeD. Both this approach and a biopsy-centered approach to CeD have room for improvement related to patient selection, laboratory standardization, documentation, and quality of specimen acquisition and interpretation. There is concern that widespread adoption of a biopsy-free approach may lead to an over-reliance on serologies that fall short of the criteria that would lead to an accurate diagnosis. Advances in understanding the natural history of seropositivity may lead to changes in recommendations regarding whom to biopsy. Parallel advances in digital pathology, machine learning, and transcriptomics may lead to an era wherein the biopsy provides far more rich data on diagnosis, response to therapy, and prognosis.

References

1. Guandalini S, Newland C. Can we really skip the biopsy in diagnosing symptomatic children with celiac disease. J Pediatr Gastroenterol Nutr 2013;57(4):e24. https://doi.org/10.1097/MPG.0b013e3182a1cda3.
2. O'Connell J, Murray JA, Kaukinen K. Uncertain diagnosis of celiac disease and implications for management. N Engl J Med 2021;384:2346–2348.
3. Shiha MG, Raju SA, Sidhu R, et al. The debate in the diagnosis of coeliac disease - time to go 'no-biopsy'? Curr Opin Gastroenterol 2023;39:192–199.

4. Johnston RD, Chan YJ, Mubashar T, et al. No-biopsy pathway following the interim BSG guidance reliably diagnoses adult coeliac disease. Frontline Gastroenterol 2022;13:73–76.
5. Rubio-Tapia A, Hill ID, Semrad C, et al. American College of Gastroenterology guidelines update: diagnosis and management of celiac disease. Am J Gastroenterol 2023;118:59–76.
6. Waddingham W, Kamran U, Kumar B, et al. Complications of diagnostic upper gastrointestinal endoscopy: common and rare - recognition, assessment and management. BMJ Open Gastroenterol 2022;9(1):e000688. https://doi.org/10.1136/bmjgast-2021-000688.
7. Paul SP, Sandhu BK, Spray CH, et al. Evidence supporting serology-based pathway for diagnosing celiac disease in asymptomatic children from high-risk groups. J Pediatr Gastroenterol Nutr 2018;66:641–644.
8. Irvine AJ, Sanders DS, Hopper A, et al. How does tolerability of double balloon enteroscopy compare to other forms of endoscopy? Frontline Gastroenterol 2016; 7:41–46.
9. Sheppard AL, Elwenspoek MMC, Scott LJ, et al. Systematic review with meta-analysis: the accuracy of serological tests to support the diagnosis of coeliac disease. Aliment Pharmacol Ther 2022;55:514–527.
10. Fuchs V, Kurppa K, Huhtala H, et al. Serology-based criteria for adult coeliac disease have excellent accuracy across the range of pre-test probabilities. Aliment Pharmacol Ther 2019;49:277–284.
11. Penny HA, Raju SA, Lau MS, et al. Accuracy of a no-biopsy approach for the diagnosis of coeliac disease across different adult cohorts. Gut 2021;70:876–883.
12. Hoyle A, Gillett P, Gillett HR, et al. No-biopsy strategy for coeliac disease is applicable in adult patients: a 'real-world' Scottish experience. Frontline Gastroenterol 2023; 14:97–102.
13. Baykan AR, Cerrah S, Ciftel S, et al. A no-biopsy approach for the diagnosis of celiac disease in adults: can it be real? Cureus 2022;14(7):e26521. https://doi.org/10.7759/cureus.26521.
14. Zhou H, Yang C, Dong C, et al. Predictive power for type 2 diabetes mellitus using dynamic change of metabolic syndrome, dynamic change of fasting plasma glucose, metabolic syndrome and fasting plasma glucose. Iran J Public Health 2014;43:432–440.
15. Ciacci C, Bai JC, Holmes G, et al. Serum anti-tissue transglutaminase IgA and prediction of duodenal villous atrophy in adults with suspected coeliac disease without IgA deficiency (Bi.A.CeD): a multicentre, prospective cohort study. Lancet Gastroenterol Hepatol 2023; 8:1005–1014.
16. Ravelli A, Villanacci V. Tricks of the trade: how to avoid histological pitfalls in celiac disease. Pathol Res Pract 2012;208:197–202.
17. Lebwohl B, Kapel RC, Neugut AI, et al. Adherence to biopsy guidelines increases celiac disease diagnosis. Gastrointest Endosc 2011;74:103–109.
18. Taylor MA, Blanshard RJ, Naylor G, et al. Do gastroenterologists have medical inertia towards coeliac disease? A UK multicentre secondary care study. BMJ Open Gastroenterol 2021;8(1):e000544. https://doi.org/10.1136/bmjgast-2020-000544.
19. Corazza GR, Villanacci V, Zambelli C, et al. Comparison of the interobserver reproducibility with different histologic criteria used in celiac disease. Clin Gastroenterol Hepatol 2007;5:838–843.
20. Beltran L, Koenig M, Egner W, et al. High-titre circulating tissue transglutaminase-2 antibodies predict small bowel villous atrophy, but decision cut-off limits must be locally validated. Clin Exp Immunol 2014;176:190–198.
21. Thompson JS, Lebwohl B, Reilly NR, et al. Increased incidence of eosinophilic esophagitis in children and adults with celiac disease. J Clin Gastroenterol 2012;46(1):e6–e11. https://doi.org/10.1097/MCG.0b013e318221aefd.
22. Jensen ET, Eluri S, Lebwohl B, et al. Increased risk of esophageal eosinophilia and eosinophilic esophagitis in patients with active celiac disease on biopsy. Clin Gastroenterol Hepatol 2015;13:1426–1431.
23. Lebwohl B, Green PH, Genta RM. The coeliac stomach: gastritis in patients with coeliac disease. Aliment Pharmacol Ther 2015;42:180–187.
24. Maimaris S, Schiepatti A, Gabrielli GM, et al. Low prevalence of upper endoscopic gastrointestinal findings despite high frequency of alarm symptoms at the time of diagnosis in adult coeliac disease. Eur J Gastroenterol Hepatol 2020;32:1447–1451.
25. Biagi F, Bianchi PI, Vattiato C, et al. Influence of HLA-DQ2 and DQ8 on severity in celiac disease. J Clin Gastroenterol 2012;46:46–50.
26. Stefanolo JP, Zingone F, Gizzi C, et al. Upper gastrointestinal endoscopic findings in celiac disease at diagnosis: a multicenter international retrospective study. World J Gastroenterol 2022;28:6157–6167.
27. Corrao G, Corazza GR, Bagnardi V, et al. Mortality in patients with coeliac disease and their relatives: a cohort study. Lancet 2001;358(9279):356–361.
28. Lebwohl B, Green PHR, Söderling J, et al. Association between celiac disease and mortality risk in a Swedish population. JAMA 2020;323:1277–1285.
29. Biagi F, Schiepatti A, Maiorano G, et al. Risk of complications in coeliac patients depends on age at diagnosis and type of clinical presentation. Dig Liver Dis 2018; 50:549–552.
30. Biagi F, Trotta L, Alfano C, et al. Prevalence and natural history of potential celiac disease in adult patients. Scand J Gastroenterol 2013;48:537–542.
31. Trovato CM, Montuori M, Valitutti F, et al. The challenge of treatment in potential celiac disease. Gastroenterol Res Pract 2019;2019:8974751. https://doi.org/10.1155/2019/8974751.
32. Nemteanu R, Clim A, Hincu CE, et al. Is there a time and a place for the gluten-free diet in potential celiac disease? Nutrients 2023;15(18):4064. https://doi.org/10.3390/nu15184064.
33. Lee AR, Wolf RL, Lebwohl B, et al. Persistent economic burden of the gluten free diet. Nutrients 2019;11(2):399. https://doi.org/10.3390/nu11020399.
34. Lebovits J, Lee AR, Ciaccio EJ, et al. Impact of celiac disease on dating. Dig Dis Sci 2022;67:5158–5167.

35. Pinto Sanchez I, BJ, Gibson P et al. How to assess and manage nutrition phenotype and metabolism in celiac disease. How safe is the gluten-free diet? Gastroenterology.
36. Silvester JA, Graff LA, Rigaux L, et al. Symptomatic suspected gluten exposure is common among patients with coeliac disease on a gluten-free diet. Aliment Pharmacol Ther 2016;44:612–619.
37. Husby S, Koletzko S, Korponay-Szabó IR, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr 2012;54:136–160.
38. Husby S, Koletzko S, Korponay-Szabó I, et al. European Society Paediatric Gastroenterology, Hepatology and Nutrition guidelines for diagnosing coeliac disease 2020. J Pediatr Gastroenterol Nutr 2020;70:141–156.
39. Meijer CR, Schweizer JJ, Peeters A, et al. Efficient implementation of the 'non-biopsy approach' for the diagnosis of childhood celiac disease in the Netherlands: a national prospective evaluation 2010-2013. Eur J Pediatr 2021;180:2485–2492.
40. Wolf J, Petroff D, Richter T, et al. Validation of antibody-based strategies for diagnosis of pediatric celiac disease without biopsy. Gastroenterology 2017;153:410–419.e17.
41. López RV, Cid CM, García GR, et al. Influence of the 2012 European Guidelines in diagnosis and follow-up of coeliac children with selective IgA deficiency. J Pediatr Gastroenterol Nutr 2020;71:59–63.
42. Hill ID, Fasano A, Guandalini S, et al. NASPGHAN clinical report on the diagnosis and treatment of gluten-related disorders. J Pediatr Gastroenterol Nutr 2016; 63:156–165.
43. Bours MJ. Bayes' rule in diagnosis. J Clin Epidemiol 2021;131:158–160.
44. Sugai E, Moreno ML, Hwang HJ, et al. Celiac disease serology in patients with different pretest probabilities: is biopsy avoidable? World J Gastroenterol 2010;16:3144–3152.
45. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Screening for celiac disease: US Preventive Services Task Force Recommendation Statement. JAMA 2017; 317:1252–1257.
46. Nevoral J, Kotalova R, Hradsky O, et al. Symptom positivity is essential for omitting biopsy in children with suspected celiac disease according to the new ESPGHAN guidelines. Eur J Pediatr 2013;173:497–502.
47. Elfström P, Sundström J, Ludvigsson JF. Systematic review with meta-analysis: associations between coeliac disease and type 1 diabetes. Aliment Pharmacol Ther 2014;40:1123–1132.
48. Gould MJ, Mahmud FH, Clarke ABM, et al. Accuracy of screening tests for celiac disease in asymptomatic patients with type 1 diabetes. Am J Gastroenterol 2021; 116:1545–1549.
49. Sentato Della Repubblica. Disegno Di Legge. Accessed XXXXX. https://www.senato.it/japp/bgt/showdoc/19/DDLPRES/0/1378257/index.html?part=ddlpres_ddlpres1-articolato_articolato1
50. Volta U, Caio G, Giancola F, et al. Features and progression of potential celiac disease in adults. Clin Gastroenterol Hepatol 2016;14:686–693.e1.
51. Ludvigsson JF, Montgomery SM, Ekbom A, et al. Small-intestinal histopathology and mortality risk in celiac disease. JAMA 2009;302:1171–1718.
52. Rubio-Tapia A, Ludvigsson JF, Choung RS, et al. Increased mortality among men aged 50 years old or above with elevated IgA anti-transglutaminase antibodies: NHANES III. BMC Gastroenterol 2016;16(1):136. https://doi.org/10.1186/s12876-016-0547-8.
53. Robert ME, Crowe SE, Burgart L, et al. Statement on best practices in the use of pathology as a diagnostic tool for celiac disease. Am J Surg Pathol 2018; 42:e44–e58. https://doi.org/10.1097/PAS.0000000000001107.
54. Pellegrino S, Furfaro F, Tortora A, et al. The importance of disease prevalence in assessing the diagnostic value of a test: endoscopic markers in celiac disease. Digestion 2013;87:254–261.
55. Sheiko MA, Feinstein JA, Capocelli KE, et al. The concordance of endoscopic and histologic findings of 1000 pediatric EGDs. Gastrointest Endosc 2015; 81:1385–1391.
56. Pais WP, Duerksen DR, Pettigrew NM, et al. How many duodenal biopsy specimens are required to make a diagnosis of celiac disease? Gastrointest Endosc 2008; 67:1082–1087.
57. Rubio-Tapia A, Hill ID, Kelly CP, et al. ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol 2013;108:656–676; quiz 677.
58. Allen JI, Katzka D, Robert M, et al. American Gastroenterological Association Institute technical review on the role of upper gastrointestinal biopsy to evaluate dyspepsia in the adult patient in the absence of visible mucosal lesions. Gastroenterology 2015;149:1088–1118.
59. Husby S, Murray JA, Katzka DA. AGA clinical practice update on diagnosis and monitoring of celiac disease-changing utility of serology and histologic measures: expert review. Gastroenterology 2019;156:885–889.
60. Ravelli A, Bolognini S, Gambarotti M, et al. Variability of histologic lesions in relation to biopsy site in gluten-sensitive enteropathy. Am J Gastroenterol 2005; 100:177–185.
61. Hopper AD, Cross SS, Sanders DS. Patchy villous atrophy in adult patients with suspected gluten-sensitive enteropathy: is a multiple duodenal biopsy strategy appropriate? Endoscopy 2008;40:219–224.
62. Prasad KK, Thapa BR, Nain CK, et al. Assessment of the diagnostic value of duodenal bulb histology in patients with celiac disease, using multiple biopsy sites. J Clin Gastroenterol 2009;43:307–311.
63. Ravelli A, Villanacci V, Monfredini C, et al. How patchy is patchy villous atrophy?: distribution pattern of histological lesions in the duodenum of children with celiac disease. Am J Gastroenterol 2010;105:2103–2110.
64. Latorre M, Lagana SM, Freedberg DE, et al. Endoscopic biopsy technique in the diagnosis of celiac disease: one bite or two? Gastrointest Endosc 2015;81:1228–1233.
65. Kuitunen P, Kosnai I, Savilahti E. Morphometric study of the jejunal mucosa in various childhood enteropathies with special reference to intraepithelial lymphocytes. J Pediatr Gastroenterol Nutr 1982;1:525–531.

66. Lähdeaho ML, Scheinin M, Vuotikka P, et al. Safety and efficacy of AMG 714 in adults with coeliac disease exposed to gluten challenge: a phase 2a, randomised, double-blind, placebo-controlled study. Lancet Gastroenterol Hepatol 2019;4:948–959.
67. Marsh MN, Crowe PT. Morphology of the mucosal lesion in gluten sensitivity. Baillieres Clin Gastroenterol 1995; 9:273–293.
68. Murray JA, Rubio-Tapia A, Van Dyke CT, et al. Mucosal atrophy in celiac disease: extent of involvement, correlation with clinical presentation, and response to treatment. Clin Gastroenterol Hepatol 2008;6:186–193; quiz 125.
69. Leffler DA, Dennis M, Hyett B, et al. Etiologies and predictors of diagnosis in nonresponsive celiac disease. Clin Gastroenterol Hepatol 2007;5:445–450.
70. Ritter J, Zimmermann K, Jöhrens K, et al. T-cell repertoires in refractory coeliac disease. Gut 2018; 67:644–653.
71. Branchi F, Wiese JJ, Heldt C, et al. The combination of clinical parameters and immunophenotyping of intraepithelial lymphocytes allows to assess disease severity in refractory celiac disease. Dig Liver Dis 2022; 54:1649–1656.
72. Rubio-Tapia A, Murray JA. Classification and management of refractory coeliac disease. Gut 2010; 59:547–557.
73. Mubarak A, Nikkels P, Houwen R, et al. Reproducibility of the histological diagnosis of celiac disease. Scand J Gastroenterol 2011;46:1065–1073.
74. Adelman DC, Murray J, Wu TT, et al. Measuring change in small intestinal histology in patients with celiac disease. Am J Gastroenterol 2018;113:339–347.
75. Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology 1992;102:330–354.
76. Oberhuber G. Histopathology of celiac disease. Biomed Pharmacother 2000;54:368–372.
77. Corazza GR, Villanacci V. Coeliac disease. J Clin Pathol 2005;58:573–574.
78. Ensari A. Gluten-sensitive enteropathy (celiac disease): controversies in diagnosis and classification. Arch Pathol Lab Med 2010;134:826–836.
79. Perera DR, Weinstein WM, Rubin CE. Symposium on pathology of the gastrointestinal tract-part II. Small intestinal biopsy. Hum Pathol 1975;6:157–217.
80. Shidrawi RG, Przemioslo R, Davies DR, et al. Pitfalls in diagnosing coeliac disease. J Clin Pathol 1994; 47:693–694.
81. Patel N, Leffler D, Al-Toma A, et al. Clinical data do not reliably predict duodenal histology at follow-up in celiac disease: a 13 center correlative study. Am J Surg Pathol 2024;48:212–220.
82. Taavela J, Viiri K, Popp A, et al. Histological, immunohistochemical and mRNA gene expression responses in coeliac disease patients challenged with gluten using PAXgene fixed paraffin-embedded duodenal biopsies. BMC Gastroenterol 2019;19:189. https://doi.org/10.1186/s12876-019-1089-7.
83. Taavela J, Viiri K, Välimäki A, et al. Apolipoprotein A4 defines the villus-crypt border in duodenal specimens for celiac disease morphometry. Front Immunol 2021;12: 713854. https://doi.org/10.3389/fimmu.2021.713854.
84. Schuppan D, Mäki M, Lundin KEA, et al. A randomized trial of a transglutaminase 2 inhibitor for celiac disease. N Engl J Med 2021;385:35–45.
85. Tye-Din JA, Daveson AJM, Goel G, et al. Efficacy and safety of gluten peptide-based antigen-specific immunotherapy (Nexvax2) in adults with coeliac disease after bolus exposure to gluten (RESET CeD): an interim analysis of a terminated randomised, double-blind, placebo-controlled phase 2 study. Lancet Gastroenterol Hepatol 2023;8:446–457.
86. Maxwell JR, Isola J, Välimäki A, et al. Strategies for improving inter-reader variability of villus height and crypt depth measurements across different institutions [meeting abstract]. Gastroenterology 2023;164:S487–S487.
87. Zarella MD, McClintock DS, Batra H, et al. Artificial intelligence and digital pathology: clinical promise and deployment considerations. J Med Imaging (Bellingham) 2023;10(5):051802. https://doi.org/10.1117/1.Jmi.10.5.051802.
88. Halloran PF, Madill-Thomsen KS. The molecular microscope diagnostic system: assessment of rejection and injury in heart transplant biopsies. Transplantation 2023; 107:27–44.
89. Bragde H, Jansson U, Fredrikson M, et al. Celiac disease biomarkers identified by transcriptome analysis of small intestinal biopsies. Cell Mol Life Sci 2018;75:4385–4401.
90. Leonard MM, Bai Y, Serena G, et al. RNA sequencing of intestinal mucosa reveals novel pathways functionally linked to celiac disease pathogenesis. PLoS One 2019; 14(4):e0215132. https://doi.org/10.1371/journal.pone.0215132.
91. Loberman-Nachum N, Sosnovski K, Di Segni A, et al. Defining the celiac disease transcriptome using clinical pathology specimens reveals biologic pathways and supports diagnosis. Sci Rep 2019;9(1):16163. https://doi.org/10.1038/s41598-019-52733-1.
92. Ramírez-Sánchez AD, Tan IL, Gonera-de Jong BC, et al. Molecular biomarkers for celiac disease: past, present and future. Int J Mol Sci 2020;21(22):8528.
93. Dotsenko V, Oittinen M, Taavela J, et al. Genome-wide transcriptomic analysis of intestinal mucosa in celiac disease patients on a gluten-free diet and postgluten challenge. Cell Mol Gastroenterol Hepatol 2021;11:13–32.
94. Ramírez-Sánchez AD, Chu X, Modderman R, et al. Single-cell RNA sequencing of peripheral blood mononuclear cells from pediatric coeliac disease patients suggests potential pre-seroconversion markers. Front Immunol 2022;13: 843086. https://doi.org/10.3389/fimmu.2022.843086.
95. Atlasy N, Bujko A, Bækkevold ES, et al. Single cell transcriptomic analysis of the immune cell compartment in the human small intestine and in celiac disease. Nat Commun 2022;13(1):4920. https://doi.org/10.1038/s41467-022-32691-5.
96. Smithson G, Siegelman J, Oki T, et al. The evolving landscape of biomarkers in celiac disease: leading the

way to clinical development. Front Immunol 2021;12: 665756. https://doi.org/10.3389/fimmu.2021.665756.

97. Oberhuber G, Granditsch G, Vogelsang H. The histopathology of celiac disease: time for a standardized report scheme for pathologists. Eur J Gastroenterol Hepatol 1999;11:1185–1194.

Received November 19, 2023. Accepted January 24, 2024.

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Conflicts of interest
This author discloses the following: Marie E. Robert is a consultant for Takeda. The remaining authors disclose no conflicts.

Funding
Supported by a National Institute of Diabetes and Digestive and Kidney Diseases grant (U01DK136523) to Benjamin Lebwohl.