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REVIEW

Optimising the Diagnosis of Adult Coeliac Disease: Current Evidence and Future Directions

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Abstract

Coeliac disease is a common autoimmune disorder that affects nearly 1% of the general population. Current diagnostic strategies involve active case finding, serological tests, and endoscopy with biopsies. However, many patients with coeliac disease remain undiagnosed due to a wide gap between clinical guidelines and real-world practice in the diagnosis of adult coeliac disease. This highlights the need for increased education, training, and targeted quality-improvement interventions to optimise the diagnosis of coeliac disease.

Key words: coeliac disease; glutens; diagnosis; gluten-free

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Introduction

Coeliac disease is a unique autoimmune disorder as both its major genetic predisposition, Human leukocyte antigen (HLA)-DQ2 and -DQ8, and its environmental trigger, dietary gluten, are well-defined and understood (Green and Cellier, 2007). Coeliac disease is characterised by an inappropriate T-cell-mediated immune response to gluten in genetically predisposed individuals, leading to inflammation and damage to the intestinal villi. Although coeliac disease primarily affects the small bowel, it is increasingly recognised as a multi-system disorder. Beyond the classic gastrointestinal symptoms, patients with coeliac disease experience a wide range of extraintestinal manifestations, such as anaemia, fatigue, osteoporosis, migraine and neurological disturbances (Elwenspoek et al, 2021).

Recent epidemiological studies have shown increased prevalence and incidence of coeliac disease over time. The pooled global prevalence of biopsy-proven coeliac disease is estimated to range between 0.5% to 0.9%, with variations observed according to sex, age and geographical location (Singh et al, 2018). The incidence of coeliac disease has been rising by approximately 7.5% per year (King et al, 2020). Notably, among all autoimmune disorders, coeliac disease had the largest rise in incidence over the past two decades, with an incidence rate ratio of 2.19 (Conrad et al, 2023). The growing prevalence and incidence highlight that coeliac disease is a global health problem that requires more resources for diagnosis, treatment, and awareness campaigns. However, despite the increased awareness about coeliac

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disease and improved diagnostic pathways, approximately two-thirds of patients remain undiagnosed, misdiagnosed or experiencing significant delays in diagnosis, leading to the concept of the coeliac iceberg where the tip of the iceberg represents the diagnosed cases, while the submerged part symbolises a large number of undiagnosed or misdiagnosed individuals (Fig. 1) (Anderson, 2022; Kårhus et al, 2022; West et al, 2019).

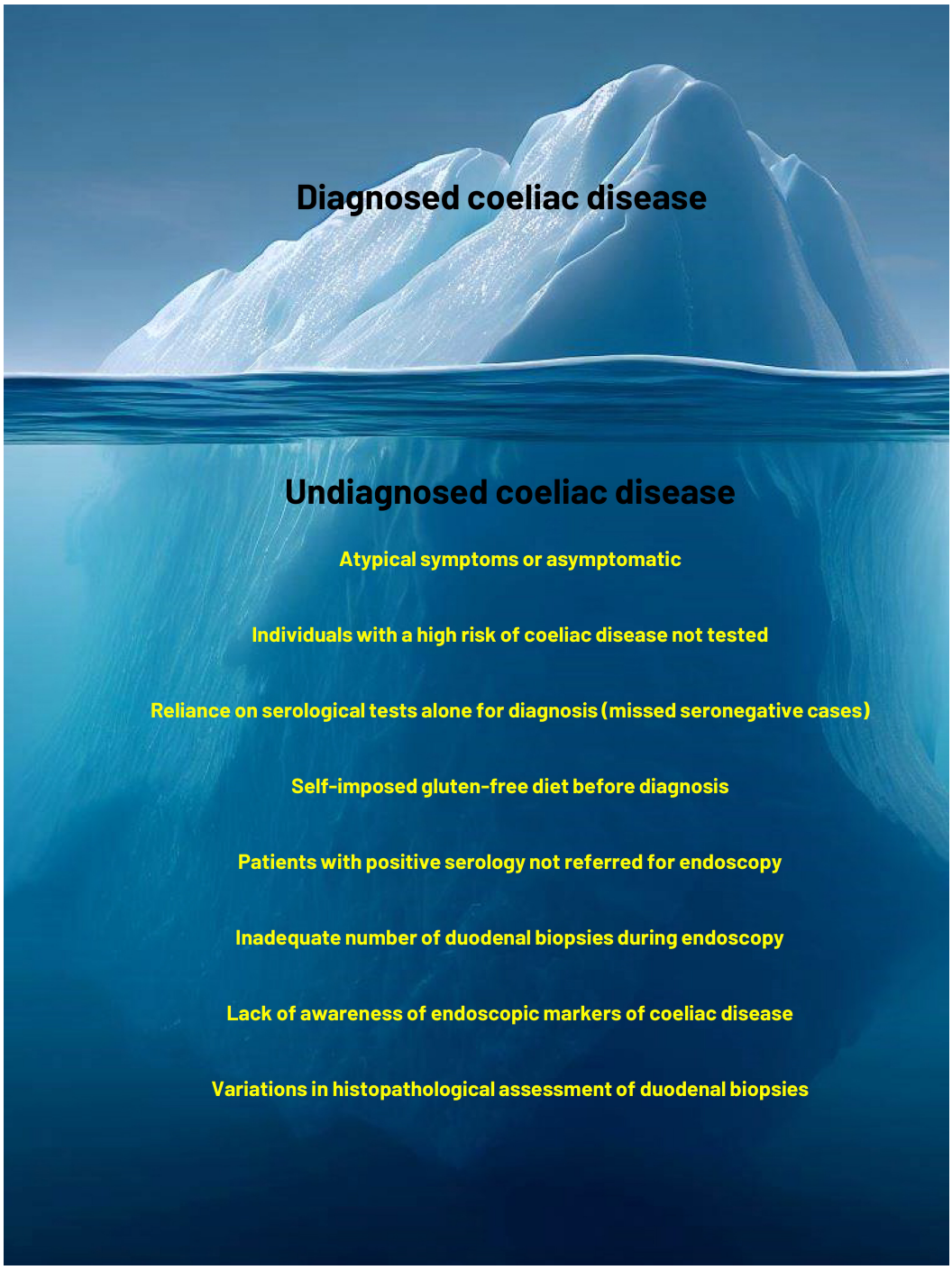

Fig. 1. The coeliac iceberg illustrates the proportion of diagnosed and undiagnosed patients with coeliac disease and lists the common reasons for undiagnosed coeliac disease. (Created using GPT-4o, OpenAI, San Francisco, CA, USA).

Table 1. Indications of testing for coeliac disease according to the National Institute for Health and Care Excellence guidelines (Downey et al, 2015).

Testing recommended	Testing considered
• Persistent unexplained gastrointestinal symptoms	• Metabolic bone disorder (reduced bone mineral density or osteomalacia)
• Faltering growth	• Unexplained neurological symptoms (particularly peripheral neuropathy or ataxia)
• Prolonged fatigue	• Unexplained subfertility or recurrent miscarriage
• Severe or persistent mouth ulcers	• Persistently raised liver enzymes with unknown cause
• Unexplained iron, vitamin B12, or folate deficiency	• Dental enamel defects
• Type 1 diabetes, at diagnosis	• Down's syndrome
• Autoimmune thyroid disease, at diagnosis	• Turner's syndrome
• Irritable bowel syndrome in adults	
• First-degree relative of people with coeliac disease	

Undiagnosed and untreated coeliac disease is associated with significant morbidity and increased risk of serious complications such as nutrient deficiencies, fragility fractures, cardiovascular disease, and malignancy (Kaukinen, 2021; Malamut and Cellier, 2015). An early and accurate diagnosis with strict adherence to a gluten-free diet promotes mucosal healing and may prevent long-term complications (Schiepatti et al, 2023). In this review, we aim to provide a comprehensive overview of current diagnostic strategies and discuss future directions and emerging technologies that might help to optimise the diagnosis of coeliac disease.

Who to Test for Coeliac Disease?

Current evidence does not support mass population screening for coeliac disease. Therefore, clinical guidelines recommend active case-finding for symptomatic patients and targeted screening for high-risk patients as outlined in Table 1 (Al-Toma et al, 2019; Downey et al, 2015; Ludvigsson et al, 2014; Rubio-Tapia et al, 2023). Nonetheless, these strategies have failed to fully address the underdiagnosis and delayed diagnosis of coeliac disease, highlighting the need for a more proactive and comprehensive approach to identifying patients at risk of coeliac disease (Fuchs et al, 2018; Lionetti et al, 2023).

Historically, coeliac disease was suspected in Caucasian children with classic symptoms such as diarrhoea, failure to thrive, and overt malabsorption. However, our contemporary understanding has evolved to recognise coeliac disease as a more prevalent condition that affects individuals from all ethnic backgrounds and all age groups, with a broader range of clinical presentations and non-classical symptoms (Sanders et al, 2002). Elderly patients with coeliac disease tend to present with more subtle and non-specific symptoms compared with younger individuals (Collin et al, 2018; Shiha et al, 2020). Although the incidence of coeliac disease diagnosis in the elderly has increased over time, the diagnosis could be easily overlooked in elderly patients, leading to potential complications and reduced quality of life (Shiha et al,

2020). Clinicians should suspect coeliac disease when reviewing elderly patients with unexplained nutritional deficiencies, fragility fractures, vague or unexplained symptoms (Collin et al, 2018; Shiha et al, 2020).

Individuals with irritable bowel syndrome (IBS)-type symptoms including abdominal pain, bloating, diarrhoea or constipation have a fourfold increased chance of having coeliac disease compared with controls with no such symptoms (Irvine et al, 2017). Screening patients with IBS-type symptoms for coeliac disease has been shown to be beneficial and cost-effective (Mohseninejad et al, 2013). Therefore, current guidelines recommend testing all patients with IBS-type symptoms for coeliac disease (Vasant et al, 2021).

Patients with coeliac disease may also present nutritional deficiencies such as folate, B12, vitamin D and iron, due to villous atrophy and the subsequent reduction in the absorptive surface area in the small bowel. Anaemia, particularly iron deficiency anaemia, is a common finding in patients with newly diagnosed coeliac disease, and could be the only presenting symptom (Harper et al, 2007). Conversely, the pooled prevalence of biopsy-proven coeliac disease in patients with iron deficiency anaemia is 3.2% (Mahadev et al, 2018). Hence, testing patients with iron deficiency or unexplained anaemia for coeliac disease is recommended by various international clinical guidelines (Ludvigsson et al, 2014; Rubio-Tapia et al, 2023; Snook et al, 2021).

Other non-classical symptoms of coeliac disease include persistent or recurrent mouth ulcers, dermatitis herpetiformis, peripheral neuropathy, ataxia, chronic fatigue, recurrent miscarriages and unexplained liver transaminitis (Downey et al, 2015). Early recognition of the neurological manifestations of coeliac disease, such as gluten ataxia and neuropathy, is important as these gluten-dependent neurological complications are often irreversible but commonly overlooked (Mearns et al, 2019). Moreover, emerging evidence suggests a bi-directional relationship between migraine and coeliac disease, and the potential symptomatic benefits of following a gluten-free diet in patients with coeliac disease and migraine (Elwenspoek et al, 2021; Wojciechowska et al, 2023). Considering that migraine is the leading cause of disability in those aged 15 to 49 years, testing patients with migraine for coeliac disease could have substantial benefits to afflicted individuals and society (Steiner et al, 2018).

First-degree relatives of people with coeliac disease and those with other autoimmune conditions such as type 1 diabetes and autoimmune thyroid disease are at increased risk of having coeliac disease compared with the general population (Elfström et al, 2014; Singh et al, 2015; Sun et al, 2016). Screening these high-risk groups, including the asymptomatic, is a valuable strategy to identify patients with coeliac disease at an early stage and to ensure timely management and improved health outcomes.

While awareness about the classical and non-classical symptoms of coeliac disease has increased over the last few decades, recent reports still consistently find unsatisfactory levels of knowledge on coeliac disease among healthcare professionals (Faraj et al, 2022; Riznik et al, 2021; Sahin et al, 2022). In a recent Polish

survey of patients with coeliac disease, more than half the respondents rated their family doctor's knowledge of coeliac disease as "bad" (Majsiak et al, 2023). Even among gastroenterologists, one in three failed to recognise that coeliac disease has a greater prevalence than inflammatory bowel disease (Taylor et al, 2021). These worrying figures highlight the need for urgent efforts to address these knowledge gaps through medical education, public health campaigns and targeted quality improvement initiatives.

Serological and Genetic Testing

The diagnosis of adult coeliac disease is currently based on a two-tier process that starts with serological testing, followed by endoscopy and duodenal biopsies to confirm the diagnosis in those with positive serology (Fig. 2). The main serological markers of coeliac disease are antibodies directed towards endogenous or food-derived proteins, including anti-tissue transglutaminase (tTG) and endomysial antibodies (EMA) (Penny et al, 2020b). Immunoglobulin (Ig)A-tTG is recommended as the first-line serological test for patients with suspected coeliac disease due to its high sensitivity, wide availability and low cost (Al-Toma et al, 2019; Ludvigsson et al, 2014; Rubio-Tapia et al, 2023). Conversely, IgA-EMA is susceptible to inter-observer variability, requires immunofluorescence and bears higher costs but has 99–100% specificity for coeliac disease in adults (Sheppard et al, 2022). Therefore, its use is reserved as a confirmatory test in equivocal cases such as after borderline IgA-tTG results.

It is important to keep in mind that there are several reasons why a proportion of patients with coeliac disease may have negative serology during initial assessment. First, some patients, particularly those with severe symptoms, may have already started excluding gluten from their diet. Self-imposing a gluten-free diet or reducing gluten intake during the diagnostic process reduces the reliability of serology and biopsy for diagnosis. Therefore, ensuring that patients remain on a gluten-containing diet before diagnosis is crucial to avoid false-negative results. In cases where patients have already self-imposed a gluten-free diet, a gluten challenge is required to induce a pathological immune response. Conventionally, the gluten challenge required ingesting 3 to 10 grams of gluten per day (2 grams is roughly equivalent to a slice of bread) for 6 to 8 weeks prior to testing. However, more recent evidence suggests that a 10 gram/day gluten challenge for 2 weeks may be sufficient to induce enteropathy in patients with coeliac disease (Leonard et al, 2021). Second, selective IgA deficiency affects approximately 2% of patients with coeliac disease (Chow et al, 2012). Those affected may have negative IgA-based antibody tests despite having coeliac disease. Hence, total IgA levels should be routinely measured together with IgA-tTG/EMA (Nazario et al, 2022). While IgG-based serology tests provide an alternative to patients with IgA deficiency, endoscopy and biopsy are often warranted if the clinical suspicion of coeliac disease is high. Third, patients on immunosuppressive medication may not be able to mount a serological response to gluten ingestion and negative antibody results should not preclude proceeding to endoscopy and biopsy in these individuals. Fi-

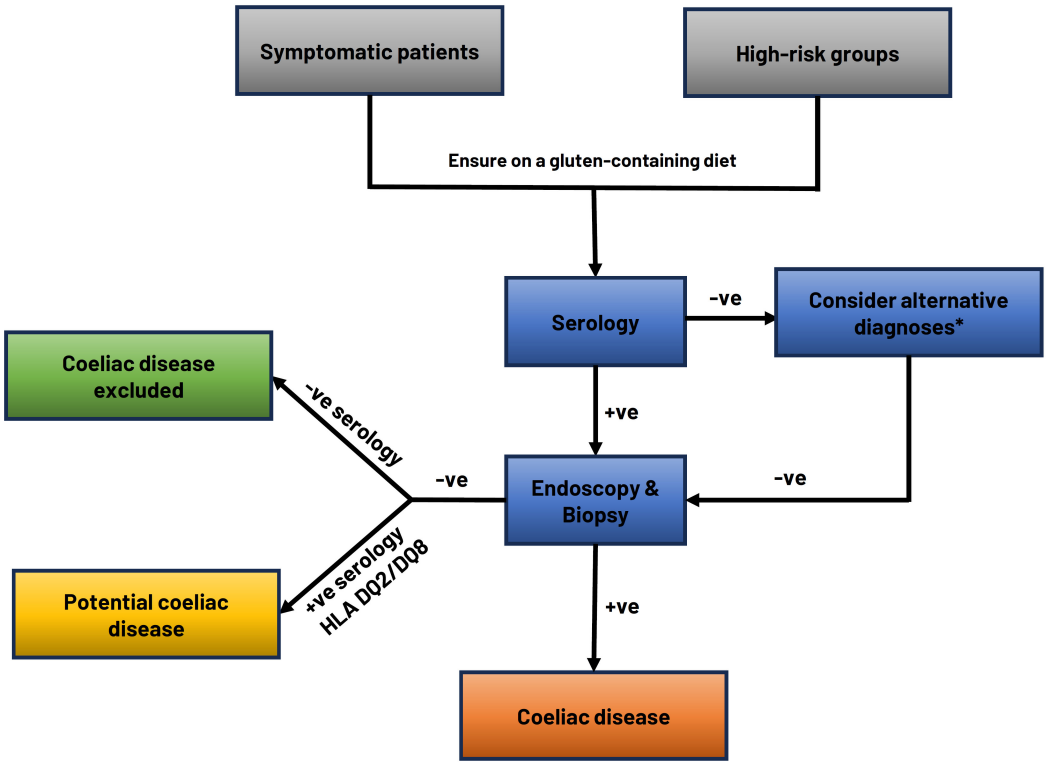

Fig. 2. Simplified diagnostic algorithm for coeliac disease. (Created using Microsoft PowerPoint, Microsoft Office 2021, Microsoft Corporation, Redmond, WA, USA). *Patients with high suspicion of coeliac disease and negative serology should undergo further evaluation including Human leukocyte antigen (HLA) typing and assessment for alternative diagnoses, if suspicion of coeliac disease remained, they should be referred for endoscopy and biopsy. +ve, positive; -ve, negative.

nally, true seronegative coeliac disease, albeit uncommon, can be easily overlooked, and is associated with adverse disease course and worse outcomes compared with seropositive disease (Schiepatti et al, 2021).

HLA molecules are genetically determined and play a pivotal role in the pathogenesis of coeliac disease. Almost all patients with coeliac disease carry the HLA-DQ2/DQ8 alleles. However, 30–40% of the general population carry these HLA alleles but only around 1% develop coeliac disease (Karell et al, 2003). Therefore, HLA genotyping in patients with suspected coeliac disease is not diagnostic but has a high negative predictive value and provides a useful tool for patients with diagnostic uncertainty, negative serology and those unwilling to undergo a gluten-challenge after starting a gluten-free diet (Kaukinen et al, 2002).

Although clinical guidelines recommend that all adult patients with positive coeliac disease should undergo endoscopy and duodenal biopsies to confirm the diagnosis, real-world data have shown variations in adherence to these recommendations (Guz-Mark et al, 2020; Joelson et al, 2019; Johnston et al, 2022). Studies from the USA, Israel and the UK reported that between 21%–47.1% of adult patients with positive coeliac serology were not referred for confirmatory biopsy (Guz-Mark et al, 2020; Joelson et al, 2019; Johnston et al, 2022). Compared with those diagnosed according to the guidelines, patients who received an inappropriate serology-based diagnosis were less likely to seek nutritional counseling, more

likely to have persistent symptoms after following a gluten-free diet and more likely to use unapproved nutritional supplements to "aid with gluten digestion" (Joelson et al, 2019). The poor adherence to guidelines may stem from the lack of awareness about the potential consequences of inappropriate serology-based diagnosis, inadequate understanding of coeliac disease within the medical community and a degree of medical inertia and nihilism to coeliac disease (Greenaway et al, 2022). As will be discussed further, serology plays an ever-increasing role in coeliac diagnosis, and efforts should focus on supporting primary and secondary physicians in understanding the current role of serological testing to help expedite the appropriate diagnosis of coeliac disease.

Endoscopy and Histopathology

Upper gastrointestinal endoscopy allows direct visualisation of the duodenal mucosa and the acquisition of biopsy samples to confirm the diagnosis of coeliac disease. Endoscopic features of coeliac disease include scalloping of the duodenal folds, mosaicism, fissuring and bulb atrophy (Balaban et al, 2015). Yet, these features are commonly under-reported by endoscopists and lack the necessary sensitivity to preclude the need for biopsies (Dickey and Hughes, 2001).

The mucosal damage in coeliac disease follows a patchy distribution, whereby the same biopsy sample may show variable degrees of villous atrophy and even areas of normal mucosa (Ravelli et al, 2010). Therefore, multiple biopsies of the distal duodenum should be performed to increase the diagnostic yield and to detect the most severe lesions (Hopper et al, 2008a). Furthermore, adding one or two biopsies from the duodenal bulb may further increase the diagnostic yield in cases where villous atrophy is limited to the duodenal bulb (Evans et al, 2011).

The optimal strategy for biopsy acquisition is a matter of ongoing debate (Rettally, 2023). A single tertiary-centre prospective study found that obtaining a single-biopsy specimen with each pass of the forceps provides improved orientation compared with the commonly used double-biopsy technique (Latorre et al, 2015). However, there was no statistically significant difference in the final Marsh scores between the single- and double-biopsy techniques (Latorre et al, 2015). The correct orientation of biopsy specimens in the endoscopy room prevents wrong histological interpretation and subsequent misdiagnosis by pathologists as poorly oriented biopsy samples may result in an overestimation of interepithelial lymphocyte count and can give a false impression of reduced villous/crypt ratio (Villanacci et al, 2023).

Endoscopy with duodenal biopsies remains widely upheld as the gold standard test for diagnosing coeliac disease. However, even gold standards have inherent limitations and subtle nuances upon close examination. Endoscopy is an invasive and costly procedure, frequently requires sedation, and is associated with discomfort and increased levels of anxiety for some patients (Jones et al, 2004). The high demand for endoscopic procedures also means that patients with positive serology are often advised to continue eating gluten, irrespective of their symptoms, for several months while awaiting an endoscopy appointment (Taylor et al, 2021). Gluten avoidance whilst awaiting endoscopy increases the risk of false-negative histology,

and lengthy delays alongside the requirement for continued gluten ingestion may explain why a proportion of patients choose not to undergo endoscopy (Johnston et al, 2022).

The quality of endoscopy remains highly operator-dependent, and varies between different endoscopists (Januszewicz and Kaminski, 2020). A multi-centre study in the UK found that only 40% of endoscopists adhered to the biopsy guidelines for coeliac disease, which reduced the diagnostic yield by over 50% (Taylor et al, 2021). Surgeons were significantly less likely to adhere to guidelines compared with gastroenterologists (18.2% vs. 41.5%), reflecting the direct influence of knowledge and awareness of coeliac disease on practice (Taylor et al, 2021). The poor awareness of endoscopic features of coeliac disease among endoscopists may also compromise the quality of endoscopy and the chance of early diagnosis. Notably, almost 1-in-10 patients with newly diagnosed coeliac disease had at least one non-diagnostic endoscopy where no biopsies were taken in the 5 years before diagnosis (Taylor et al, 2021). An earlier study of 132,352 patients who underwent duodenal biopsy in the US reported similarly low adherence to biopsy guidelines (39.5%), which significantly reduced the diagnostic yield (Kelly et al, 2015). With nearly 10 years of difference between the two studies, little progress has been made and a substantial proportion of endoscopists continue to have low adherence to best practice guidelines (Kelly et al, 2015; Taylor et al, 2021). This increases the risk of missed diagnosis and contributes to the significant delays in diagnosis experienced by patients with coeliac disease (Kårhus et al, 2022).

The final step of the current diagnostic pathway for adult coeliac disease is histopathological assessment. Identification of the characteristic changes of coeliac disease such as increased intraepithelial lymphocytes, crypt hyperplasia and villous atrophy, confirms the diagnosis within the right clinical context (Marsh, 1990). However, variability in reporting mucosal changes exists between different pathologists even in the setting of clinical research studies. A recent large multi-centre study found 7.1% discordance regarding coeliac disease diagnosis between local and central pathologists (Werkstetter et al, 2017). Similarly, earlier work showed that histological interpretation of duodenal biopsies in coeliac disease can vary in 10%–25% of cases between independent evaluations, with disagreement more common in cases with milder mucosal changes (Marsh 1, 2 and 3a) than those at the ends of the disease spectrum (Marsh 0 and 3c) (Arguelles-Grande et al, 2012; Mubarak et al, 2011). This underscores the importance of using a systematic approach to the histopathological assessment of appropriately sampled and orientated biopsies in coeliac disease.

Future Directions

No-Biopsy Approach

The diagnostic accuracy of IgA-tTG for coeliac disease outperforms most antibody-based tests for other autoimmune and inflammatory conditions (Leffler and Schuppan, 2010). However, a slight elevation in IgA-tTG levels, could be transient, lacks sufficient sensitivity and specificity to supplant biopsy, and has a positive pre-

dictive value (PPV) as low as 28% (Hopper et al, 2008b). Conversely, consistent reports from the paediatric and adult literature have shown that very high titers of IgA-tTG (≥10× upper limit of normal (ULN)) correlate with the presence of villous atrophy in almost all cases (Alessio et al, 2012; Beltran et al, 2014; Fuchs et al, 2019; Hill and Holmes, 2008; Penny et al, 2021; Previtali et al, 2018; Werkstetter et al, 2017). This questioned the need for confirmatory biopsies in children with IgA-tTG ≥10× ULN, given the invasive and distressing nature of endoscopy, which requires the use of general anaesthesia. In 2012, the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guidelines for the diagnosis of coeliac disease incorporated a no-biopsy diagnostic pathway, whereby symptomatic children with IgA-tTG ≥10× ULN, HLA-DQ2/DQ8, and positive EMA in a second blood samples could be diagnosed with coeliac disease without biopsies (Husby et al, 2012). A large international prospective study validated the accuracy of the no-biopsy approach in children with a PPV >99% and showed that HLA-typing is not necessary for the serology-based diagnosis (Werkstetter et al, 2017). The latest iteration of the ESPGHAN guidelines reflected this new evidence and omitted the need for HLA-typing and the presence of symptoms to confirm a serology-based diagnosis for coeliac disease in children with IgA-tTG ≥10× ULN and positive EMA in a second blood sample (Husby et al, 2020).

Although the no-biopsy approach has been used in clinical practice for children for over a decade, extrapolating this approach to adults remains a contentious subject. A recent international study including adult cohorts with different pre-test probabilities of coeliac disease showed that IgA-tTG ≥10× ULN has a PPV >95% for predicting villous atrophy in adults with suspected coeliac disease (Penny et al, 2021). Notably, all those with false-positive results had compatible HLA, symptoms suggestive of coeliac disease and a marked reduction in IgA-tTG levels after following a gluten-free diet (Penny et al, 2021). The findings of this study were further validated by another international prospective study, which showed a similar PPV of IgA-tTG ≥10× ULN to identify patients with villous atrophy (Ciacci et al, 2023). A more recent meta-analysis of 18 studies, including over 12,000 participants, found that IgA-tTG ≥10× ULN has a 100% specificity and an unconditional PPV of 98% (95% CI, 96%–99%). However, the high PPV varied according to the pre-test probability of coeliac disease, suggesting that the no-biopsy approach in adults may be less reliable in patients with a low pre-test probability of coeliac disease or in low prevalence settings such as primary care (Shiha et al, 2024c).

With the highest population prevalence of coeliac disease worldwide, Finland was the first country to adopt a no-biopsy diagnostic pathway for adults in their 2018 national guidelines (Working group set up by the Finnish Medical Society Duodecim and the Finnish Gastroenterology Society, 2018). During the COVID-19 pandemic, the British Society of Gastroenterology also issued interim guidance that recommended a serology-based diagnosis for symptomatic adults <55 years with IgA-tTG ≥10× ULN, positive EMA and no alarm symptoms (Penny et al, 2020a). More recently, the updated American College of Gastroenterology guidelines for the diagnosis of coeliac disease suggested that adults unwilling or unable to undergo endoscopy may be diagnosed as “likely coeliac disease” (Rubio-Tapia

et al, 2023). The guidelines suggested that a PPV of 95% may be unacceptably low to recommend a no-biopsy approach given the lifelong implications of a gluten-free diet (Rubio-Tapia et al, 2023). Conversely, implementing the no-biopsy approach in clinical practice may have benefits such as streamlining the diagnostic process and reducing healthcare costs associated with endoscopy and biopsy (Shiha et al, 2024a). Moreover, recent data suggest that avoiding duodenal biopsies did not affect dietary adherence or healthcare-related quality of life in children with coeliac disease, which is reassuring for potential implications in adults (Antonius et al, 2024).

Barriers to the implementation of the no-biopsy approach include the significant heterogeneity between different IgA-tTG assays, the variable availability of EMA testing and the lack of routine reporting of total IgA levels (Paul et al, 2017). Concerns have also been raised about missing co-existing pathology in the absence of performing a gastroscopy. However, recent studies do not support this, and gastroscopy and biopsies should still be undertaken if red flag symptoms are present, or there is a high index of suspicion for concurrent pathology, irrespective of the IgA-tTG titre (Hoyle et al, 2022; Stefanolo et al, 2022). Furthermore, an index biopsy can be useful when reviewing a patient who presents with ongoing symptoms to evaluate for persistent inflammation despite a gluten-free diet, but the time course of mucosal healing in coeliac disease is highly variable, meaning comparison with reference histology is not straightforward. Moreover, interpreting the no-biopsy approach as a "no-referral" approach may lead to increased inappropriate diagnosis of coeliac disease in primary care, or missing significant pathology in patients who have concurrent alarm symptoms. Addressing these barriers requires increased awareness and education, clear referral pathways from primary to secondary care, standardisation of IgA-tTG assay kits, and a shared decision-making process involving patients and gastroenterologists.

Serum Interleukin-2

Within hours of gluten exposure, multiple systemic cytokines are released and are implicated in driving the reactivation of immunity towards gluten in patients with coeliac disease, including the development of early symptoms. Interleukin-2 (IL-2) was found to be one of the earliest and most abundant cytokines to be released after gluten ingestion, with a 15-fold change at 4 hours (Goel et al, 2019; Tye-Din et al, 2019). IL-2 is primarily produced by CD4+ T cells and has pleiotropic effects on the immune system, including in part regulating CD4+ T cell differentiation and function, as well as effector and memory responses of CD8+ T cells (Spolski et al, 2018).

Gluten challenge studies have shown that the acute rise in IL-2 levels occurs even after exposure to a single bolus 3-gram dose of gluten (Leonard et al, 2021). Furthermore, a recent randomized, double-blinded, sham-controlled gluten challenge study showed significant plasma IL-2 elevations after gluten ingestion occur only in patients with coeliac disease and not in those with self-reported non-coeliac gluten sensitivity or healthy controls (Cartee et al, 2022). Interestingly, symptoms were not a reliable indicator of gluten exposure in patients with coeliac disease

and non-coeliac gluten sensitivity (Cartee et al, 2022). Therefore, measurement of plasma IL-2 after a single gluten challenge could provide an objective biomarker to differentiate coeliac disease from non-coeliac gluten sensitivity. Moreover, IL-2 appears to present a more reliable and tolerable alternative to a lengthy gluten challenge followed by endoscopy and biopsy in patients already on a gluten-free diet prior to diagnosis. This may be particularly useful in those with severe reactions to gluten, who find the gluten challenge distressing and importantly may not be able to consume enough gluten to induce pathological changes and thus invalidate the test. Future larger studies are required to define the optimal role of IL-2 in the diagnosis of coeliac disease and whether it could be used as a single biomarker or in combination with serological tests for diagnosis.

HLA-DQ–Gluten Tetramers

The HLA-DQ2/DQ8 molecules play a vital role in the pathogenesis of coeliac disease by presenting gluten-derived peptides to cognate CD4+ T cells. The activation of gluten-specific CD4+ T cells drives a pro-inflammatory response which, alongside intra-epithelial lymphocytes, contributes to small intestinal mucosal inflammation and damage (Meresse et al, 2012). A flow cytometric assay for gluten-specific T cells in blood, using HLA-DQ-gluten tetramers, has been developed and early studies suggest that it is a reliable maker for coeliac disease regardless of gluten consumption (Sarna et al, 2018a,b). In a study of 143 HLA-DQ2.5^{+} subjects, the HLA-DQ–gluten tetramer test was able to identify those with coeliac disease on a gluten-free diet from those without coeliac disease with a sensitivity and specificity of 97% and 95%, respectively (Sarna et al, 2018a). However, the test has not been validated in multicenter studies and has so far only been designed around a specific HLA-DQ construct (HLA-DQ2.5), meaning the accuracy of the test may not be maintained in patients carrying other HLA-DQ genotypes (Sarna et al, 2018a). Also, the test relies on flow cytometric analysis which is not widely available and time-consuming (7-hour protocol). Despite these limitations, if widely validated, the HLA-DQ–gluten tetramer test could provide an attractive and useful alternative to the gluten challenge for patients with diagnostic uncertainty on self-imposed gluten-free diets at specialist centres that employ flow cytometry in routine practice.

Endoscopic Enhanced Imaging

The endoscopic markers of coeliac disease on conventional white-light endoscopy could be very subtly and easily missed (Dickey and Hughes, 2001). Multiple novel endoscopic imaging techniques, including water-immersion, dye-based chromoendoscopy, high-resolution magnification, optical coherence tomography and confocal laser endomicroscopy, have demonstrated a higher accuracy in the evaluation of duodenal villous morphology compared with white-light endoscopy (Ianiro et al, 2015). However, these techniques are costly, time-consuming, not widely available, and may require dedicated training. Such limitations hinder their use in routine clinical practice. Conversely, narrow-band imaging (NBI), an enhanced imaging technique available with a push of a button on contemporary gastroscopes, provides an accurate assessment of duodenal villous morphology at no

Table 2. Suggested Key Performance Indicators for coeliac disease diagnosis.

	Key Performance Indicators (KPIs)
Symptoms recognition and screening	- Proportion of patients with symptoms suggestive of coeliac disease tested. - Proportion of high-risk groups (e.g., first-degree relatives of people with coeliac disease, type 1 diabetes, autoimmune thyroid disease) screened for coeliac disease.
Gluten intake reporting and documentation	- Proportion of patients in whom gluten intake is reported before testing and recommended gluten-challenge when indicated.
Initial serological testing	- Proportion of patients with suspected coeliac disease tested with IgA-tTG as a first-line serological test. - Proportion of patients tested for total IgA levels. - The time between initial presentation/symptoms onset and IgA-tTG testing.
IgA deficiency	- Proportion of patients with IgA deficiency who receive IgG-based serological testing or are referred for endoscopy and biopsies.
Confirmatory serological testing	- Proportion of patients with borderline IgA-tTG results who undergo confirmatory testing using repeat IgA-tTG or IgA-EMA.
HLA genotyping	- Proportion of patients with diagnostic uncertainty or negative serology and high clinical suspicion who undergo HLA genotyping to aid in decision-making.
Referral to endoscopy	- Proportion of patients with positive serology referred for confirmatory endoscopy and biopsies.
High-quality endoscopy and biopsies	- Proportion of endoscopies where macroscopic duodenal findings have been reported. - Proportion of endoscopies where an adequate number duodenal of biopsies have been obtained. - Proportion of patients with confirmed coeliac disease who underwent non-diagnostic endoscopy in the 3–5 years prior to diagnosis.
Recognition of seronegative cases	- Proportion of patients with seronegative coeliac disease among all confirmed cases.
Quality of histological assessment and reporting	- Proportion of duodenal biopsy samples assessed and reported according to the Marsh criteria.

Ig, immunoglobulin; tTG, tissue transglutaminase; EMA, endomysial antibodies.

extra cost and with minimal training (Dutta and Chacko, 2015). In a recent systematic review and meta-analysis, we found that NBI has a summary sensitivity of 93% and specificity of 95% to detect villous atrophy in patients with suspected coeliac disease (Shiha et al, 2024b). Future studies using a validated NBI classification are required to determine the role of NBI in the diagnosis of coeliac disease (Gulati et al, 2021).

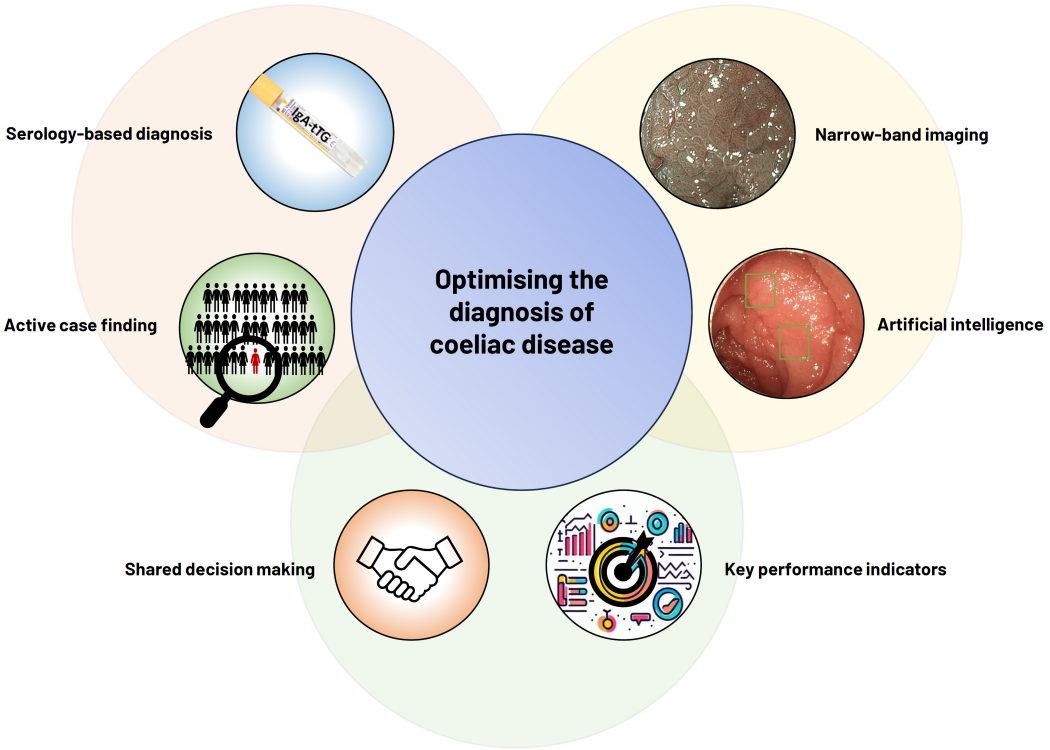

Fig. 3. Emerging strategies to help optimising the diagnosis of adult coeliac disease. (Created using Microsoft PowerPoint, Microsoft Office 2021, Microsoft Corporation, Redmond, WA, USA).

Artificial Intelligence

The role of artificial intelligence (AI) in gastroenterology has exponentially expanded over the last few years. The promising new technology offers unprecedented capabilities to analyze and interpret large datasets of medical records, endoscopic and histological data (Beam et al, 2023). AI-assisted endoscopy has been shown to be superior to conventional endoscopy in the detection of subtle mucosal abnormalities in the upper and lower gastrointestinal (GI) tract (Lui et al, 2020; Shiha et al, 2023). Although real-time detection of villous atrophy with AI has not been studied in clinical trials to date, AI deep learning algorithms outperformed expert and non-expert endoscopists in the detection of villous atrophy on endoscopic still images (Scheppach et al, 2023). Using real-time AI systems during endoscopy could reduce the reliance on biopsies for the diagnosis of coeliac disease, offering a more accurate and timely diagnosis.

Automated detection of coeliac disease on biopsies using a deep learning model identified coeliac disease, non-specific duodenitis, and normal tissue with an area under receiver operating characteristic curve >0.95 across all classes (Wei et al, 2019). Therefore, using AI could reduce the variations in the interpretation of histopathological samples and increase the confidence in diagnosis.

Key Performance Indicators in Coeliac Disease

Key Performance Indicators (KPIs) are measurable outcomes that allow monitoring of a healthcare process for benchmarking and facilitating recognition of areas for improvement. KPIs are well established in endoscopic practice in the UK and have recently been developed across other GI conditions such as inflammatory bowel disease (Quraishi et al, 2023). In 2015, the National Institute of Clinical Excellence outlined five Quality Standards covering the diagnosis and management of coeliac disease, but consensus KPIs do not currently exist (Downey et al, 2015). In Table 2, we suggest a comprehensive set of KPIs that encompass the entire patient journey from the first presentation to assessing the quality of the histological assessment of duodenal biopsies in coeliac disease. The regular auditing and monitoring of these KPIs could lead to improvement in the quality of care for patients with coeliac disease, ensure adherence to national guidelines and reduce variations in practice. The overall aim is that the standardisation of high-quality diagnostic pathways for coeliac disease will lead to accurate, timely and equitable patient care.

Conclusion

In conclusion, there is a wide gap between clinical guidelines and real-world practice in the diagnosis of coeliac disease. Optimising the diagnosis of coeliac disease requires increased education, training, and targeted quality-improvement interventions, as well as collaboration between healthcare providers, policymakers and patient advocacy groups to refine diagnostic pathways based on the latest available evidence. Several emerging technologies may help with diagnosis, and further studies validating these approaches are eagerly awaited. Improved adherence to guidelines and evidence-based practice, establishing benchmarking standards such as Key Performance Indicators, and embracing emerging technologies (Fig. 3) may lead to a more accurate and timely diagnosis of coeliac disease.

Key Points

- Coeliac disease is a global health problem with rising prevalence and incidence.
- Many patients with coeliac disease remain undiagnosed or experience significant delays in diagnosis.
- Small intestinal biopsies are required to confirm the diagnosis of coeliac disease. However, a serology-based diagnosis is possible in selected patients with very high levels of coeliac-specific antibodies.
- Increased awareness about coeliac disease and better adherence to guidelines may lead to earlier diagnosis and better patient outcomes.

Availability of Data and Materials

Not applicable.

Author Contributions

Conception: MGS and HAP. Initial drafting of the manuscript: MGS. Critical revisions for important intellectual content, interpretation of data, and approval of the final version: MGS, NH, DSS and HAP. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

Mohamed G Shiha and Hugo A Penny received speaker honoraria from Thermo Fisher. The other authors declare no conflict of interest.

References

Alessio MG, Tonutti E, Brusca I, Radice A, Licini L, Sonzogni A, et al. Correlation between IgA tissue transglutaminase antibody ratio and histological finding in celiac disease. Journal of Pediatric Gastroenterology and Nutrition. 2012; 55: 44–49. https://doi.org/10.1097/MPG.0b013e3182470249

Al-Toma A, Volta U, Auricchio R, Castillejo G, Sanders DS, Cellier C, et al. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. United European Gastroenterology Journal. 2019; 7: 583–613. https://doi.org/10.1177/2050640619844125

Anderson RP. Review article: Diagnosis of coeliac disease: a perspective on current and future approaches. Alimentary Pharmacology & Therapeutics. 2022; 56: S18–S37. https://doi.org/10.1111/apt.16840

Antonius E, Kho Y, Roovers L, Wessels M. With or without biopsy in coeliac children?—Impact on dietary compliance and quality of life. European Journal of Pediatrics. 2024. (online ahead of print) https://doi.org/10.1007/s00431-024-05686-1

Arguelles-Grande C, Tennyson CA, Lewis SK, Green PHR, Bhagat G. Variability in small bowel histopathology reporting between different pathology practice settings: impact on the diagnosis of coeliac disease. Journal of Clinical Pathology. 2012; 65: 242–247. https://doi.org/10.1136/jclinpath-2011-200372

Balaban DV, Popp A, Vasilescu F, Haidautu D, Purcarea RM, Jinga M. Diagnostic yield of endoscopic markers for celiac disease. Journal of Medicine and Life. 2015; 8: 452–457.

Beam AL, Drazen JM, Kohane IS, Leong TY, Manrai AK, Rubin EJ. Artificial Intelligence in Medicine. The New England Journal of Medicine. 2023; 388: 1220–1221. https://doi.org/10.1056/NEJMe2206291

Beltran L, Koenig M, Egner W, Howard M, Butt A, Austin MR, et al. High-titre circulating tissue transglutaminase-2 antibodies predict small bowel villous atrophy, but decision cut-off limits must be locally validated. Clinical and Experimental Immunology. 2014; 176: 190–198. https://doi.org/10.1111/cei.12249

Cartee AK, Choung RS, King KS, Wang S, Dzuris JL, Anderson RP, et al. Plasma IL-2 and Symptoms Response after Acute Gluten Exposure in Subjects With Celiac Disease or Non-celiac Gluten Sensitivity. The American Journal of Gastroenterology. 2022; 117: 319–326. https://doi.org/10.14309/ajg.0000000000001565

Chow MA, Lebwohl B, Reilly NR, Green PHR. Immunoglobulin A deficiency in celiac disease. Journal of Clinical Gastroenterology. 2012; 46: 850–854. https://doi.org/10.1097/MCG.0b013e320122277

Ciacci C, Bai JC, Holmes G, Al-Toma A, Biagi F, Carroccio A, 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. The Lancet. Gastroenterology & Hepatology. 2023; 8: 1005–1014. https://doi.org/10.1016/S2468-1253(23)00205-4

Collin P, Vilppula A, Luostarinen L, Holmes GKT, Kaukinen K. Review article: coeliac disease in later life must not be missed. Alimentary Pharmacology & Therapeutics. 2018; 47: 563–572. https://doi.org/10.1111/apt.14490

Conrad N, Misra S, Verbakel JY, Verbeke G, Molenberghs G, Taylor PN, et al. Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: a population-based cohort study of 22 million individuals in the UK. Lancet. 2023; 401: 1878–1890. https://doi.org/10.1016/S0140-6736(23)00457-9

Dickey W, Hughes D. Disappointing sensitivity of endoscopic markers for villous atrophy in a high-risk population: implications for celiac disease diagnosis during routine endoscopy. The American Journal of Gastroenterology. 2001; 96: 2126–2128. https://doi.org/10.1111/j.1572-0241.2001.03947.x

Downey L, Houten R, Murch S, Longson D, Guideline Development Group. Recognition, assessment, and management of coeliac disease: summary of updated NICE guidance. BMJ (Clinical Research Ed.). 2015; 351: h4513. https://doi.org/10.1136/bmj.h4513

Dutta AK, Chacko A. Emerging role of narrow band imaging in duodenum. World Journal of Gastrointestinal Endoscopy. 2015; 7: 1216–1221. https://doi.org/10.4253/wjge.v7.i16.1216

Elfström P, Sundström J, Ludvigsson JF. Systematic review with meta-analysis: associations between coeliac disease and type 1 diabetes. Alimentary Pharmacology & Therapeutics. 2014; 40: 1123–1132. https://doi.org/10.1111/apt.12973

Elwenspoek MMC, Jackson J, O'Donnell R, Sinobas A, Dawson S, Everitt H, et al. The accuracy of diagnostic indicators for coeliac disease: A systematic review and meta-analysis. PLoS ONE. 2021; 16: e0258501. https://doi.org/10.1371/journal.pone.0258501

Evans KE, Aziz I, Cross SS, Sahota GRK, Hopper AD, Hadjivassiliou M, et al. A prospective study of duodenal bulb biopsy in newly diagnosed and established adult celiac disease. The American Journal of Gastroenterology. 2011; 106: 1837–1742. https://doi.org/10.1038/ajg.2011.171

Faraj SMS, Almndeel NSI, Alkheder RSF, Alhazmi TME. Physicians awareness of Celiac disease screening in high risk pediatric age groups in King Abdulaziz Medical City, National Guard Health Affairs, Riyadh, Saudi Arabia. Middle East Journal of Family Medicine. 2022; 7: 34. https://doi.org/10.5742/mewfm.2023.95251499

Fuchs V, Kurppa K, Huhtala H, Laurila K, Mäki M, Collin P, et al. Serology-based criteria for adult coeliac disease have excellent accuracy across the range of pre-test probabilities. Alimentary Pharmacology & Therapeutics. 2019; 49: 277–284. https://doi.org/10.1111/apt.15109

Fuchs V, Kurppa K, Huhtala H, Mäki M, Kekkonen L, Kaukinen K. Delayed celiac disease diagnosis predisposes to reduced quality of life and incremental use of health care services and medicines: A prospective nationwide study. United European Gastroenterology Journal. 2018; 6: 567–575. https://doi.org/10.1177/2050640617751253

Goel G, Tye-Din JA, Qiao SW, Russell AK, Mayassi T, Ciszewski C, et al. Cytokine release and gastrointestinal symptoms after gluten challenge in celiac disease. Science Advances. 2019; 5: eaaw7756. https://doi.org/10.1126/sciadv.aaw7756

Green PHR, Cellier C. Celiac disease. The New England Journal of Medicine. 2007; 357: 1731–1743. https://doi.org/10.1056/NEJMra071600

Greenaway EA, Raju SA, Sanders DS. Why Is There Medical Inertia and Nihilism to Celiac Disease? Comment on Pivetta et al. In Elderly Anemic Patients without Endoscopic Signs of Bleeding Are Duodenal Biopsies Always Necessary to Rule out Celiac Disease? *Diagnostics* 2022, *12*, 678. Diagnostics. 2022; 12: 1510. https://doi.org/10.3390/diagnostics12071510

Gulati S, Emmanuel A, Ong M, Pavlidis P, Patel M, El-Menabawey T, et al. Near-focus narrow-band imaging classification of villous atrophy in suspected celiac disease: development and international validation. Gastrointestinal Endoscopy. 2021; 94: 1071–1081. https://doi.org/10.1016/j.gie.2021.06.031

Guz-Mark A, Feldman BS, Ghilai A, Hoshen M, Cohen HA, Shkalim Zemer V, et al. High rates of serology testing for coeliac disease, and low rates of endoscopy in serologically positive children and adults in Israel: lessons from a large real-world database. European Journal of Gastroenterology & Hepatology. 2020; 32: 329–334. https://doi.org/10.1097/MEG.0000000000001613

Harper JW, Holleran SF, Ramakrishnan R, Bhagat G, Green PHR. Anemia in celiac disease is multifactorial in etiology. American Journal of Hematology. 2007; 82: 996–1000. https://doi.org/10.1002/ajh.20996

Hill PG, Holmes GKT. Coeliac disease: a biopsy is not always necessary for diagnosis. Alimentary Pharmacology & Therapeutics. 2008; 27: 572–577. https://doi.org/10.1111/j.1365-2036.2008.03609.x

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. 2008a; 40: 219–224. https://doi.org/10.1055/s-2007-995361

Hopper AD, Hadjivassiliou M, Hurlstone DP, Lobo AJ, McAlindon ME, Egner W, et al. What is the role of serologic testing in celiac disease? A prospective, biopsy-confirmed study with economic analysis. Clinical Gastroenterology and Hepatology. 2008b; 6: 314–320. https://doi.org/10.1016/j.cgh.2007.12.008

Hoyle A, Gillett P, Gillett HR, Borg R, Nottley S, Farrow S, et al. No-biopsy strategy for coeliac disease is applicable in adult patients: a 'real-world' Scottish experience. Frontline Gastroenterology. 2022; 14: 97–102. https://doi.org/10.1136/flgastro-2022-102254

Husby S, Koletzko S, Korponay-Szabó I, Kurppa K, Mearin ML, Ribes-Koninckx C, et al. European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020. Journal of Pediatric Gastroenterology and Nutrition. 2020; 70: 141–156. https://doi.org/10.1097/MPG.0000000000002497

Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips A, Shamir R, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. Journal of Pediatric Gastroenterology and Nutrition. 2012; 54: 136–160. https://doi.org/10.1097/MPG.0b013e3201223d0

Ianiro G, Bibbò S, Pecere S, Gasbarrini A, Cammarota G. Current technologies for the endoscopic assessment of duodenal villous pattern in celiac disease. Computers in Biology and Medicine. 2015; 65: 308–314. https://doi.org/10.1016/j.compbiomed.2015.04.033

Irvine AJ, Chey WD, Ford AC. Screening for Celiac Disease in Irritable Bowel Syndrome: An Updated Systematic Review and Meta-analysis. The American Journal of Gastroenterology. 2017; 112: 65–76. https://doi.org/10.1038/ajg.2016.466

Januszewicz W, Kaminski MF. Quality indicators in diagnostic upper gastrointestinal endoscopy. Therapeutic Advances in Gastroenterology. 2020; 13: 1756284820916693. https://doi.org/10.1177/1756284820916693

Joelson AM, Geller MG, Zylberberg HM, Green PHR, Lebwohl B. Numbers and Features of Patients With a Diagnosis of Celiac Disease Without Duodenal Biopsy, Based on a National Survey. Clinical Gastroenterology and Hepatology. 2019; 17: 1089–1097.e2. https://doi.org/10.1016/j.cgh.2018.09.006

Johnston RD, Chan YJ, Mubashar T, Bailey JR, Paul SP. No-biopsy pathway following the interim BSG guidance reliably diagnoses adult coeliac disease. Frontline Gastroenterology. 2022; 13: 73–76. https://doi.org/10.1136/flgastro-2020-101624

Jones MP, Ebert CC, Sloan T, Spanier J, Bansal A, Howden CW, et al. Patient anxiety and elective gastrointestinal endoscopy. Journal of Clinical Gastroenterology. 2004; 38: 35–40. https://doi.org/10.1097/00004836-200401000-00009

Karell K, Louka AS, Moodie SJ, Ascher H, Clot F, Greco L, et al. HLA types in celiac disease patients not carrying the DQA1*05-DQB1*02 (DQ2) heterodimer: results from the European Genetics Cluster on Celiac Disease. Human Immunology. 2003; 64: 469–477. https://doi.org/10.1016/s0198-8859(03)00027-2

Kårhus LL, Hansen S, Rumessen JJ, Linneberg A. Diagnostic Delay in Coeliac Disease: A Survey among Danish Patients. Canadian Journal of Gastroenterology & Hepatology. 2022; 2022: 5997624. https://doi.org/10.1155/2022/5997624

Kaukinen K. Updates on systemic consequences of coeliac disease. Nature Reviews. Gastroenterology & Hepatology. 2021; 18: 87–88. https://doi.org/10.1038/s41575-020-00387-0

Kaukinen K, Partanen J, Mäki M, Collin P. HLA-DQ typing in the diagnosis of celiac disease. The American Journal of Gastroenterology. 2002; 97: 695–699. https://doi.org/10.1111/j.1572-0241.2002.05471.x

Kelly CP, Bai JC, Liu E, Leffler DA. Advances in diagnosis and management of celiac disease. Gastroenterology. 2015; 148: 1175–1186. https://doi.org/10.1053/j.gastro.2015.01.044

King JA, Jeong J, Underwood FE, Quan J, Panaccione N, Windsor JW, et al. Incidence of Celiac Disease Is Increasing Over Time: A Systematic Review and Meta-analysis. The American Journal of Gastroenterology. 2020; 115: 507–525. https://doi.org/10.14309/ajg.0000000000000523

Latorre M, Lagana SM, Freedberg DE, Lewis SK, Lebwohl B, Bhagat G, et al. Endoscopic biopsy technique in the diagnosis of celiac disease: one bite or two? Gastrointestinal Endoscopy. 2015; 81: 1228–1233. https://doi.org/10.1016/j.gie.2014.10.024

Leffler DA, Schuppan D. Update on serologic testing in celiac disease. The American Journal of Gastroenterology. 2010; 105: 2520–2524. https://doi.org/10.1038/ajg.2010.276

Leonard MM, Silvester JA, Leffler D, Fasano A, Kelly CP, Lewis SK, et al. Evaluating Responses to Gluten Challenge: A Randomized, Double-Blind, 2-Dose Gluten Challenge Trial. Gastroenterology. 2021; 160: 720–733.e8. https://doi.org/10.1053/j.gastro.2020.10.040

Lionetti E, Pjetraj D, Gatti S, Catassi G, Bellantoni A, Boffardi M, et al. Prevalence and detection rate of celiac disease in Italy: Results of a SIGENP multicenter screening in school-age children. Digestive and Liver Disease. 2023; 55: 608–613. https://doi.org/10.1016/j.dld.2022.12.023

Ludvigsson JF, Bai JC, Biagi F, Card TR, Ciacci C, Ciclitira PJ, et al. Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. Gut. 2014; 63: 1210–1228. https://doi.org/10.1136/gutjnl-2013-306578

Lui TKL, Tsui VWM, Leung WK. Accuracy of artificial intelligence-assisted detection of upper GI lesions: a systematic review and meta-analysis. Gastrointestinal Endoscopy. 2020; 92: 821–830.e9. https://doi.org/10.1016/j.gie.2020.06.034

Mahadev S, Laszkowska M, Sundström J, Björkholm M, Lebwohl B, Green PHR, et al. Prevalence of Celiac Disease in Patients With Iron Deficiency Anemia-A Systematic Review With Meta-analysis. Gastroenterology. 2018; 155: 374–382.e1. https://doi.org/10.1053/j.gastro.2018.04.016

Majsiak E, Choina M, Cukrowska B. The Opinion of Polish Coeliac Patients on the Knowledge of Medical Professionals and Support Groups about Coeliac Disease-A Pilot Study. International Journal of Environmental Research and Public Health. 2023; 20: 3990. https://doi.org/10.3390/ijerph20053990

Malamut G, Cellier C. Complications of coeliac disease. Best Practice & Research. Clinical Gastroenterology. 2015; 29: 451–458. https://doi.org/10.1016/j.bpg.2015.05.005

Marsh MN. Grains of truth: evolutionary changes in small intestinal mucosa in response to environmental antigen challenge. Gut. 1990; 31: 111–114. https://doi.org/10.1136/gut.31.1.111

Mearns ES, Taylor A, Thomas Craig KJ, Puglielli S, Leffler DA, Sanders DS, et al. Neurological Manifestations of Neuropathy and Ataxia in Celiac Disease: A Systematic Review. Nutrients. 2019; 11: 380. https://doi.org/10.3390/nu11020380

Meresse B, Malamut G, Cerf-Bensussan N. Celiac disease: an immunological jigsaw. Immunity. 2012; 36: 907–919. https://doi.org/10.1016/j.immuni.2012.06.006

Mohseninejad L, Feenstra T, van der Horst HE, Woutersen-Koch H, Buskens E. Targeted screening for Coeliac Disease among irritable bowel syndrome patients: analysis of cost-effectiveness and value of information. The European Journal of Health Economics: HEPAC: Health Economics in Prevention and

Care. 2013; 14: 947–957. https://doi.org/10.1007/s10198-012-0441-4

Mubarak A, Nikkels P, Houwen R, Ten Kate F. Reproducibility of the histological diagnosis of celiac disease. Scandinavian Journal of Gastroenterology. 2011; 46: 1065–1073. https://doi.org/10.3109/00365521.2011.589471

Nazario E, Lasa J, Schill A, Duarte B, Berardi D, Paz S, et al. IgA Deficiency Is Not Systematically Ruled Out in Patients Undergoing Celiac Disease Testing. Digestive Diseases and Sciences. 2022; 67: 1238–1243. https://doi.org/10.1007/s10620-021-06939-x

Paul SP, Harries SL, Basude D. Barriers to implementing the revised ESPGHAN guidelines for coeliac disease in children: a cross-sectional survey of coeliac screen reporting in laboratories in England. Archives of Disease in Childhood. 2017; 102: 942–946. https://doi.org/10.1136/archdischild-2016-312027

Penny HA, Gillett H, Gillett P. BSG Interim Guidance: COVID-19 spcific non-biopsy protocol those with suspected coeliac disease [WWW Document]. 2020a. Available at: https://www.bsg.org.uk/covid-19-advice/covid-19-specific-non-biopsy-protocol-guidance-for-those-with-suspected-coeliac-disease/ (Accessed: 9 December 2023).

Penny HA, Raju SA, Lau MS, Marks LJ, Baggus EM, Bai JC, et al. Accuracy of a no-biopsy approach for the diagnosis of coeliac disease across different adult cohorts. Gut. 2021; 70: 876–883. https://doi.org/10.1136/gutjnl-2020-320913

Penny HA, Raju SA, Sanders DS. Progress in the serology-based diagnosis and management of adult celiac disease. Expert Review of Gastroenterology & Hepatology. 2020b; 14: 147–154. https://doi.org/10.1080/17474124.2020.1725472

Previtali G, Licini L, D'Antiga L, Marseglia A, Ravasio R, Nembrini F, et al. Celiac Disease Diagnosis Without Biopsy: Is a 10× ULN Antitransglutaminase Result Suitable for a Chemiluminescence Method? Journal of Pediatric Gastroenterology and Nutrition. 2018; 66: 645–650. https://doi.org/10.1097/MPG.0000000000001773

Quraishi MN, Dobson E, Ainley R, Din S, Wakeman R, Cummings F, et al. Establishing key performance indicators for inflammatory bowel disease in the UK. Frontline Gastroenterology. 2023; 14: 407–414. https://doi.org/10.1136/flgastro-2023-102409

Ravelli A, Villanacci V, Monfredini C, Martinazzi S, Grassi V, Manenti S. How patchy is patchy villous atrophy? Distribution pattern of histological lesions in the duodenum of children with celiac disease. The American Journal of Gastroenterology. 2010; 105: 2103–2110. https://doi.org/10.1038/ajg.2010.153

Rettally C. Duodenal Biopsies: Individual or Multiple Samples? The American Journal of Gastroenterology. 2023; 118: 911–912. https://doi.org/10.14309/ajg.0000000000002229

Riznik P, De Leo L, Dolinsek J, Gyimesi J, Klemenak M, Koletzko B, et al. The Knowledge About Celiac Disease Among Healthcare Professionals and Patients in Central Europe. Journal of Pediatric Gastroenterology and Nutrition. 2021; 72: 552–557. https://doi.org/10.1097/MPG.0000000000003019

Rubio-Tapia A, Hill ID, Semrad C, Kelly CP, Greer KB, Limketkai BN, et al. American College of Gastroenterology Guidelines Update: Diagnosis and Management of Celiac Disease. The American Journal of Gastroenterology. 2023; 118: 59–76. https://doi.org/10.14309/ajg.0000000000002075

Sahin Y, Sevinc E, Bayrak NA, Varol FI, Akbulut UE, Bükülmez A. Knowledge regarding celiac disease among healthcare professionals, patients and their caregivers in Turkey. World Journal of Gastrointestinal Pathophysiology. 2022; 13: 178–185. https://doi.org/10.4291/wjgp.v13.i6.178

Sanders DS, Hurlstone DP, Stokes RO, Rashid F, Milford-Ward A, Hadjivassiliou M, et al. Changing face of adult coeliac disease: experience of a single university hospital in South Yorkshire. Postgraduate Medical Journal. 2002; 78: 31–33. https://doi.org/10.1136/pmj.78.915.31

Sarna VK, Lundin KEA, Mørkrid L, Qiao SW, Sollid LM, Christophersen A. HLA-DQ-Gluten Tetramer Blood Test Accurately Identifies Patients With and Without Celiac Disease in Absence of Gluten Consumption. Gastroenterology. 2018a; 154: 886–896.e6. https://doi.org/10.1053/j.gastro.2017.11.006

Sarna VK, Skodje GI, Reims HM, Risnes LF, Dahal-Koirala S, Sollid LM, et al. HLA-DQ:gluten tetramer test in blood gives better detection of coeliac patients than biopsy after 14-day gluten challenge. Gut. 2018b; 67: 1606–1613. https://doi.org/10.1136/gutjnl-2017-314461

Scheppach MW, Rauber D, Stallhofer J, Muzalyova A, Otten V, Manzeneder C, et al. Detection of duodenal villous atrophy on endoscopic images using a deep learning algorithm. Gastrointestinal Endoscopy. 2023;

97: 911–916. https://doi.org/10.1016/j.gie.2023.01.006

Schiepatti A, Maimaris S, Raju SA, Green OL, Mantica G, Therrien A, et al. Persistent villous atrophy predicts development of complications and mortality in adult patients with coeliac disease: a multicentre longitudinal cohort study and development of a score to identify high-risk patients. Gut. 2023; 72: 2095–2102. https://doi.org/10.1136/gutjnl-2023-329751

Schiepatti A, Rej A, Maimaris S, Cross SS, Porta P, Aziz I, et al. Clinical classification and long-term outcomes of seronegative coeliac disease: a 20-year multicentre follow-up study. Alimentary Pharmacology & Therapeutics. 2021; 54: 1278–1289. https://doi.org/10.1111/apt.16599

Sheppard AL, Elwenspoek MMC, Scott LJ, Corfield V, Everitt H, Gillett PM, et al. Systematic review with meta-analysis: the accuracy of serological tests to support the diagnosis of coeliac disease. Alimentary Pharmacology & Therapeutics. 2022; 55: 514–527. https://doi.org/10.1111/apt.16729

Shiha MG, Marks LJ, Sanders DS. Diagnosing coeliac disease in the elderly: a United Kingdom cohort study. Gastroenterology and Hepatology from Bed to Bench. 2020; 13: 37–43.

Shiha MG, Nandi N, Hutchinson AJ, Raju SA, Tai FWD, Elli L, et al. Cost-benefits and environmental impact of the no-biopsy approach for the diagnosis of coeliac disease in adults. Frontline Gastroenterology. 2024a; 15: 95–98. https://doi.org/10.1136/flgastro-2023-102494

Shiha MG, Oka P, Raju SA, Tai FWD, Ching HL, Thoufeeq M, et al. Artificial intelligence–assisted colonoscopy for adenoma and polyp detection: an updated systematic review and meta-analysis. iGIE. 2023; 2: 333–343.e8. https://doi.org/10.1016/j.igie.2023.05.001

Shiha MG, Nandi N, Oka P, Raju SA, Penny HA, Hopper AD, et al. Narrow-band imaging for optical diagnosis of duodenal villous atrophy in patients with suspected coeliac disease: A systematic review and meta-analysis. Digestive and Liver Disease. 2024b; 56: 971–977. https://doi.org/10.1016/j.dld.2023.08.053

Shiha MG, Nandi N, Raju SA, Wild G, Cross SS, Singh P, et al. Accuracy of the No-Biopsy Approach for the Diagnosis of Celiac Disease in Adults: A Systematic Review and Meta-Analysis. Gastroenterology. 2024c; 166: 620–630. https://doi.org/10.1053/j.gastro.2023.12.023

Singh P, Arora A, Strand TA, Leffler DA, Catassi C, Green PH, et al. Global Prevalence of Celiac Disease: Systematic Review and Meta-analysis. Clinical Gastroenterology and Hepatology. 2018; 16: 823–836.e2. https://doi.org/10.1016/j.cgh.2017.06.037

Singh P, Arora S, Lal S, Strand TA, Makharia GK. Risk of Celiac Disease in the First- and Second-Degree Relatives of Patients With Celiac Disease: A Systematic Review and Meta-Analysis. The American Journal of Gastroenterology. 2015; 110: 1539–1548. https://doi.org/10.1038/ajg.2015.296

Snook J, Bhala N, Beales ILP, Cannings D, Kightley C, Logan RP, et al. British Society of Gastroenterology guidelines for the management of iron deficiency anaemia in adults. Gut. 2021; 70: 2030–2051. https://doi.org/10.1136/gutjnl-2021-325210

Spolski R, Li P, Leonard WJ. Biology and regulation of IL-2: from molecular mechanisms to human therapy. Nature Reviews. Immunology. 2018; 18: 648–659. https://doi.org/10.1038/s41577-018-0046-y

Stefanolo JP, Zingone F, Gizzi C, Marsilio I, Espinet ML, Smecuol EG, et al. Upper gastrointestinal endoscopic findings in celiac disease at diagnosis: A multicenter international retrospective study. World Journal of Gastroenterology. 2022; 28: 6157–6167. https://doi.org/10.3748/wjg.v28.i43.6157

Steiner TJ, Stovner LJ, Vos T, Jensen R, Katsarava Z. Migraine is first cause of disability in under 50s: will health politicians now take notice? The Journal of Headache and Pain. 2018; 19: 17. https://doi.org/10.1186/s10194-018-0846-2

Sun X, Lu L, Yang R, Li Y, Shan L, Wang Y. Increased Incidence of Thyroid Disease in Patients with Celiac Disease: A Systematic Review and Meta-Analysis. PLoS ONE. 2016; 11: e0168708. https://doi.org/10.1371/journal.pone.0168708

Taylor MA, Blanshard RJ, Naylor G, Penny HA, Mooney PD, Sanders DS. Do gastroenterologists have medical inertia towards coeliac disease? A UK multicentre secondary care study. BMJ Open Gastroenterology. 2021; 8: e000544. https://doi.org/10.1136/bmjgast-2020-000544

Tye-Din JA, Daveson AJM, Ee HC, Goel G, MacDougall J, Acaster S, et al. Elevated serum interleukin-2 after gluten correlates with symptoms and is a potential diagnostic biomarker for coeliac disease. Alimentary Pharmacology & Therapeutics. 2019; 50: 901–910. https://doi.org/10.1111/apt.15477

Vasant DH, Paine PA, Black CJ, Houghton LA, Everitt HA, Corsetti M, et al. British Society of Gastroenterology guidelines on the management of irritable bowel syndrome. Gut. 2021; 70: 1214–1240. https://doi.org/10.1136/gutjnl-2021-324598

Villanacci V, Del Sordo R, Casella G, Becheanu G, Oberti A, Belfekih B, et al. The correct methodological approach to the diagnosis of celiac disease: the point of view of the pathologist. Gastroenterology and Hepatology from Bed to Bench. 2023; 16: 129–135. https://doi.org/10.22037/ghfbb.v16i2.2704

Wei JW, Wei JW, Jackson CR, Ren B, Suriawinata AA, Hassanpour S. Automated Detection of Celiac Disease on Duodenal Biopsy Slides: A Deep Learning Approach. Journal of Pathology Informatics. 2019; 10: 7. https://doi.org/10.4103/jpi.jpi_87_18

Werkstetter KJ, Korponay-Szabó IR, Popp A, Villanacci V, Salemme M, Heilig G, et al. Accuracy in Diagnosis of Celiac Disease Without Biopsies in Clinical Practice. Gastroenterology. 2017; 153: 924–935. https://doi.org/10.1053/j.gastro.2017.06.002

West J, Otete H, Sultan AA, Crooks CJ. Changes in Testing for and Incidence of Celiac Disease in the United Kingdom: A Population-based Cohort Study. Epidemiology. 2019; 30: e23–e24. https://doi.org/10.1097/EDE.0000000000001006

Wojciechowska K, Ślósarz T, Turek M, Piątkowska K, Walęcik-Kot W. Celiac Disease and Migraine Headaches: Current Knowledge and Future Directions. Journal of Education, Health and Sport. 2023; 36: 75–81. https://doi.org/10.12775/JEHS.2023.36.01.008

Working group set up by the Finnish Medical Society Duodecim and the Finnish Gastroenterology Society. Celiac disease. Current care guidelines [WWW Document]. 2018. Available at: https://www.kaypahoito.fi/hoi08001 (Accessed: 9 December 2023).