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European Society for the Study of Coeliac Disease 2025 Updated Guidelines on the Diagnosis and Management of Coeliac Disease in Adults. Part 1: Diagnostic Approach

Abdulbaqi Al-Toma[1] | Fabiana Zingone[2,3] | Federica Branchi[4] | Annalisa Schiepatti[5,6] | Georgia Malamut[7,8] | Cristina Canova[9] | Isabella Rosato[9] | Honoria Ocagli[9] | Nick Trott[10,11] | Luca Elli[12,13] | Alina Popp[14] | Carmen Gianfrani[15] | Renata Auricchio[16] | Andra Neefjes-Borst[17] | David S. Sanders[10] | Christophe Cellier[18] | Chris J. Mulder[19] | Gerd Bouma[19] | Knut E. A. Lundin[20,21,22] | Ludvig M. Sollid[21] | Michael Schumann[4]

[1]Department of Gastroenterology and Hepatology, St Antonius Hospital, Nieuwegein, the Netherlands | [2]Department of Surgery, Oncology and Gastroenterology, University of Padova, Padua, Italy | [3]Unit of Gastroenterology, Azienda Ospedale Università Padova, Padua, Italy | [4]Charité—Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Medizinische Klinik für Gastroenterologie, Infektiologie und Rheumatologie, Berlin, Germany | [5]Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy | [6]Istituti Clinici Scientifici Maugeri IRCCS, Gastroenterology Unit of Pavia Institute, Pavia, Italy | [7]Department of Gastroenterology, AP-HP. Centre- Université Paris Cité, Hôpital Cochin, Paris, France | [8]Université de Paris, INSERM UMR 1163 and Imagine Institute, Laboratory of Intestinal Immunity, Université Paris Cité, Paris, France | [9]Unit of Biostatistics, Epidemiology and Public Health, Department of Cardiac, Thoracic, Vascular Sciences, and Public Health, University of Padova, Padova, Italy | [10]Academic Unit of Gastroenterology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK | [11]Division of Clinical Medicine, School of Medicine and Population Health, University of Sheffield, Sheffield, UK | [12]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy | [13]Centre for Prevention and Diagnosis of Coeliac Disease-Gastroenterology and Endoscopy Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy | [14]University of Medicine and Pharmacy "Carol Davila", National Institute for Mother and Child Health, Bucharest, Romania | [15]Institute of Biochemistry and Cell Biology-CNR, Naples, Italy | [16]Department of Translational Medicine & European Laboratory for the Investigation of Food-Induced Diseases, University Federico II, Naples, Italy | [17]Department of Pathology, Amsterdam University Medical Centre, Amsterdam, the Netherlands | [18]Department of Gastroenterology and Endoscopy, CELAC Network, AP-HP Centre, Hôpital Européen Georges Pompidou, Université de Paris, Cité and Institut National du Cancer, Paris, France | [19]Department of Gastroenterology, Amsterdam University Medical Centre, Amsterdam, the Netherlands | [20]Department of Gastroenterology, Oslo University Hospital, Rikshospitalet, Oslo, Norway | [21]Norwegian Coeliac Disease Research Centre, Institute of Clinical Medicine, University of Oslo, Oslo, Norway | [22]Department of Immunology, Oslo University Hospital, Rikshospitalet, Oslo, Norway

Correspondence: Abdulbaqi Al-Toma (a.altoma@antoniusziekenhuis.nl)

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ABSTRACT

Introduction: Since the publication of the first European Society for the Study of Coeliac Disease (ESsCD) guidelines in 2019, significant advancements have emerged in the diagnosis of coeliac disease (CeD) in adults. These 2025 guidelines incorporate new evidence to refine diagnostic strategies, aiming for improved accuracy of testing, and enhance overall quality of clinical care.

Abbreviations: AGA, Antigliadin Antibodies; CeD, Coeliac Disease; CoE, Certainty of Evidence; DAE, Device-Assisted Enteroscopy; DGP, Deamidated Gluten Peptides; DH, Dermatitis Herpetiformis; EATL, Enteropathy-associated T cell Lymphoma; ESPGHAN, European Society Paediatric Gastroenterology, Hepatology and Nutrition; ESsCD, European Society for the Study of Coeliac Disease; GFD, Gluten-Free Diet; HLA, Human Leucocyte Antigen; IBD, Inflammatory Bowel Disease; IBS, Irritable Bowel Syndrome; IEL, Intraepithelial Lymphocytes; IgA anti-EMA, anti-Endomysial Antibodies; NCWS, Non-Coeliac Wheat Sensitivity; NPV, Negative Predictive Value; POCT, Point-of-care testing; PPV, Positive Predictive Value; SNCD, Seronegative Coeliac Disease; T1DM, Type 1 Diabetes Mellitus; TG2, Tissue Transglutaminase 2; UGPS, Ungraded Good Practice Statement; ULN, Upper Limit of Normal; VCE, Video Capsule Endoscopy.

Methods: A multidisciplinary panel of experts revised the ESsCD guidelines using the AGREE II instrument (Appraisal of Guidelines for Research and Evaluation II) and the GRADE methodology (The Grading of Recommendations Assessment, Development, and Evaluation). Clinical questions were structured using the PICO format, and statements and recommendations were finalised through a Delphi consensus process. Literature quality was assessed using AMSTAR-2 and QUADAS-2 tools.
Results: The updated guidelines are presented in two parts. Part 1 focuses on adult CeD diagnosis, introducing major changes such as a conditional no-biopsy approach for selected adults with high-titre IgA anti-TG2 serology (≥ 10 × ULN). Regarding serology, the use of validated high-performance ELISAs displaying a high diagnostic accuracy is emphasised, while routine use of IgA anti-Endomysium serology is no longer recommended for confirmation. Revised duodenal biopsy protocols now mandate at least four samples from the second part of the duodenum, with bulb biopsies conditionally included. The guidelines provide structured approaches for diagnosing potential CeD, seronegative villous atrophy, and CeD in individuals already on a gluten-free diet. HLA-DQ2/DQ8 typing is recommended for diagnostic clarification in select cases.
Conclusions: The updated 2025 ESsCD guidelines provide a comprehensive framework for the diagnosis of CeD in adults. By integrating evolving diagnostic strategies, minimising over-testing, and patient-centred care approaches, they aim to optimise patient outcomes, quality of life and use of diagnostic resources at the same time.

1 | Introduction

The updated guidelines for coeliac disease (CeD), presented in two parts, provide a comprehensive revision of the 2019 European Society for the Study of Coeliac Disease (ESsCD) Guidelines on the Management of CeD and Other Gluten-Related Disorders. Part 1 focuses on the diagnosis of CeD in adults, while Part 2 addresses its management, follow-up, and the approach to non-responsive and refractory CeD [1].

The major changes to the approach for diagnosing CeD in adults compared to the 2019 version are:

1. *Serological Testing*: IgA anti-TG2 remains the primary screening test. Routine use of IgA anti-endomysium serology is no longer recommended, but it may be reserved for ambiguous cases to improve diagnostic accuracy and cost-effectiveness. Instead, validated high-performance IgA anti-TG2 assays should be used for diagnosis.
2. *Standardised Biopsy Protocols and Histological Reporting*: A minimum of four biopsies from the second part of the duodenum and two from the duodenal bulb is mandated. The modified Marsh classification remains the reference standard.
3. *Introduction of a No-Biopsy Diagnostic Option for Adults*: An approach to establish a CeD diagnosis in a patient with the suspicion for CeD without performing an endoscopy to collect duodenal mucosal biopsies is now conditionally recommended for adults under 45 years with IgA anti-TG2 levels ≥ 10 × the upper limit of normal (ULN). A confirmation of the coeliac serology in a second blood sample is required.
4. *Expanded Guidance for Difficult-to-Diagnose Cases*: New structured approaches are provided for potential CeD, seronegative villous atrophy, and cases diagnosed after a gluten-free diet (GFD) has already been initiated.
5. *Clarified Approach to Marsh-I Histological Stage*: negative serology with Marsh-I stage makes CeD unlikely; alternative causes should be sought.
6. *Role for HLA-DQ2/8 typing*: Although not routinely used, HLA-DQ2/8 typing is recommended when there is uncertainty about the diagnosis (e.g., ambiguous results, GFD started before testing, potential CeD, or seronegative cases) and in the screening of certain risk groups for developing CeD.
7. *Clarification on Use of Point-of-Care and Non-Blood Tests*: A positive POCT result should always be confirmed by formal serologic testing and, if appropriate, duodenal biopsy. The guidelines discourage the use of saliva and stool-based tests due to poor diagnostic performance.
8. *Patient-Centred Diagnostic Approach*: shared decision-making, particularly around the no-biopsy option or when deciding on a gluten challenge, with a focus on reducing unnecessary procedures while ensuring diagnostic certainty.

Together, these updates present a more streamlined and accurate diagnostic process, improve alignment with current clinical realities, and prioritize the reduction of unnecessary procedures in appropriate patient populations.

2 | Summary of Recommendations

Table 1 shows an overview of the recommendations and (sub-) statements.

3 | Methodology

3.1 | Aims of the Guidelines and Specific Objectives

The guidelines present an update to the 2019 European Society for the Study of Coeliac Disease (ESsCD) Guidelines on the Management of CeD and Other Gluten-Related Disorders [1]. Part 1 of the guidelines provides a comprehensive framework for the clinical management of CeD in adults, addressing the indications for serologic testing, diagnostic algorithms, and the

TABLE 1 | Overview of recommendations and statements regarding diagnostic approach to coeliac disease in adults.

Section and number	Statement/recommendation	Certainty of evidence	Grade of recommendation	Agreement (%)
Serological testing for CeD in adults				
Q.II.1. Which serological test is most suitable for initial testing for CeD?	We recommend: 1. IgA anti-tissue transglutaminase (TG2) antibody as a single test for initial testing for CeD at any age. 2. Measure total IgA concurrently to exclude IgA deficiency. 3. Perform testing while the patient is on a gluten-containing diet.	Moderate	Strong	95
Q.II.2. How does the technical performance of the CeD serological assays affect the diagnostic accuracy and outcome of a specific test?	Standardized serological assays with proven sensitivity, specificity, and reproducibility are essential for improving CeD diagnosis. Widely validated anti-TG2 antibody tests should remain central to this process. However, achieving global standardization of assay quality remains challenging, underscoring the need for certification systems and clear guidance for healthcare providers.	Moderate	Strong	95
Q.II.3. How is the quality of serological assays for CeD controlled?	Anti-TG2 ELISA tests target conformational epitopes but are prone to variability in assay design and quality control, potentially affecting performance. Reliable results require rigorously validated tests with strict quality control and external quality assurance participation. A certification system for assay standardization could enhance consistency and reliability across laboratories.	Low	Strong	100
Q.II.4. For initial testing in suspected coeliac disease, is there a rationale for using a combination of multiple serological tests?	We recommend against the routine combination of serological tests for the initial diagnosis of CeD, due to minimal added value and potentially increasing cost and complexity.	Low-moderate	Strong	95
Q.II.5. Is anti-endomysial antibody (IgA anti-EMA) testing required as a confirmatory test for diagnosing CeD?	Although IgA anti-EMA tests are highly specific, their labour-intensive nature and limited availability reduce their role in routine adult CeD diagnostics. However, they can be reserved for unclear cases to ensure diagnostic accuracy and cost-effectiveness, such as in patients with other autoimmune or liver diseases before proceeding with a duodenal biopsy.	Low	Conditional	95
Q.II.6. How to test for CeD in patients with IgA deficiency?	In patients with confirmed total IgA deficiency, CeD serology should be performed using IgG-based assays, such as IgG anti-TG2 or IgG anti-DGP	Low	Strong	100

(Continues)

TABLE 1 | (Continued)

Section and number	Statement/recommendation	Certainty of evidence	Grade of recommendation	Agreement (%)
	antibodies. Due to the lower sensitivity of these tests, a negative IgG result does not exclude the diagnosis. In individuals with signs of malabsorption suggestive of CeD, upper GI endoscopy with duodenal biopsies should be undertaken regardless of IgG serology results.			
Q.II.7. What is the diagnostic accuracy of stool and saliva serological tests for CeD?	Saliva and faecal tests for CeD have low sensitivity and specificity, therefore, their use in clinical practice should be discouraged.	Low	Strong	100
Histopathology				
Q.III.1. What is the recommended number and location of duodenal biopsies for CeD diagnosis?	For the diagnosis of CeD, it is recommended to take at least four biopsies from the distal duodenum, plus two from the duodenal bulb.	Moderate	Strong	100
Q.III.2. Do the sub-classifications (A, B, C) of Marsh-III stage in the modified Marsh classification add clinically relevant information?	The Marsh-III stage sub-classifications (A, B, C) in the modified Marsh classification describe mucosal damage in CeD but have limited clinical relevance in routine practice. They do not significantly influence treatment decisions or outcomes but may help monitor inflammatory activity.	Low	Conditional	95
Q.III.3. How should duodenal biopsies be processed for optimal evaluation in CeD diagnosis?	For optimal histopathological assessment in CeD, well-oriented duodenal biopsies are essential. Haematoxylin and Eosin (H & E) staining is recommended for routine diagnostic purposes.	Moderate	Strong	100
Q.III.4. What is the impact of interobserver variability in the histological interpretation of duodenal biopsies for coeliac disease, and how can diagnostic agreement be improved?	There is substantial interobserver variability in the histological interpretation of duodenal biopsies for coeliac disease, particularly in cases with mild or borderline mucosal changes (e.g., Marsh I–II). To enhance diagnostic accuracy and consistency, histological assessment should be performed in conjunction with clinical and serological information. The use of classification systems (the modified Marsh classification), comprehensive pathology reporting, and adequate biopsy sampling are essential components of high-quality diagnostic practice.	Low	Ungraded good practice statement (UGPS)	95
Q.III.5. Can advanced endoscopic techniques replace standard histopathology in the assessment of	While advanced endoscopic techniques enhance mucosal assessment, they do not replace standard histopathology for diagnosis	Low	UGPS	100

(Continues)

TABLE 1 | (Continued)

Section and number	Statement/recommendation	Certainty of evidence	Grade of recommendation	Agreement (%)
small bowel mucosal damage in CeD?	of CeD. Instead, they may serve as valuable adjuncts that reduce unnecessary biopsies and improve targeted sampling.			
Confirmation of CeD diagnosis in adults				
Q.IV.1.1. How can the diagnosis of CeD in adults be established?	A positive CeD-specific serology in patients with Marsh-II stage or Marsh-III stage confirms the diagnosis of CeD.	High	Strong	100
Q.IV.1. 2. Can diagnosis be made solely on serology without histological confirmation (the no-biopsy approach)?	The confirmation of a CeD diagnosis in adults can be based on positive serology only (no-biopsy approach), when the initial IgA anti-TG2 level ≥ 10 times the upper limit of normal (ULN).	Moderate	Conditional	95
	Key considerations include:			
	The initial IgA anti-TG2 result needs to be confirmed in a second blood sample. The patient must remain on a gluten-containing diet until confirmation. In this independent blood sample any positive result should be considered confirmatory.	NA	Ungraded expert opinion	95
	The decisions on omission of endoscopy/duodenal biopsies and confirmation of the final diagnosis should be made in secondary health care settings.	NA	UGPS	
	A shared decision-making with the patient regarding the potential benefits and limitations of omitting duodenal biopsies is crucial.	NA	UGPS	
	This approach is not appropriate, if red flags for alternative conditions are present (e.g., haematochezia, dysphagia, or signs of obstruction).	NA	UGPS	
	Until more safety data are available, the no-biopsy approach should be limited to patients under 45 years.	Low	Ungraded expert opinion	
Q.IV.1.3. Can symptom response to gluten withdrawal reliably predict a coeliac disease diagnosis?	Improvement of symptoms after gluten withdrawal or exacerbation after re-introduction of gluten has a very low predictive value for CeD and should not be used for diagnosis in the absence of other supportive evidence.	NA	UGPS	100
Q.IV.2. Can the diagnosis of CeD be made in individuals with persistently positive CeD serology but architecturally normal duodenal histology?	In adults with persistently positive IgA anti-TG2 serology but architecturally normal duodenal histology (Marsh 0–I), a definitive diagnosis of CeD cannot be established. However, if these individuals carry the HLA-DQ2 and/or	Low	Strong	95

(Continues)

TABLE 1 | (Continued)

Section and number	Statement/recommendation	Certainty of evidence	Grade of recommendation	Agreement (%)
	DQ8 haplotype, they may be classified as having potential coeliac disease.			
Q.IV.3. What is the approach to Marsh-I stage with negative CeD serology?	In cases of Marsh-I stage with negative coeliac disease serology, CeD is unlikely, and other causes should be explored.	Low	Strong	100
Q.IV.4. What is the approach to villous atrophy in the absence of CeD-specific serology?	After excluding other causes of seronegative villous atrophy, diagnosis of CeD should rely on the clinical and histological response to a GFD in individuals with HLA-DQ2 or HLA-DQ8 haplotypes.	Low	Strong	95
Q.IV.5. What is the role of HLA-DQ typing in the screening for and diagnosis of CeD?	HLA testing has a poor positive predictive value (PPV) but a high negative predictive value (NPV) for CeD; therefore, the guideline panel recommends that HLA-DQ2/8 testing should not be used routinely in the initial diagnosis of CeD. It is indicated when there is uncertainty about the diagnosis and in the screening of certain risk groups for developing CeD.	Moderate	Strong	100
Q.IV.8. How to diagnose CeD in adults who are already following a GFD without the diagnosis having been made?	A gluten challenge is required if a patient suspected of having CeD has reduced or eliminated gluten from the diet before appropriate diagnostic evaluation. Key considerations include:) 1. The indication, test requirements, and implications of possible outcomes should be discussed with the patient at the outset. This ensures informed decision-making and improves tolerance and convenience during the testing period. 2. Confirm HLA-DQ2/DQ8 before starting a gluten challenge, as a negative result rules out CeD. 3. A minimum of 3 g/day gluten for 6 weeks balances diagnostic accuracy and extent of discomfort. Higher doses or longer durations improve precision if tolerated. Adjustments based on patient preference and symptom tolerance can enhance adherence. 4. Duodenal histology is the preferred endpoint for the gluten challenge. Symptom monitoring and serology can provide additional diagnostic certainty. However, serology may be considered a substitute for histology	Low	Strong	100

(Continues)

TABLE 1 | (Continued)

Section and number	Statement/recommendation	Certainty of evidence	Grade of recommendation	Agreement (%)
	when the IgA anti-TG2 titre is ≥ 10 times the ULN. 5. Patients need guidance on gluten intake. Low-FODMAP gluten foods help reduce symptoms, and intake can be spread out throughout the day.			
Q.IV.9. When Non-Coeliac Wheat Sensitivity (NCWS) can be considered and what are the requirements to make a diagnosis of NCWS?	NCWS may be considered in patients with reproducible gluten-related intestinal and/or extra-intestinal complaints who have normal CeD serology and wheat allergy (WA) tests while on a gluten-containing diet and after the exclusion of major organic GI disorders. However, it is important to acknowledge the potential role of the nocebo effect in symptom development, as clinical manifestation in NCWS may be influenced by expectancy and actual gluten intake.	Moderate	Strong	89

Abbreviations: AGA, Antigliadin Antibodies; CeD, Coeliac Disease; CoE, Certainty of Evidence; DGP, Deamidated Gluten Peptides; GFD, Gluten-Free Diet; GI, Gastrointestinal; HLA, Human Leucocyte Antigen; IEL, Intraepithelial Lymphocytes; IgA anti-EMA, anti-Endomysial antibodies; NCWS, Non-Coeliac Wheat Sensitivity; NPV, Negative Predictive Value; PPV, Positive Predictive Value; SNCD, Seronegative Coeliac Disease; TG2, Tissue Transglutaminase 2; UGPS, Ungraded Good Practice Statement; ULN, Upper Limit of Normal.

criteria required to confirm the diagnosis. The guidelines also delineate appropriate circumstances for gluten challenge and HLA genotyping.

In the second part of the guidelines, management strategies are going to be dealt with, including the principles of a GFD, the role of multidisciplinary support, and preventive care measures (e.g., immunisations and strategies to mitigate bone mineral density loss). Guidance is also provided on the monitoring of GFD adherence. Finally, a systematic approach is outlined for the assessment and management of patients with delayed symptomatic response to a GFD and those with suspected or confirmed refractory coeliac disease.

The overall objective of these guidelines is to provide evidence-based recommendations for the diagnosis and management of CeD in adults.

3.2 | Target Users

The target users of the guidelines are clinicians involved in the care of adult patients with CeD.

Policy makers interested in these guidelines include those involved in developing local, national or international plans dealing with care for CeD. This document may also serve as the basis for adaptation by local, regional or national guideline panels.

3.3 | Organisation, Panel Composition, Planning and Coordination

The ESsCD Governing Board appointed a panel of experts to develop these guidelines. The entire group consisted of 21 members from different European countries, including gastroenterologists, paediatricians, immunologist, pathologists, dietitians and statisticians with expertise in scientific methodology, evidence-based medicine and clinical and therapeutic management of CeD. A total of six working groups were established (1: serology in CeD; 2: histopathological diagnosis; 3: diagnosis; 4: management; 5: follow-up and monitoring; 6: non-responsive and refractory CeD), each consisting of 3–4 group members.

The Association of European Coeliac Societies (AOECS), which is an umbrella organisation of European member societies which represents the interests of people affected by CeD, was consulted at an early stage in the preparation process. The AOECS has reviewed the manuscript and provided insights regarding the management of CeD from patients' organisations perspectives.

The panel's initial task was to review the previous ESsCD guidelines published in 2019 and identify topics that had recently seen significant changes, but also to fully revise the evidence for all the fundamental sections of the 2019 guidelines. Initially, each subgroup identified key clinical questions in their area, and the entire group then finalized the set of questions to address.

3.4 | Literature Search and Assessment of Evidence

A comprehensive literature search was conducted across PubMed, Embase, Google Scholar, and Scopus, with keywords including 'coeliac', 'coeliac', 'non-tropical sprue', 'gluten', 'dermatitis herpetiformis', 'enteropathy', and 'ataxia', without language restrictions.

The search strategy was based on the PICO (Population, Intervention, Comparator, Outcome) framework, ensuring that relevant studies were identified for each clinical question. We included systematic reviews and other documents providing a critical synthesis of the scientific literature, as well as randomized clinical trials when available. Primary studies already included in systematic reviews were not assessed separately, as we prioritised the systematic reviews. When primary studies overlapped across systematic reviews, all relevant reviews were retained and included in the assessment of the certainty of evidence. In cases where high-quality systematic reviews were unavailable or outdated, individual primary studies published after the last search date were identified and considered to maintain a current evidence base.

The panel identified and prioritized critical and important outcomes based on their relevance to clinical decision-making and patient-centred care. For each included publication, data were extracted regarding the study characteristics, including objectives, participants and setting, interventions, study design, main results and conclusions, which were summarised in tables according to each PICO question (Supporting Information S1).

The methodological quality of the included systematic reviews and meta-analyses was assessed using AMSTAR-2 (A MeaSurement Tool to Assess Systematic Reviews 2), which evaluates methodological rigour and transparency across several domains. The quality of diagnostic accuracy studies was assessed using QUADAS-2 (Quality Appraisal Tool for Diagnostic Accuracy Studies), which evaluates study design, risk of bias, and methodological soundness (Supporting Information S1) [2, 3].

3.5 | Grading of Evidence and Recommendations

These guidelines were developed following the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology (https://www.gradeworkinggroup.org/) to ensure a transparent, systematic, and evidence-based approach to formulating recommendations for the management of coeliac disease. The GRADE method was consistently applied to assess both the certainty of evidence and the strength of recommendations.

For each PICO question, summary of findings tables were created, providing information on the number and type of studies assessed for each outcome of interest, as well as the certainty of evidence (Supporting Information S1). In accordance with the GRADE methodology, studies on diagnostic accuracy stated at a high level of certainty when diagnostic accuracy was the outcome of interest, as they directly assessed the performance of diagnostic tests. The certainty was subsequently downgraded based on risk of bias, inconsistency, indirectness, imprecision, or publication bias. For other non-diagnostic outcomes, initial certainty was based on study design, with observational studies starting at low certainty unless upgraded due to compelling factors. Where no direct evidence was available, certainty was rated as very low [4].

Importantly, the guidelines panel distinguished between the certainty of evidence (reflecting the quality of underlying studies) and the strength of recommendations (reflecting confidence that the desirable effects outweigh the undesirable effects). The strength of each recommendation was determined through a structured assessment of relevant factors—including balance of benefits and harms, patient values and preferences, resource implications, feasibility, acceptability, and equity. These judgements were documented in the evidence-to-decision (EtD) tables, which applied up to 17 criteria for diagnostic questions and 12 for therapeutic interventions. Where strong recommendations were issued based on low-certainty evidence, this was explicitly justified by contextual or implementation considerations.

Recommendations were classified as strong, conditional or weak. Where high-certainty evidence was lacking and expert consensus was relied upon, recommendations were labelled as '*ungraded good practice statements*' (UGPS). Each recommendation includes the clinical question, the recommendation itself, the certainty of evidence, the strength of the recommendation, and the panel's level of agreement. UGPS are applied when there is clear consensus that a practice is beneficial, safe, and self-evident, and therefore does not require formal evidence grading. In contrast, '*ungraded expert opinion*' is used when evidence is insufficient or uncertain, but a statement is still needed to guide practice, reflecting the panel's collective judgement rather than strong data.

To enhance methodological robustness and transparency, three expert statisticians with experience in systematic reviews and GRADE appraisal were involved in critically reviewing the certainty ratings and refining the EtD tables.

The evidence-to-decision tables are presented in Supporting Information S2.

3.6 | Integration of the Delphi Method

To strengthen the consensus process, the Delphi method was employed alongside the GRADE approach [5]. The Delphi process included a series of online meetings and one in-person meeting during the 20th International CeD Symposium (ICDS) in Sheffield, UK, in September 2024, as follows:

Round 1: Experts independently formulated PICO questions based on the importance of clinical issues and key outcomes, providing justifications.

Rounds 2 and 3: Results from the first round were summarized and shared with participants in online meetings. Participants refined their responses based on collective feedback.

Round 4 (In-person meeting, ICDS 2024): Key topics were discussed, including: The no-biopsy approach for CeD diagnosis in adults, and management strategies for follow-up and non-responsive CeD. This round was followed by writing the first draft of the manuscript.

Subsequent Review: Representatives of AOECS (Association of European Coeliac Societies) reviewed the manuscript and provided insights from the perspective of patient organizations regarding CeD management.

Rounds 5 and Beyond: Online voting and additional meetings were conducted to refine the recommendations. Further several online voting rounds were held until consensus was reached on the critical recommendations.

3.7 | Handling of Disagreements

Disagreements in the recommendation-making process were resolved through structured Delphi rounds, ensuring that all expert opinions were systematically considered. To handle disagreements, the working group established a predefined threshold (80% agreement) for final recommendations. In cases of persistent disagreement it was agreed, that a core steering committee, including representatives from ESsCD, was responsible for reviewing unresolved issues and providing final decision based on the balance of evidence and expert opinion. However, this step was not required, as consensus was reached through the Delphi process.

3.8 | Voting and Formulating Recommendations

The questions and recommendations were uploaded to the Delphi platform for voting. The panel members were asked to vote on all the recommendations and statements selecting one of the following options (*Agree strongly; Agree with minor reservation; Agree with major reservation; Disagree with major reservation; Disagree with minor reservation; Disagree strongly*) and then to provide any comments on the questions and recommendation. Questions with less than 80% agreement were discussed in a subsequent online meeting, followed by a second round of voting.

3.9 | Guideline Development Funding

Development of these guidelines was not financially funded.

3.10 | How to Use This Guideline

ESsCD guidelines are primarily intended to help clinicians make decisions about diagnostic and treatment alternatives. Other purposes are to inform policy, education, and advocacy, and to state future research needs. Patients may also use them. Clinicians must make decisions based on the clinical presentation of each individual patient, taking in consideration patients preferences in a shared-decision manner.

These guidelines may not include all appropriate methods of care for the clinical scenarios described. As science advances and new evidence become available, recommendations may become outdated. Following these guidelines cannot guarantee successful outcomes.

3.11 | Plan for Updating the Guidelines

The ESsCD governing Board decided to update the guidelines after a term of 5 years; however, an earlier update may be considered when there are developments that significantly influence the diagnosis and management of CeD.

4 | Clinical and Epidemiological Aspects

4.1 | Clinical Aspects

Gluten consumption is associated with various medical conditions, known collectively as gluten-related disorders. The most important of these is *Coeliac Disease* (CeD), an inflammatory disorder in genetically predisposed persons triggered by an immune response to gluten, proteins present in wheat, barley, and rye. CeD is a chronic small-bowel enteropathy in which specific antibodies are systemically detectable [6].

The other disorders within this spectrum are:

1. *Dermatitis herpetiformis (DH):* DH is the specific cutaneous manifestation of CeD. Both diseases occur in gluten-sensitive individuals, share the same HLA haplotypes and improve following a GFD [7]. Histological changes similar to CeD enteropathy have been reported in 75% of patients with DH, and the remaining have minor changes consistent with possible latent CeD [8]. Minor GI complaints are the most common findings in DH. Signs of malabsorption are rare.

The diagnosis of DH is confirmed by direct immunofluorescence (DIF) examination of perilesional skin showing granular IgA deposits in the papillary dermis and positive anti-tissue transglutaminase 2 (TG2) serology [9].

2. *Gluten-related neurological manifestations*: These complications may be the prime presentation of CeD, reported in 10%–22% of adults with CeD [10].

Research suggests that neuro-coeliac manifestations can be immune-mediated related to gluten, including antibody cross-reaction, deposition of immune-complex, direct neurotoxicity, and in severe cases, vitamins or nutrients deficiency. Post-mortem examination from patients with gluten ataxia showed patchy loss of Purkinje cells and infiltration of T cells within the cerebellum. Lymphocytic infiltrates are found in dorsal root

ganglia in patients with CeD with sensory neuropathy or with myopathy [11].

Gluten ataxia (GA) is the most frequently reported neurological disturbance in CeD. Less than 10% of patients with GA have GI symptoms but a third have enteropathy on biopsy [12].

Gluten neuropathy is idiopathic neuropathy with serological evidence of gluten sensitivity. Presentations include symmetrical sensorimotor axonal peripheral neuropathy, asymmetrical neuropathy, sensory ganglionopathy and small-fibre neuropathy [10]. Only a third has enteropathy. Effect of a GFD on peripheral neuropathy is disappointing [13].

Other neurological disorders: Gluten encephalopathy, temporal lobe epilepsy with hippocampal sclerosis, gradually progressive neurological disease and gluten sensitivity associated with white matter lesions, mimicking multiple sclerosis, have been described.

Mild cognitive symptoms called 'foggy brain', which improves when gluten-restriction is started, but re-appears with dietary contamination [14]. Concentration and attention difficulties, episodic memory deficits, word-retrieval problems, reduced mental acuity and episodes of confusion or disorientation are common recognised features in CeD [15].

Psychiatric disorders: Depression, bipolar disorder, apathy, excessive anxiety, schizophrenia, eating disorders, attention-deficit/hyperactivity disorder, autism and sleep disturbances [16, 17]. Anxiety disorders are usually reactive in patients with CeD and improve with a GFD. Depressive disturbances may significantly impair QoL and are a good predictor of lack of dietary compliance [16]. A prolonged GFD might improve some patients.

3. *Non-coeliac wheat sensitivity (NCWS):* A condition characterized by irritable bowel syndrome (IBS)-like symptoms and extra-intestinal manifestations, occurring after ingestion of gluten-containing food, improving rapidly with gluten withdrawal and relapsing soon after gluten challenge. Pre-requisite for suspecting NCWS is the exclusion of CeD, wheat allergy and major GI disorders when the patient is still on a gluten-containing diet.

4.2 | Epidemiological Aspects

4.2.1 | What Is the Prevalence of Coeliac Disease?

Summary of evidence: The global prevalence of CeD has increased significantly over the past five to 6 decades, yet a substantial proportion of cases remain undiagnosed [18]. While the overall occurrence is similar between males and females, diagnosis remains more frequent in females, with reported female-to-male ratios ranging from 2:1 to 1.5:1 [19, 20].

In western countries, the prevalence is around 0.7% histologically-confirmed and 1%–1.6% in serological screening of the general population [19, 20]. A comprehensive European systematic review estimated the histology-based prevalence of previously undiagnosed CeD to range from 0.10% to 3.03% (median: 0.70%) [21]. Since 2000, prevalence has been highest in northern Europe (1.60%), followed by eastern (0.98%), southern (0.69%), and western Europe (0.60%). The incidence of diagnosed CeD has also risen markedly, reaching up to 50 per 100,000 person-years in regions such as Scandinavia, Finland, and Spain.

CeD affects individuals across all age groups. Historically, more than 70% of diagnoses were made in adults aged 20 years or older [22]. However, recent trends indicate a substantial rise in paediatric diagnoses, particularly in older children and adolescents. The median age at diagnosis has increased from 1.9 years before 1990 to 7.6 years since 2000. This shift likely reflects an increased recognition of milder and asymptomatic cases, supported by the widespread adoption of highly specific serological testing, including anti-endomysial antibodies and anti-TG2 antibodies. These findings underscore the importance of considering CeD across all age groups, and regional variations should be acknowledged.

First-degree relatives of CeD patient have 5%–10% lifetime risk of having CeD; second-degree relatives are less at risk [23]. Monozygotic twins showed significantly higher concordance than dizygotic twins (70% vs. 9% cumulative probability of having symptomatic or silent forms of CeD, respectively, within 5 years) [24].

Coeliac disease is frequently associated with other conditions, particularly type 1 diabetes mellitus (T1DM), autoimmune thyroid diseases (such as Hashimoto's thyroiditis and Graves' disease), Down syndrome, and a range of other autoimmune or genetic syndromes, including autoimmune hepatitis, Addison's disease, selective IgA deficiency, Turner syndrome, and Williams syndrome. The coexistence of these conditions underscores the need for targeted screening in at-risk populations [23, 25].

4.2.2 | What Is the Genetic Background of CeD?

Summary of evidence: The specific role of the human leucocyte antigen (HLA)-DQA1 and HLA-DQB1 genes in the presentation of gluten peptides as antigens makes the MHC-HLA locus the most important genetic factor in CeD [26–28]. The majority (90%–95%) of patients with CeD carry HLA-DQ2.5 heterodimers, encoded by *DQA1*05* and *DQB1*02* alleles, which may be inherited together on the same chromosome (*cis* configuration) or separately on two homologous chromosomes (*trans* configuration) [29, 30]. The remaining 5%–10% carry either HLA-DQ8 heterodimers encoded by *DQA1*03* and *DQB1*03:02* or they carry HLA-DQ2.2 encoded by *DQA1*02:01* and *DQB1*02*. Rare patients (< 1%) not carrying these heterodimers carry *DQA1*05* often as part of the HLA-DQ7.5 heterodimers [28, 30].

Homozygous HLA-DQ2.5 carries the highest CeD risk, up to 30%, versus 3% risk in other genotypes, and is associated with a more classical presentation and complicated CeD [31].

The presence of HLA risk alleles is a necessary, but not a sufficient, factor for the development of CeD [32].

HLA genes alone confer approximately 35%–40% of the genetic risk, emphasizing the significant role of a huge number of non-HLA genes in the immune pathogenesis of CeD [30, 32].

4.3 | What Are the Environmental Factors That Play a Role in Development of CeD?

Summary of evidence: Gluten exposure is essential for the development of CeD. Upon ingestion, gluten peptides resist complete digestion in the gastrointestinal tract, leading to the formation of immunogenic peptides. These fragments are presented in an HLA-DQ2 or HLA-DQ8-dependent manner to gliadin-specific T-cells, that then trigger an inflammatory response in the small bowel, ultimately resulting in villous atrophy and malabsorption. Loss of gluten tolerance can occur at any age as a consequence of other triggers besides gluten. Gastrointestinal (GI) infections, medications, α-interferon, and surgery have also been implicated as trigger factors [33–35]. On the other hand, long-suspected factors as the duration of breastfeeding and/or the timing of gluten introduction to the diet were not shown to impact the risk of developing CeD [18, 36, 37].

5 | Questions, Recommendations and Evidence

5.1 | Diagnostic Approach

5.1.1 | Indications for Testing or Screening for CeD in Adults

Summary of evidence: Traditionally, patients with CeD present with malabsorption dominated by diarrhoea, steatorrhoea, weight loss or failure to thrive [6]. However, CeD can present with a wide range of non-classical symptoms, such as vague abdominal complaints, dyspepsia, fatigue, neurological manifestations, dermatological disorders, anaemia, or unexplained liver enzyme abnormalities. In some cases, patients can be asymptomatic at diagnosis (subclinical CeD) [6].

A shared genetic background is recognized for T1DM and CeD [38], while symptoms associated with IBS or microscopic colitis can overlap with those of CeD. Patients affected by associated conditions should be tested for CeD because at higher risk of disease [39]. Most of these conditions have an autoimmune pathogenesis [40–43]. Meta-analyses found biopsy-proven CeD in 6.2% of children and 2.7% of adults with autoimmune thyroid disease [44], while pooled prevalence rates in T1DM range from 5.1% to 6.0% [45–47]. There is a strong association between CeD and DH (hazard ratio [HR] = 70.42) [48].

Several case reports suggest that upper GI surgeries, such as fundoplication, gastrectomy, Whipple's pancreaticoduodenectomy, and bariatric gastric bypass, may unmask previously undiagnosed CeD [49–51].

Recently, there are case reports linking development of CeD to the use of Immune checkpoint inhibitors (ICIs), which are a class of immunotherapy drugs that enhance the immune system's ability to target cancer cells. ICIs are associated with immune-related adverse events (irAEs) that can affect various organs, including the gastrointestinal tract. One emerging irAE is ICI-associated small-bowel involvement which includes CeD (ICI-CeD), a condition that mimics classical CeD but arises in patients undergoing treatment with ICIs, non-CeD villous atrophy, and ulcerative jejunitis [52, 53].

Active case-finding through serological testing in high-risk groups has improved the detection and diagnosis of CeD, potentially providing a favourable cost-benefit ratio [54, 55]. In a mass screening of 4438 children, 40.2% had a genetic predisposition, and 60% of CeD cases were previously undiagnosed [56].

The reported risk of conditions associated with CeD varies across studies. Testing for CeD should be considered in conditions where the prevalence of undiagnosed, biopsy-confirmed cases is at least 2%–2.5%, as this represents a significantly higher risk compared to the general population. This threshold aligns with cost-effectiveness considerations and current recommendations for testing high-risk groups [57, 58].

Currently, there is insufficient evidence to support mass screening for CeD, given the potential benefits and drawbacks [59].

The indication for CeD testing or screening are summarized in Table 2.

5.1.2 | Serological Testing

5.1.2.1 | Q.II.1. Which Serological Test Is Most Suitable for Initial Testing for CeD? *Recommendations*: We recommend:

1. IgA anti-tissue transglutaminase (TG2) antibody as a single test for initial testing for CeD at any age.
2. Measure total IgA concurrently to exclude IgA deficiency.
3. Perform testing while the patient is on a gluten-containing diet.

Certainty of Evidence (CoE): Moderate; GR: Strong; Agreement: 95%

Summary of evidence: Autoantibodies such as anti-endomysial antibodies (IgA anti-EMA) and anti-TG2 have significantly improved the diagnostic accuracy for CeD compared to older tests like IgA anti-gliadin antibodies (AGA) [62]. Whilst AGA have been in use for decades, there is a wide variability in their diagnostic accuracy [63]. Both IgA and IgG-AGA antibodies have sensitivities and specificities inferior to those of the IgA anti TG2 and IgA anti-DGP assays and should no longer be included in the routine testing for CeD. In terms of predictive values, the positive predictive value (PPV) and negative predictive value (NPV) of IgA anti-TG2 are 90% and 98%, respectively. For comparison, PPV and NPV are 100% and 97% for IgA anti-EMA, 94% and 90% for IgA anti-AGA, and 70% and 98% for IgG anti-AGA [64].

Some variation in the sensitivity and specificity of the IgA anti-TG2 test has been observed across studies, primarily due to differences in cut-off thresholds and study populations.

TABLE 2 | Who should be tested or screened for CeD?[a].

Category	Indications for testing
Individuals who should be *tested for* CeD (symptomatic or associated conditions)	
Symptoms and signs suggestive of CeD	Chronic (non-bloody) diarrhoea, steatorrhoea, unexplained weight loss, chronic iron deficiency and unexplained anaemia, postprandial bloating, dyspepsia, recurrent abdominal pain, constipation, unexplained high-output ileostomy or colostomy
Gastrointestinal disorders	Autoimmune atrophic gastritis, irritable bowel syndrome, microscopic colitis, unexplained acute or chronic pancreatitis, unexplained liver enzyme abnormalities, autoimmune hepatitis, primary biliary cholangitis, hyposplenism or functional asplenia
Neurological disorders	Unexplained ataxia, peripheral neuropathy, unexplained epilepsy
Dermatological and oral disorders	Dermatitis herpetiformis, refractory psoriasis, recurrent aphthous ulcerations, dental enamel defects [60], molar incisor hypomineralization [61]
Endocrinological and autoimmune disorders	Type 1 diabetes mellitus, Hashimoto's thyroiditis, Grave's disease, Sjögren's syndrome
Gynaecological disorders	Delayed menarche, premature menopause, unexplained infertility with recurrent miscarriages
Other indications	Suspicion of immune checkpoint inhibitor-associated CeD, chronic fatigue syndrome, selective IgA deficiency, pulmonary hemosiderosis, findings on video capsule endoscopy or radiological imaging suggestive of villous atrophy, 'premature' osteoporosis with low-impact fractures IgA nephropathy (test if other features suggestive of CeD are present; consider in early-onset, atypical, or refractory IgA nephropathy, or if there is coexisting autoimmune disease or a family history of CeD)
Individuals who should be *screened for* CeD (high-risk but asymptomatic or mildly symptomatic)	
Genetic conditions	Down syndrome, Turner syndrome, Williams syndrome
Family history	First-degree relatives of individuals with CeD, even if asymptomatic

[a]See corresponding sections for details.

However, there is strong overall consistency in its high diagnostic performance. The findings also consistently show that IgA anti-DGPs have slightly lower diagnostic accuracy values to IgA anti-TG2. IgA anti-TG2 is highly sensitive (90.7%, 95% CI: 87.3%–93.2%) and specific (87.4%, 95% CI: 84.4%–90.0%) for CeD diagnosis in adults, with automated assays reaching 99% sensitivity and 100% specificity [65, 66]. IgA anti-EMA offers high specificity (99.6%, 95% CI: 92.3%–100%) but lower sensitivity (88.0%) [65]. IgA/IgG anti-DGP shows strong sensitivity (96.4%, 95% CI: 91.7%–98.5%) and specificity (95.4%), useful in anti-TG2-negative cases [65, 67]. Test performance varies with thresholds and settings.

To avoid false-negative results due to selective IgA deficiency—which occurs more commonly in patients with CeD than in the general population—total IgA should be measured concurrently with IgA-based serologic testing [68].

Furthermore, testing should be conducted while the patient is consuming a gluten-containing diet, as serological markers typically normalize on a gluten-free diet and may lead to missed diagnoses.

While IgA-anti-EMA is highly specific, it is labour-intensive and operator-dependent, making the IgA anti-TG2 ELISA the preferred first-line test [65, 66, 69]. The IgA anti-TG2 ELISA test is more technically straightforward, less labour-intensive, and allows for greater standardisation and automation [66, 69].

Anti-deamidated gluten peptides (DGP) antibodies testing has higher specificity than native gluten antibodies but is less predictive than anti-TG2 for early diagnosis [70]. IgA/IgG antibodies to non-DGPs or to DGPs alone are not predictive of CeD before anti-TG2 antibodies appear, confirming IgA anti-TG2 as the most reliable first-line test for CeD diagnosis [71]. Also, isolated positivity for IgA/IgG-DGP in low-risk patients predicts CeD in only 15% of cases, with most being false positives [67].

5.1.2.2 | Q.II.2. How Does the Technical Performance of the CeD Serological Assays Affect the Diagnostic Accuracy and Outcome of a Specific Test?

Statement: Standardised serological assays with proven sensitivity, specificity, and reproducibility are essential for improving CeD diagnosis. Widely validated anti-TG2 antibody tests should remain central to this process. However, achieving global standardization of assay quality remains challenging, underscoring the need for certification systems and clear guidance for healthcare providers.

CoE: Moderate; GR: Strong; Agreement: 95%

Summary of evidence: The literature search retrieved several references that addressed this question [72–78]. These studies

collectively underscore that the technical performance of serological assays—particularly those targeting TG2 and DGP—has a significant impact on both diagnostic accuracy and patient outcomes [76].

The relevance of TG2 and DGP in serological testing stems from their central roles in CeD pathogenesis. TG2 is the primary autoantigen in CeD, and it modifies gluten peptides into deamidated forms (DGP), enhancing their binding to HLA-DQ2/8 molecules and promoting a pathogenic T cell response. In turn, TG2-and DGP-specific B cells act as antigen-presenting cells and trigger the production of highly specific autoantibodies [79].

However, the diagnostic utility of these assays is highly dependent on their technical execution:

TG2-based assays require the enzyme to maintain its native (correctly folded) conformation to expose the relevant epitopes for antibody binding. Many commercial assays fail to adequately verify antigen integrity, which may reduce sensitivity or result in false-negative results. While, DGP-based assays, although more robust in terms of antigen structure, vary in performance depending on whether IgA, IgG, or combined antibody responses are measured, and on the peptide composition used [80].

Studies comparing different commercial kits have demonstrated significant variation in sensitivity and specificity—particularly for TG2 IgA tests [78, 79, 81, 82]. Assays with low analytical fidelity (e.g., improper antigen folding, suboptimal signal detection systems, or poor reproducibility) can lead to false negatives or false positives, ultimately affecting clinical decision-making, especially when considering non-biopsy diagnosis strategies [75].

Furthermore, high-quality assays are critical in specific populations such as: Patients with low or borderline TG2 titres, individuals on a gluten-reduced diet, seronegative CeD cases, and when serological tests may be used to avoid biopsy [83].

Thus, the technical robustness of an assay—covering factors such as antigen quality, reproducibility, and standardisation—is fundamental to achieving high diagnostic accuracy, reducing misdiagnosis risk, and improving clinical outcomes. As a result, laboratories and clinicians must choose assays with validated high performance, and clinicians should interpret results in light of assay limitations [79, 81, 82].

5.1.2.3 | Q.II.3. How Is the Quality of Serological Assays for CeD Controlled?

Statement: Anti-TG2 ELISA tests target conformational epitopes but are prone to variability in assay design and quality control, potentially affecting performance. Reliable results require rigorously validated tests with strict quality control and external quality assurance participation. A certification system for assay standardisation could enhance consistency and reliability across laboratories.

CoE: Low; GR: Strong; Agreement: 100%

Summary of evidence: Many commercial anti-TG2 and anti-DGP assays exist with varying performance [75, 78]. The *ProCeDE* study revealed significant differences in assay accuracy, especially for anti-TG2 [72]. In a cohort of 707 children, tests from local laboratories showed up to 20% discordance with central lab results at 10 times ULN. Even within the central laboratory, performance varied among eight IgA anti-TG2 assays, with some achieving close to 100% positive predictive value (PPV) at 2 times ULN, while others required 5–7 times ULN. Given these variations, establishing an independent certification body for CeD serological assays could improve diagnostic accuracy and guide clinicians in selecting high-performance tests.

Point-of-care tests (POCT) for CeD typically measure anti-TG2 and/or anti-DGP antibodies [84, 85]. They may offer value in resource-limited environments or for preliminary screening; however, their diagnostic performance—particularly sensitivity and specificity—is generally lower than that of validated laboratory-based assays. Test accuracy may also vary depending on operator technique and interpretation. Because these tests are not yet standardized to the same extent as central laboratory assays and are prone to design and implementation variability, they are not suitable as standalone diagnostic tools in adults [85–87]. A positive POCT result should always be confirmed by formal serologic testing and, if appropriate, duodenal biopsy.

The use of POCT highlights the need for test quality certification and clinician awareness of its limitations to avoid misdiagnosis and inappropriate treatment decisions.

5.1.2.4 | Q.II.4. For Initial Testing in Suspected Coeliac Disease, Is There a Rationale for Using a Combination of Multiple Serological Tests?

Recommendations: We recommend against the routine combination of serological tests for the initial diagnosis of CeD, due to minimal added value and potentially increasing cost and complexity.

CoE: low-moderate; GR: strong; Agreement: 95%

Summary of evidence: 105 studies were identified through a systematic literature search, with seven studies included. The anti-TG2/DGP combined assay is accurate for diagnosing CeD and presents a practical alternative to IgA anti-EMA, with the potential to reduce both costs and variability due to operator interpretation [88]. However, a systematic review showed no significant improvement in sensitivity or specificity when combining IgA anti-TG2 and IgA anti-EMA [65]. Similarly, a study by Oyaert et al. reported that combining IgA anti-TG2 with IgG anti-DGP, particularly when antibody titres are taken into account, may modestly improve diagnostic performance in paediatric populations, but this benefit was not consistently observed across all age groups [89]. Porcelli et al. investigated a combined anti-TG2/DGP screening assay that detects both IgA and IgG isotypes simultaneously, suggesting potential for reducing reliance on duodenal biopsies, although further validation is required [90, 91].

Overall, while certain combinations may offer marginal improvements in specific contexts, the routine use of multiple serological assays for initial screening is not supported by strong evidence and may unnecessarily increase cost and complexity.

5.1.2.5 | Q.II.5. Is Anti-Endomysial Antibody (IgA anti-EMA) Testing Required as a Confirmatory Test for Diagnosing CeD?

Recommendations: Although IgA anti-EMA tests are highly specific, their labour-intensive nature and limited availability reduce their role in routine adult CeD diagnostics. However, they can be reserved for unclear cases to ensure diagnostic accuracy and cost-effectiveness, such as in patients with other autoimmune or liver diseases before proceeding with a duodenal biopsy.

CoE: low; GR: conditional; Agreement: 95%

Summary of evidence: The literature search found 374 results, with two studies addressing this question. Dahele et al. reported that IgA anti-EMA-negative CeD is not uncommon and detection is only modestly improved by testing for IgA anti-TG2 antibodies [92]. IgA anti-EMA testing, while highly specific, is technically demanding and operator-dependent, making it less suitable for widespread initial screening. However, in diagnostically ambiguous situations - particularly in patients with concomitant autoimmune or hepatic disorders - EMA testing may provide added value and help avoid unnecessary duodenal biopsies [66, 69].

5.1.2.6 | Q.II.6. How to Test for Coeliac Disease in Patients With Total IgA Deficiency?

Recommendations: In patients with confirmed total IgA deficiency, coeliac disease serology should be performed using IgG-based assays, such as IgG anti-TG2 or IgG anti-DGP antibodies. Due to the lower sensitivity of these tests, a negative IgG result does not exclude the diagnosis. In individuals with signs of malabsorption suggestive of CeD, upper GI endoscopy with duodenal biopsies should be undertaken regardless of IgG serology results.

CoE: low; GR: strong; Agreement: 100%

Summary of evidence: Total IgA deficiency is defined by serum IgA levels < 7 mg/dL. While IgA deficiency is regarded as partial when serum IgA levels are > 7 mg/dL, but below the lower limit of the normal range according to the age [93]. IgA deficiency affects 2%–3% of patients with CeD, whereas paediatric studies report a prevalence of CeD as high as 10% among individuals with selective IgA deficiency [94, 95].

The presence of IgA deficiency leads to false negatives on IgA-based serology tests [68]. Therefore, total IgA levels should be measured concurrently with CeD serology. For serological testing of CeD in patients with IgA deficiency, IgG-based tests (such as IgG anti-TG2 or IgG anti-DGP) are required [67, 96, 97]. Accuracy data for IgG-based serological tests are limited, with sensitivity of IgG anti-DGP assays varies between 74.4% and 86.0% at a cut-off corresponding to a specificity of 98%. Specificity ranges from 97.3% to 99.3% [70]. Therefore, to avoid missing CeD diagnosis, in individuals with clinical features suggestive of coeliac disease, upper GI endoscopy with duodenal biopsies should be undertaken regardless of IgG serology results [98]. However, a positive IgG serology may be useful for monitoring disease progression and assessing adherence to a gluten-free diet, although titres decline more slowly than those of IgA serology.

HLA-DQ2/8 genotyping may be considered in selected clinical scenarios where both IgG-based serological testing and duodenal biopsy are inconclusive or not feasible [94]. A negative result effectively excludes CeD and eliminates the need for further testing.

5.1.2.7 | Q.II.7. What Is the Diagnostic Accuracy of Stool and Saliva Serological Tests for CeD?

Recommendation: Saliva and faecal tests for CeD have low sensitivity and specificity, therefore, their use in clinical practice should be discouraged.

CoE: low; GR: strong; Agreement: 100%

Summary of evidence: Saliva tests for anti-TG2-IgA have shown lower sensitivity and specificity compared to blood-based anti-TG2-IgA tests [99, 100]. Faecal tests for anti-TG2-IgA and DGP-IgG antibodies have shown mixed results. Some studies indicate reasonable sensitivity and specificity, while others report lower accuracy compared to blood tests [101].

5.1.3 | Histopathology

5.1.3.1 | Q.III.1. What Is the Recommended Number and Location of Duodenal Biopsies for CeD Diagnosis?

Recommendation: For the diagnosis of CeD, it is recommended to take at least four biopsies from the distal duodenum, plus two from the duodenal bulb.

CoE: moderate; GR: strong; Agreement: 100%

Summary of evidence: When CeD is suspected, duodenal biopsies should be taken even when the endoscopic appearance of duodenal mucosa is grossly normal. It is generally believed that in CeD, mucosal lesions may have a patchy distribution [102–104]. For this reason different studies concluded that multiple biopsies are needed a minimum of four biopsies from the distal duodenum and 1–2 from the duodenal bulb are needed [103].

The inclusion of duodenal bulb biopsies may improve the detection of early or localised involvement (ultrashort CeD) [105, 106]. A meta-analysis showed that the pooled rate of increase in diagnostic yield with bulb biopsy was 6.9% [107]. To achieve optimal orientation of biopsy samples for histological examination, single-bite biopsy forceps are recommended during endoscopy procedures. Subsequently, in pathology units, biopsy samples should be processed individually rather than combined in a single paraffin block. Bulb biopsies should be placed in a separate vial from those taken from the distal duodenum. Histologically, the duodenal bulb harbours Brunner's glands resulting in a reduced villous height, which creates difficulty in interpretation. In addition, peptic duodenitis and the potential presence of gastric metaplasia at the bulb make a histological diagnosis of CeD difficult when only bulb biopsies are taken [108, 109].

5.1.3.2 | Q.III.2. Do the Sub-Classifications (A, B, C) of Marsh-III Stage in the Modified Marsh Classification Add Clinically Relevant Information?

Statement: The sub-classifications (A, B, C) of the Marsh-III stage in the

modified Marsh classification describe mucosal damage in CeD but have limited clinical relevance in routine practice. They do not significantly influence treatment decisions or outcomes but may help monitor inflammatory activity.

CoE: low; GR: conditional; Agreement: 95%

Summary of evidence: The Marsh classification was originally developed to stage histological changes in coeliac disease and was later modified to subdivide stage III (villous atrophy) into three subcategories: 3A (partial), 3B (subtotal), and 3C (total villous atrophy) [110, 111]. This modified system is widely used in clinical and research settings, despite some objections by Marsh himself regarding its application and interpretation [112].

While the sub-classifications (3A–3C) offer a more detailed description of mucosal damage, their clinical relevance in routine practice is limited [113]. Multiple studies suggest that these sub-stages do not significantly influence treatment decisions or long-term outcomes. However, they may be helpful in selected contexts, such as monitoring disease activity and mucosal healing, particularly in patients with severe enteropathy (e.g., Marsh 3C), who are at increased risk for incomplete histological recovery and may benefit from closer follow-up [112, 114–117].

Morphometric analysis has been proposed as a more objective method for assessing mucosal injury. This approach involves quantitative evaluation of the villous height-to-crypt depth (Vh:Cr) ratio and intraepithelial lymphocyte (IEL) density [118, 119]. A Vi:Cr ratio below 2 indicates villous atrophy and active disease, while treated patients with CeD typically have ratios above 3. A threshold change of 0.4 in Vi:Cr or $\geq$ 30% in T-cell IEL density is considered clinically significant [118, 120].

Despite its potential for objective histological assessment, morphometry faces challenges in clinical adoption due to practical limitations, lack of standardisation, and insufficient evidence of superiority over existing methods. One proposed approach to bridge this gap is the Q-MARSH system, which translates morphometric findings into qualitative Marsh-like categories to improve clinical utility [118, 121, 122].

Importantly, both classification systems face limitations. The Marsh staging system, while widely used, compresses a biological continuum of gluten-induced mucosal injury into discrete stages, potentially overlooking subtle but clinically relevant histologic changes within a single category [118]. Further research is needed to validate the added clinical value of both sub-classifications and morphometric techniques, particularly in guiding patient management and prognosis.

5.1.3.3 | Q.III.3. How Should Duodenal Biopsies Be Processed for Optimal Evaluation in CeD Diagnosis? *Statement*: For optimal histopathological assessment in CeD, well-oriented duodenal biopsies are essential. Haematoxylin and Eosin (H&E) staining is recommended for routine diagnostic purposes.

CoE: moderate; GR: strong; Agreement: 100%

Summary of evidence: Well-oriented duodenal biopsies enhance the sensitivity and specificity of CeD diagnosis by allowing clear assessment of villous atrophy, crypt hyperplasia, and IELs, minimising diagnostic errors [118, 123, 124]. Proper biopsy orientation is essential for reliable histological evaluation, especially in mild or early CeD [103].

HE staining is generally adequate for most cases and is practical for routine use [103], but immunohistochemical (IHC) staining, including formalin-fixed staining such as CD3 and gamma delta, is more precise for identifying IELs in challenging or borderline cases [125, 126]. Both techniques play key roles, with IHC offering greater accuracy in specific contexts [118]. CD3 T cell staining for measuring IEL density on formalin fixed biopsy samples is already used in routine, and today formalin fixed biopsies can also be used to stain the γδ-positive IELs [125].

5.1.3.4 | Q.III.4. Quality Control of Histological Assessment. What is the impact of interobserver variability in the histological interpretation of duodenal biopsies for coeliac disease, and how can diagnostic agreement be improved?

Statement: There is substantial interobserver variability in the histological interpretation of duodenal biopsies for CeD, particularly in cases with mild or borderline mucosal changes (e.g., Marsh I–II). To enhance diagnostic accuracy and consistency, histological assessment should be performed in conjunction with clinical and serological information. The use of classification systems (the modified Marsh classification), comprehensive pathology reporting, and adequate biopsy sampling are essential components of high-quality diagnostic practice.

CoE: low; GR: ungraded good practice statement; Agreement:95%

Summary of evidence: Diagnosing CeD through duodenal biopsies can be challenging, particularly due to variability in interpretation between pathologists. Interobserver variation is influenced by several factors, including differences in histopathological classification systems (e.g., Marsh vs. modified Marsh), lack of standardized criteria, and the absence of clinical context [114, 119, 127]. Studies have shown that interobserver agreement ranges from moderate to poor, particularly in borderline or mild lesions (e.g., Marsh-I and II stages). Variations between hospitals in biopsy evaluation can lead to misdiagnosis, and that access to clinical information and anti-TG2 levels may aid pathologists in unclear cases [128]. Two large studies demonstrated that adding serological data and clinical context significantly enhanced the diagnostic concordance among pathologists [127, 129].

To improve consistency and diagnostic quality, the following points need to be taken in consideration:

1. Pathologists are encouraged to use standardised classification (the modified Marsh classification) to maintain uniformity in histological lesion grading and facilitate clearer communication with clinicians and other pathologists.

2. Histological interpretation should be made in the context of clinical and serological information whenever possible.
3. The pathology reports should explicitly detail key parameters such as the number of biopsies received, the quality of orientation, Vi:Cr ratio, IEL count, and Marsh stage.
4. In cases of diagnostic uncertainty, especially when assessing mild or borderline changes, pathologists are encouraged to obtain a second opinion to increase diagnostic confidence. Furthermore, the use of digital pathology platforms and artificial intelligence-based tools is increasingly recognized as a means of supporting reproducibility and reducing interobserver variation [118].
5. Finally, obtaining an adequate number of biopsies and ensuring proper tissue orientation are essential for reliable histological evaluation.

5.1.3.5 | Q.III.5. Can Advanced Endoscopic Techniques Replace Standard Histopathology in the Assessment of Small Bowel Mucosal Damage in CeD? *Statement:* While advanced endoscopic techniques enhance mucosal assessment, they do not replace standard histopathology for diagnosis of CeD. Instead, they may serve as valuable adjuncts that may reduce unnecessary biopsies and improve targeted sampling.

CoE: low; GR: ungraded good practice statement; Agreement: 100%

Summary of evidence: Indigo carmine chromoendoscopy highlights villous atrophy and ulcers but does not enhance the detection of other subtle abnormalities associated with CeD, such as scalloping, fold loss, or the mosaic pattern. Despite this limitation, it remains useful for examining suspicious areas during small-bowel endoscopy [130].

Confocal Laser Endomicroscopy (CLE) provides high-resolution real-time images of cellular structures and can detect villous atrophy, crypt hyperplasia, and increased IELs. While it may allow for biopsy-free diagnosis in some cases, CLE is costly, requires specialised equipment and expertise, and is not widely accessible [131, 132].

Narrow-band imaging (NBI) is another non-invasive modality for detecting and excluding duodenal villous atrophy in patients with suspected CeD. While NBI has demonstrated high diagnostic accuracy, further research is required to establish a standardized and validated classification system for its interpretation. This would help define its precise role in the diagnostic algorithm for CeD and determine whether it could reduce the reliance on histopathological assessment [133–135].

Future studies should focus on refining these techniques, developing standardised classification systems, and assessing their cost-effectiveness to optimize their integration into routine clinical practice.

5.1.4 | Confirmation of the Diagnosis of CeD in Adults

5.1.4.1 | Q.IV.1.1. How Can the Diagnosis of CeD in Adults Be Established? *Recommendation:* A positive CeD-specific serology in patients with Marsh-II or Marsh-III stage confirms the diagnosis of CeD.

CoE: high; GR: strong; Agreement: 100%

5.1.4.2 | Q.IV.1.2 Can Diagnosis Be Made Solely on Serology Without Histological Confirmation (The No-Biopsy Approach)? *Recommendation:* The confirmation of a CeD diagnosis in adults can be based on positive serology only (no-biopsy approach), when the initial IgA anti-TG2 level $\geq$ 10 times the upper limit of normal (ULN).

CoE: moderate; GR: conditional; Agreement: 95%

Key considerations include:

- The initial IgA anti-TG2 result needs to be confirmed in a second blood sample. The patient must remain on a gluten-containing diet until confirmation. In this independent blood sample any positive result should be considered confirmatory. *CoE: NA; GR: ungraded expert opinion*; *Agreement: 95%*
- The decisions on omission of endoscopy/duodenal biopsies and confirmation of the final diagnosis should be made in secondary health care settings. *CoE: NA; GR: UGPS; Agreement: 95%*
- A shared decision-making with the patient regarding the potential benefits and limitations of omitting duodenal biopsies is crucial. *CoE: NA; GR: UGPS; Agreement: 95%*
- This approach is not appropriate, if red flags for alternative conditions are present (e.g., haematochezia, dysphagia, or signs of obstruction). *CoE: NA; GR: UGPS; Agreement: 95%*
- Until more safety data are available, the no-biopsy approach should be limited to patients under 45 years. *CoE: low; GR: ungraded expert opinion; Agreement: 95%*

5.1.4.3 | Q.IV.1.3. Can Symptom Response to Gluten Withdrawal Reliably Predict a Coeliac Disease Diagnosis? *Statement:* Improvement of symptoms after gluten withdrawal or exacerbation after re-introduction of gluten has a very low predictive value for CeD and should not be used for diagnosis in the absence of other supportive evidence.

CoE: NA; GR: UGPS; Agreement: 100%

Summary of evidence: The literature search yielded 68 results, from which 11 studies were selected for inclusion (comprising systematic reviews, meta-analyses, and both prospective and retrospective studies).

There is a considerable overlap between CeD and other GI disorders. Unarguably, improvement of symptoms or recurrence upon re-introduction of gluten has a very low predictive value

for CeD and should not be used as a basis for diagnosis in the absence of other supportive evidence, such as serology and histology.

Regardless of the antibody titre, a positive CeD-specific serology (anti-TG2, anti-DGP or IgA anti-EMA) in conjunction with Marsh-III (A-C) stage confirms the diagnosis of CeD [1, 110]. For Marsh-II histology, the diagnosis is generally supported by high-titre serology; however, the combination of low-level positive IgA anti-TG2 and Marsh-II histology represents a diagnostic 'grey zone' that warrants careful follow-up. In such cases, at minimum, the patient's gluten intake should be scrutinised to ensure that it is sufficient to allow accurate serological and histological interpretation. These individuals may represent evolving CeD and should remain under observation within specialist care settings.

For decades, small-bowel biopsy has been central to confirming the diagnosis of CeD. In paediatric populations, the no-biopsy approach is evidence-based and has become the standard diagnostic pathway for CeD in children [98]. In adults, however, the evidence supporting a no-biopsy diagnosis is emerging more gradually [113, 136–138]. Multicentre studies suggest that a diagnosis can be established in adults, if IgA anti-TG2 levels are $\geq$ 10 times the ULN [113]. A systematic review and meta-analysis by Shiha et al. including a total of 18 studies with 12,103 participants from 15 countries, reported that IgA-TG2 $\geq$ 10 times ULN has an overall sensitivity of 51% (95% CI, 42%–60%) and an overall specificity of 100% (95% CI, 98%–100%) for detecting CeD. The PPV was 98% (95% CI, 96%–99%), although this varied based on the pre-test probability of CeD in the studied population [136]. In patients with a positive but low-titre IgA anti-TG2 ($< 10 \times$ ULN), small-bowel biopsy remains necessary to confirm CeD. This is because lower antibody titres are less specific and may overlap with other conditions.

Particularly in asymptomatic individuals with low-titre anti-TG2 positivity (close to the cut-off), a prudent strategy may be to repeat serology after an interval of a few weeks before proceeding to biopsy, especially if immediate histological confirmation is not essential. This approach helps to reduce unnecessary procedures while monitoring for serological evolution that may clarify the clinical picture.

As discussed in the serology section (Q.II.5.), EMA testing is no longer routinely required, as anti-TG2 has largely replaced it in clinical practice [88].

To confirm the diagnosis of CeD using the no-biopsy approach, a second measurement of IgA anti-TG2 $\geq 10 \times$ the ULN on a new blood sample is conditionally recommended, where feasible. This recommendation addresses practical concerns such as potential pre-analytical errors—including sample mislabelling, technical issues, and inter-assay variability—and aims to ensure that diagnosis is established within secondary-level gastroenterological care. Although no direct evidence supports the clinical benefit of repeat serological testing in this context, these pragmatic considerations were emphasised by the expert working group in response to real-world diagnostic challenges. Establishing a lifelong diagnosis of CeD, which requires strict and sustained adherence to a GFD, based solely on a single, unrepeated serological result may contribute to patient uncertainty and does not eliminate the risk of laboratory-related errors.

Nonetheless, the diagnostic accuracy of a single IgA anti-TG2 result $\geq 10 \times$ ULN is well established, with high-quality studies consistently demonstrating a positive predictive value of $\geq$ 98%. In clinical practice, factors such as assay variability, reproducibility of results, prior dietary gluten restriction, and logistical constraints underscore the need for flexibility rather than rigid procedural mandates. This conditional recommendation is not intended to delay diagnosis or restrict access to care, but to promote high quality, reliable decision-making in settings where repeat testing is practical. Its application should be guided by clinical judgement, patient preferences, and shared decision-making.

Patient perspectives on the no-biopsy approach have also been systematically evaluated. One discrete choice experiment showed that patients generally preferred the non-invasive no-biopsy option over biopsy-based diagnosis [139]. However, a Finnish questionnaire-based study found that patients diagnosed without biopsy had less frequent dietitian follow-up, more persistent symptoms, and greater dietary-related stress [140]. This suggests a potential for suboptimal care in this group and has reinforced the importance of ensuring diagnosis and initial management occur within secondary-level gastroenterology services.

Given current evidence limitations, a no-biopsy approach in adults is suggested only for patients younger than 45 years. This age threshold reflects concerns about an increased risk of complications with advancing age in CeD, including poorer mucosal healing and higher mortality, as supported by multiple studies. While one follow-up study of 694 patients highlighted risks associated with diagnosis after age 45 [141], broader literature also indicates increased cancer and lymphoproliferative disease risks in older individuals [142, 143]. Therefore, an upper GI endoscopy with duodenal biopsies remains advised at diagnosis in this age group to ensure a complete work-up.

The requirements needed to safely adapt the no-biopsy-approach are currently studied in detail; however, factors as age at initial diagnosis, severity of clinical and laboratory parameters, or the presence of red flag symptoms suggesting ominous diagnosis or comorbidity should be taken into consideration.

Furthermore, all published studies supporting the no-biopsy strategy have been conducted in secondary or tertiary care settings; therefore, their generalizability to primary care remains uncertain. Consequently, decisions regarding the omission of endoscopy/duodenal biopsies and confirmation of the final diagnosis of CeD should be made in secondary care settings.

The term *mucosal healing* refers to a situation in which the small bowel mucosa—previously confirmed to be pathologically altered—has healed or shown significant improvement. A debate was held on whether this documentation always requires small bowel histology at the time of initial CeD diagnosis (the 'index biopsy') and during follow-up, or whether, in a specific

subgroup of patients with IgA anti-TG2 serology > 10 × ULN, the presence of Marsh-III enteropathy can be sufficiently documented by serology alone.

Considering the arguments enlisted in the previous paragraph, it is acceptable to perform a gastroduodenoscopy in a follow-up situation without having an index biopsy. If histology reveals normal mucosa, the term *mucosal healing* can be applied. Conversely, if Marsh-III stages persist, this would be considered "persistent villous atrophy".

5.1.4.4 | Q.IV.2. Can the Diagnosis of CeD Be Made in Individuals With Persistently Positive CeD Serology But Architecturally Normal Duodenal Histology?.

Recommendation: In adults with persistently positive IgA anti-TG2 serology but architecturally normal duodenal histology (Marsh 0–I), a definitive diagnosis of CeD cannot be established. However, if these individuals carry the HLA-DQ2 and/or DQ8 haplotype, they may be classified as having potential coeliac disease.

CoE: low; GR: strong; Agreement: 95%

Summary of evidence: Some individuals have positive CeD-specific serology and the HLA-DQ2/DQ8 haplotype, yet their duodenal biopsies show no architectural abnormalities such as crypt hyperplasia or villous atrophy (Marsh-0-I stages). These individuals are classified as having potential CeD, a condition that may remain stable, regress, or progress to overt CeD. They may be asymptomatic or present with clinical symptoms suggestive of CeD [144, 145].

Potential CeD has a pooled prevalence of 16% among patients with coeliac disease [144]. During follow-up, 33% of these patients on a gluten-containing diet developed villous atrophy, while another 33% showed serological normalization. Among those on a GFD, 88% reported symptom improvement [144].

Although several studies in children have demonstrated a positive correlation between anti-TG2 titres and the degree of duodenal mucosal damage, the relationship is not linear and remains insufficiently established in adults [146–148]. However, elevated IgA anti-TG2 levels—particularly those exceeding 10 × the ULN—are highly predictive of villous atrophy, especially in genetically susceptible individuals (HLA-DQ2/DQ8-positive) and when accompanied by clinical symptoms [149]. Therefore, we favour a uniform approach for individuals with IgA anti-TG2 titres < 10 × ULN and Marsh-0-I stages, without further risk sub-stratification at this time. However, in patients with strong clinical suspicion (e.g., persistent symptoms, family history), further workup—including immunohistochemistry, repeat endoscopy, or second pathology review—may be considered on a case-by-case basis.

Potential CeD should be differentiated from other conditions that lead to mild, transient elevations in coeliac serology or lymphocytic duodenitis (Marsh-I stage). These alternative causes must be thoroughly excluded before confirming a diagnosis of potential CeD [62, 150].

False-positive CeD serology can be observed in conditions such as hypergammaglobulinemia, autoimmune diseases, chronic liver disease, and enteric infections. Transient positive IgA anti-TG2 antibodies may be seen at the time of T1DM diagnosis. While insufficient gluten intake (as in patients who have started a GFD on their own, especially when there is a delay before endoscopy) may give a negative serology test result. Lastly, false negative biopsies can result from taking too few biopsies [151].

We suggest the following approach to manage these patients:

1. Repeat serology testing with IgA anti-TG2 antibodies to rule our false positive or transient positive results (ensure the patient consumes enough gluten leading to the repeat testing)
2. Make sure a sufficient number of biopsies are collected, to reduce false negatives [151].
3. HLA-DQ2/DQ8 typing should be added in high resource settings in order to rule false positive.
4. Consult a CeD specialist for complex cases and revision of the biopsies for subtle abnormalities.
5. In potential CeD with persistent symptoms, consider repeating serology in 3–6 months while continuing an unrestricted gluten intake if tolerated by the patient. If this is not tolerated, then start a GFD supervised by a dietitian.
6. In asymptomatic patients with potential CeD, the gluten-containing diet can be continued. However, clinical and endoscopic follow-up is recommended, as one-third may progress to CeD or show seroconversion.

5.1.4.5 | Q.IV.3. What Is the Approach to Marsh-I Stage With Negative Coeliac Disease Serology?.

Recommendation: In cases of Marsh-I stage with negative coeliac disease serology, CeD is unlikely, and other causes should be explored.

CoE: low; GR: strong; Agreement: 100%

Summary of evidence: Scattered intraepithelial lymphocytes (IELs) are normally present in the small bowel [152]. However, in CeD, biopsies typically show an increased concentration of IELs, particularly at the tips of the villi. A count of ≥ 25 IELs per 100 epithelial cells is considered a significant increase, consistent with a Marsh-I stage [153]. While flow cytometry has been explored for duodenal lymphogram analysis in identifying Marsh-I lesions, comparative studies with CD3-positive IEL density measured by routine immunohistochemistry are still needed [154].

However, Marsh-I histology is non-specific and has been observed in 1.3%–6% of small-bowel biopsies [155, 156]. Reported aetiologies are: gluten-related disorders (CeD, NCWS), wheat allergy, *Helicobacter pylori* infection and drug-related reactions. Less frequently, it may be secondary to inflammatory bowel disease (IBD), autoimmune conditions, immunoglobulin deficiencies, blood malignancies, infections and irritable bowel syndrome [157].

Determining the aetiology can be challenging and relies on assessment of clinical, serological and histopathological data [158].

Because the chance of progression from Marsh-I stage to full-blown villous atrophy in those with negative serology is negligible, the decision to stop further analysis is acceptable.

5.1.4.6 | Q.IV.4. What Is the Approach to Villous Atrophy in the Absence of CeD-Specific Serology?.

Recommendation: After excluding other causes of seronegative villous atrophy, diagnosis of CeD should rely on the clinical and histological response to a GFD in individuals with HLA-DQ2 or HLA-DQ8 haplotypes.

CoE: low; GR: strong; Agreement: 95%

Summary of evidence: The term seronegative villous atrophy (SNVA) refers to patients with malabsorption, negative coeliac serology and villous atrophy on duodenal biopsy. The differential diagnosis of SNVA, shown in (Table 3), is complex and should be guided by an algorithmic approach to distinguish between seronegative coeliac disease (SNCD) from non-coeliac enteropathies. Given the clinical complexity and the poor outcomes of patients with SNVA, referral to a tertiary centre should be considered [159].

HLA-DQ/DQ8 test is recommended as it has a high negative predictive value (NPV) for CeD in this setting [28].

Moreover, the histopathological findings must be integrated with clinical and pharmacological data of the patient [160].

However, SNCD is rare, accounting for approximately 2%–5% of all CeD cases [160–162]. It is characterized by a clinical and histological response to a GFD despite negative coeliac serology (IgA/IgG-anti-EMA, IgA/IgG-anti-TG2, and IgG-anti-DGP) in individuals with HLA-DQ2 or HLA-DQ8 haplotypes, after excluding other causes of villous atrophy [160].

SNCD can be seen in patients who have reduced their gluten intake prior to testing as well as in the early phases of CeD development. Immunosuppressive medications, dermatitis herpetiformis, concurrent common variable immune deficiency (CVID), and compromised immunoregulation can also be contributing factors. Patients with SNCD have worse prognosis, a more severe clinical phenotype, exhibit usual symptoms and are older at diagnosis than patients with seropositive-CeD [160, 163, 164]. A suggested approach for analysis of villous atrophy in absence of positive CeD serology is shown in Figure 1.

5.1.4.7 | Q.IV.5. What Is the Role of HLA-DQ Typing in the Screening for and Diagnosis of CeD?.

Recommendation: HLA testing has a poor PPV but a high NPV for CeD; therefore, the guideline panel recommends that HLA-DQ2/8 testing should not be used routinely in the initial diagnosis of CeD. It is indicated when there is uncertainty about the diagnosis and in the evaluation of certain risk groups for developing CeD.

CoE: moderate; GR: strong; Agreement: 100%

Summary of evidence: The genetic background of CeD is discussed earlier under Q2. A negative result for HLA-DQ2.2/DQ2.5/DQ8 genotypes effectively excludes CeD [165]. Testing for additional HLA typing to check for rare CeD-associated genotypes, such as those involving HLA-DQ9.3 (*DQA1*03:02-DQB1*03:03) or HLA-DQ7.5 (DQA1*05-DQB1*03:01*) is strongly debatable [166–170].

HLADQ2/8 testing is indicated in the following scenarios [171].

1. *Suspected CeD*:
   i. In patients who are already following a GFD before the diagnosis has been established, the symptoms have

TABLE 3 | The differential diagnosis of non-coeliac villous atrophy.

Category	Items
Infections	Viral or bacterial enteritis (often self-limiting), giardia, tuberculosis, Mycobacterium avium complex, whipple's disease, small-bowel bacterial overgrowth, tropical sprue
Medicines/treatments	NSAIDs, Angiotensin type 1 receptor blockers (ARBs) such as olmesartan and losartan, mycophenolate mofetil, methotrexate, colchicine, chemotherapy, radiation enteritis, small-bowel transplant, immune-checkpoint inhibitors
Malignancies/lymphomas	Enteropathy-associated T-cell lymphoma (EATL), monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), primary lymphoproliferative disorders of the small-bowel: Immunoproliferative small intestinal disease (IPSID), indolent CD4+ lymphoma
Other pathologies	Crohn's disease, collagenous sprue, amyloidosis (systemic or localized)
Immunodeficiency	HIV/AIDS, Common Variable Immunodeficiency (CVID), IgA deficiency
Autoimmune disorders	Autoimmune enteropathy, eosinophilic gastroenteritis
Graft-related disorders	Graft versus Host Disease (GVHD)
Idiopathic	When no causes have been found despite extensive investigations

Abbreviations: ARBs, Angiotensin type 1 receptor blockers; CVID, Common Variable Immunodeficiency; EATL, Enteropathy-associated T-cell lymphoma; GVHD, Graft versus Host Disease; HIV/AIDS. Human Immune Deficiency Virus/Acquired Immune Deficiency Syndrome; NSAIDs, Non-Steroidal anti-inflammatory drugs.

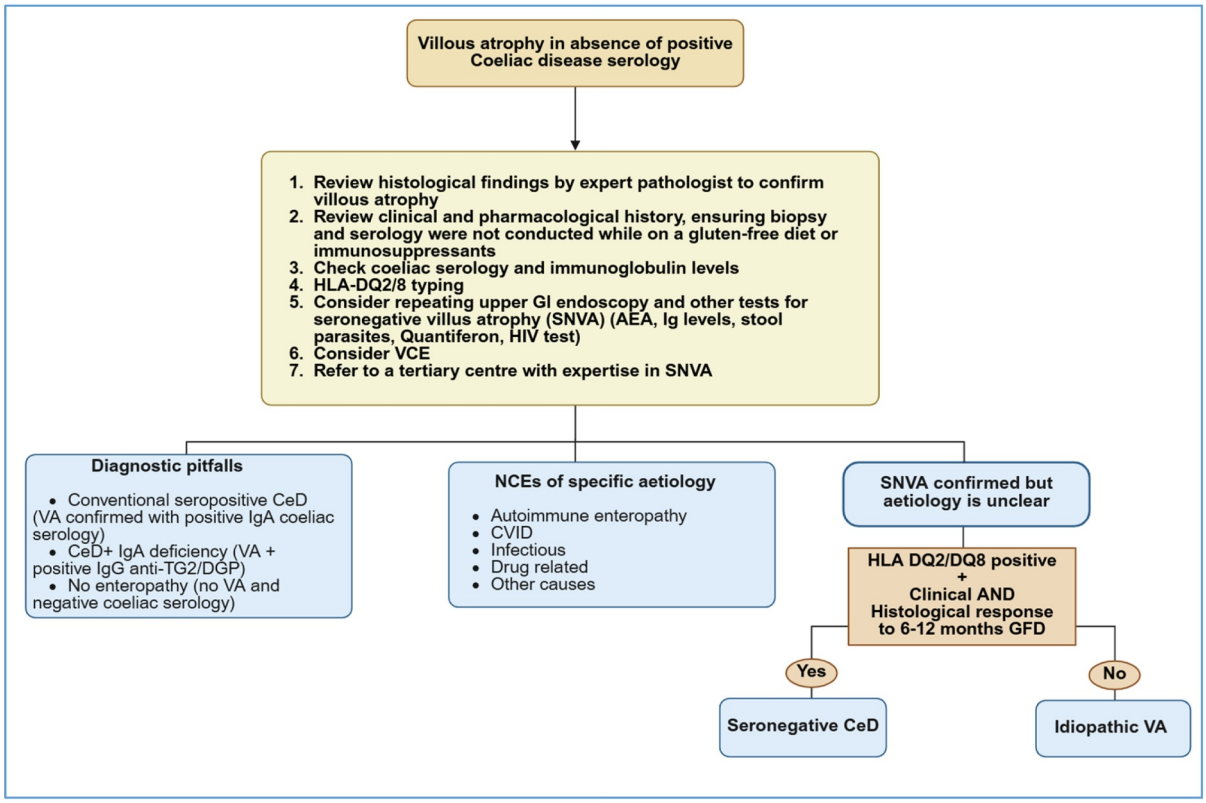

FIGURE 1 | Suggested approach for analysis of villous atrophy in absence of positive CeD serology. AEA, anti-enterocytes antibodies; AEA, Autoimmune enteropathy; CeD, Coeliac disease; CVID, Common variable immunodeficiency; GFD, Gluten-free diet; HIV, Human immune deficiency virus; Ig, immunoglobulins; NCE, non-coeliac enteropathy; SNVA, Seronegative villous atrophy; VA, villous atrophy; VCE, Video Capsule Endoscopy.

disappeared, the duodenal histology has turned mostly normal and the coeliac serology titres have already turned negative; in this situation, establishing a confident CeD diagnosis is impossible without performing a gluten challenge test. However, HLA-DQ2/8 typing, when negative, is valuable in ruling out CeD in such cases.

ii. In the evaluation of CeD patients with persistent symptoms, particularly when reassessing the accuracy of the original diagnosis.

iii. When there is a discrepancy between serology and biopsy findings, or when biopsy changes are subtle in the presence of low-titre positive coeliac disease serology.

iv. HLA-DQ2/8 typing is valuable in ruling out CeD in evaluation of patients with complains suspected to be related to gluten/wheat ingestion.

2. *Screening of at-risk groups for developing CeD*:

i. Children (first-degree relatives of patients with CeD).

ii. HLA-DQ2/8 testing is useful in individuals with IgA deficiency, patients with chromosomal disorders associated with increased CeD risk (e.g., Down syndrome, Turner syndrome, Williams syndrome), and those with Hashimoto's thyroiditis or T1DM. In these groups, the absence of HLA genetic risk allows the exclusion of the need for further serological monitoring.

5.1.4.8 | Q.IV.6. What Is the Role of Video Capsule Endoscopy and Device-Assisted Enteroscopy in the Diagnosis and Management of CeD?. *Summary of evidence:* Video capsule endoscopy (VCE) has demonstrated high diagnostic accuracy for CeD, with a sensitivity of 89% and specificity of 95%. However, its sensitivity is lower for detecting partial villous atrophy or non-atrophic lesions, making it less reliable for identifying subtle mucosal changes [172]. Despite these limitations, VCE plays an important role in the evaluation of patients with suspected complications of CeD, particularly in cases where standard duodenal biopsies are inconclusive or when symptoms persist despite adherence to a strict GFD [173, 174].

Studies have shown that both VCE and device-assisted enteroscopy (DAE), including single-balloon and double-balloon enteroscopy, can effectively detect serious complications such as ulcerative jejunitis, small-bowel lymphoma and strictures [173–176]. A meta-analysis and a prospective study confirmed the effectiveness of enteroscopy in identifying small-bowel malignancies in complicated CeD, particularly in older patients or those with a shorter duration of CeD [177, 178]. In patients with non-responsive CeD, VCE serves as a valuable non-invasive tool to assess mucosal integrity beyond the reach of conventional endoscopy [179]. If abnormalities are detected, DAE allows for targeted biopsies, which are critical for differentiating benign

inflammatory changes from premalignant or malignant conditions [174].

VCE at diagnosis was more frequently positive in patients with persistent SNVA (90.9%) and SNVA with lymphoproliferative features (80.4%) than in those with spontaneous resolution (20.5%) (= 0.0001). In seronegative CeD, a positive VCE at diagnosis was associated with adverse events ($p = 0.022$) and predicted worse outcomes, with more extensive disease linked to poorer survival [180].

While neither VCE nor DAE is indicated for the initial diagnosis of CeD, they are essential in the evaluation of complicated cases. Their use is particularly justified in patients with ongoing symptoms despite strict dietary adherence, seronegative CeD, or suspected complications such as refractory CeD (RCD) or small-bowel malignancies. These modalities help guide clinical decision-making, ensuring timely intervention in high-risk patients.

5.1.4.9 | Q.IV.7. How Do Radiological and Nuclear Medicine Techniques Contribute to the Diagnosis of Coeliac Disease Complications (e.g., Refractory CeD, Lymphoma)?. *Summary of evidence:* Radiological and nuclear medicine techniques play an important role in the evaluation of CeD, particularly in cases with atypical presentations, suspected complications, or when endoscopic and histological findings are inconclusive. Imaging techniques provide valuable additional information, especially in assessing structural changes, detecting complications, and evaluating disease severity.

Radiologists should be familiar with characteristic imaging findings suggestive of CeD. On small-bowel follow-through or enteroclysis, a reversed fold pattern, characterized by a decreased number of jejunal folds and an increased number of ileal folds, is a classic feature [181, 182]. Other common findings include small-bowel dilatation and bowel wall thickening, which may indicate mucosal atrophy and malabsorption. Transient or persistent small-bowel intussusception can also be seen, particularly in paediatric patients, though it is usually asymptomatic and self-limiting [182].

In complicated cases, radiologic imaging becomes particularly important. Cavitating mesenteric lymphadenopathy, seen as hypodense mesenteric lymph nodes with central necrosis, is strongly associated with CeD and may raise suspicion for RCD or underlying lymphoma. Other abnormalities, such as splenic atrophy and vascular abnormalities, such as increased mesenteric vascularity ('mesenteric hyperaemia'), can also be observed on imaging [183].

Cross-sectional imaging with computed tomography (CT) enterography (CTE) and magnetic resonance enterography (MRE) is valuable in detecting complications such as ulcerative jejunitis, strictures, or malignancies like enteropathy-associated T-cell lymphoma (EATL). These modalities provide detailed visualization of the small bowel and surrounding structures, helping to differentiate between inflammatory and neoplastic processes [184].

Nuclear medicine techniques, particularly positron emission tomography (PET)-CT, can be useful in assessing metabolic activity in cases of suspected lymphoma or RCD. PET-CT can help identify hypermetabolic lesions that may not be evident on conventional imaging, guiding biopsy decisions and treatment planning [185, 186].

In summary, radiology and nuclear medicine contribute significantly to the management of CeD by aiding in identifying complications, and guiding clinical decisions. Their role is particularly crucial in cases of non-responsive CeD, suspected RCD, and small-bowel malignancies.

5.1.4.10 | Q.IV.8. Gluten Challenge in the Diagnosis of CeD in Adults. How to diagnose CeD in adults who are already following a GFD without the diagnosis having been made?

Recommendations:

A gluten challenge is required if a patient suspected of having CeD has reduced or eliminated gluten from the diet before appropriate diagnostic evaluation.

CoE: low; GR: strong; Agreement: 100%

key considerations include:

- The indication, test requirements, and implications of possible outcomes should be discussed with the patient at the outset. This ensures informed decision-making and helps patients prepare for and manage the challenge period.
- Confirm HLA-DQ2/DQ8 before starting a gluten challenge, as a negative result rules out CeD.
- A minimum of 3 g/day gluten for 6 weeks balances diagnostic accuracy and likelihood of symptoms. Higher doses or longer durations improve precision if tolerated. Adjustments based on patient food preferences and anticipated symptom tolerance can support completion of the challenge phase.
- Duodenal histology is the preferred endpoint for the gluten challenge. Symptom monitoring and serology can provide additional diagnostic certainty. However, serology may be considered a substitute for histology when the IgA anti-TG2 titre is $\geq$ 10 times the ULN.
- Patients benefit from guidance on the level of gluten intake required and suitable challenge foods. The use of low FODMAP gluten-containing foods and spreading their intake throughout the day may help reduce symptoms.

Summary of evidence: A gluten challenge is required when a patient suspected of having CeD has reduced or eliminated gluten from their diet before appropriate diagnostic evaluation, as this may lead to false-negative serological and histological findings. Responses to gluten challenge vary in serological, symptomatic, and histological effects, highlighting the need for further research on optimal dose and duration [187–189].

Historical recommendations favoured challenges of up to 10 g/day for 3 months, despite limited evidence [190]. More recent trials have explored shorter challenges, such as 3 g/day for 2 weeks and 1–5 g/day over 6 weeks but these did not consistently produce diagnostic mucosal changes [123, 191]. Leonard et al. provided evidence from a randomized, double-blind study that investigated the relative abilities of multiple biomarkers to assess disease activity induced by two gluten doses, supporting a shorter challenge of 10 g/day for 2 weeks [192]. However, this is based on small sample sizes and may not be generalizable. Also, a pragmatic single-centre study trialled a low-dose gluten challenge using 60–120 mg/day via crackers over three months in adults on a GFD without prior diagnosis, with 45% developing positive serology and 87% of those biopsied showing villous atrophy. While well-tolerated and acceptable to participants, prospective multicentre studies are needed before this approach can be widely adopted [193].

Referral to a specialist dietitian with expertise in the GFD should be considered, where available, to support patients struggling with the gluten challenge. Use of low-FODMAP gluten-containing foods may help reduce symptoms, and intake can be distributed throughout the day to improve tolerability.

Consequently, the recommendations above are cautiously justified, but further research is needed to establish optimal protocols. Some patients may benefit from titrated gluten exposure over extended periods with individualised dietetic support. Testing for IL-2 in serum 4 h after an oral gluten challenge or through in vitro full-blood IL-2 release assays shows promise as a diagnostic tool but requires further validation before routine use [192].

Duodenal histological assessment is the preferred endpoint for evaluating the gluten challenge. Clinical symptom monitoring and serological testing may support the diagnosis and enhance diagnostic certainty. In cases where the serum IgA anti–TG2 antibody titre $\geq 10 \times$ the ULN, serology may be considered an acceptable alternative to histological confirmation.

The approach to diagnosis of CeD in those adults following GFD and there is a necessity to rule out or confirm CeD is shown in Figure 2.

5.1.4.11 | Q.IV.9. When Non-Coeliac Wheat Sensitivity (NCWS) Can Be Considered and What Are the Requirements to Make a Diagnosis of NCWS?. *Recommendation*: NCWS may be considered in patients with reproducible gluten-related intestinal and/or extra-intestinal complaints who have normal CeD serology and wheat allergy (WA) tests while on a gluten-containing diet and after the exclusion of major organic GI disorders. However, it is important to acknowledge the potential role of the nocebo effect in symptom development, as clinical manifestation in NCWS may be influenced by expectancy and actual gluten intake.

CoE: moderate; GR: strong; Agreement: 89%

Summary of evidence: A literature search retrieved 370 articles, with 9 selected to address NCWS diagnosis and differentiation from CeD. NCWS, historically termed non-coeliac gluten sensitivity (NCGS) since the 1970s, involves IBS-like symptoms (e.g., bloating, diarrhoea) and extra-intestinal complaints (e.g., fatigue, headache) triggered by wheat components (gluten, fructans, ATIs, WGAs) in the absence of CeD or wheat allergy [194–197]. It has global prevalence of 0.6%–13% [198].

The pathophysiology of NCWS is poorly understood. Potential triggers include gluten, fructans, Amylase Trypsin Inhibitors (ATIs), and Wheat Germ Agglutinins (WGAs) [198–200]. Exposure to wheat components leads to immune (innate, e.g., TLR-4) or non-immune responses, with FODMAPs as major triggers, similar to IBS [200–202]. Unlike CeD, NCWS lacks strong T-cell involvement or HLA-DQ2/DQ8 association. Increased intestinal permeability, hypersensitivity to food antigens, and gut microbiome changes are observed [203–205]. Additionally, a nocebo effect has been demonstrated, suggesting a possible role of the gut-brain axis in symptom development [206]. Symptom manifestation in NCWS may be influenced by both expectancy effects and actual gluten intake. Moreover, other wheat components beyond gluten—including fructo-oligosaccharides and, based on suggestive evidence, amylase–trypsin inhibitors (ATIs)—may contribute to symptom development [198–200].

NCWS diagnosis requires the following [200].

1. *Exclusion of CeD*: NCWS symptoms overlap with CeD (e.g., bloating, diarrhoea, fatigue) but differ in key features. NCWS has normal CeD serology, normal or mild histology (Marsh 0–1), no consistent HLA association, and no severe malabsorption or increased malignancy risk [202]. HLA-DQ2/DQ8 testing can aid differentiation, negative results strongly rule out CeD but are non-specific for NCWS. Because many of these patients are already on a GFD when first seen, a gluten challenge may be required.
2. *Exclusion of Wheat Allergy*: WA must be ruled out as it can mimic NCWS symptoms. A detailed history may help distinguish these conditions. Clinically, unlike NCWS, WA often involves rapid-onset symptoms (within minutes to hours) after wheat exposure, such as anaphylaxis, urticaria, or respiratory symptoms, which are rare in NCWS. Importantly, negative results on wheat-specific IgE tests (e.g., skin prick test, serum-specific IgE) are essential.
3. *Exclusion of Other GI Disorders:* NCWS diagnosis requires ruling out other GI disorders with similar symptoms. NCWS shares significant symptom overlap with IBS, particularly IBS-D (diarrhoea-predominant), as both may be triggered by FODMAPs in wheat.
4. *Reproducible Symptoms*: NCWS diagnosis hinges on demonstrating reproducible symptoms triggered by wheat ingestion, as patients often report worsening of intestinal (e.g., bloating, diarrhoea) and/or extra-intestinal (e.g., fatigue, headache) symptoms after gluten or wheat consumption [120, 207].

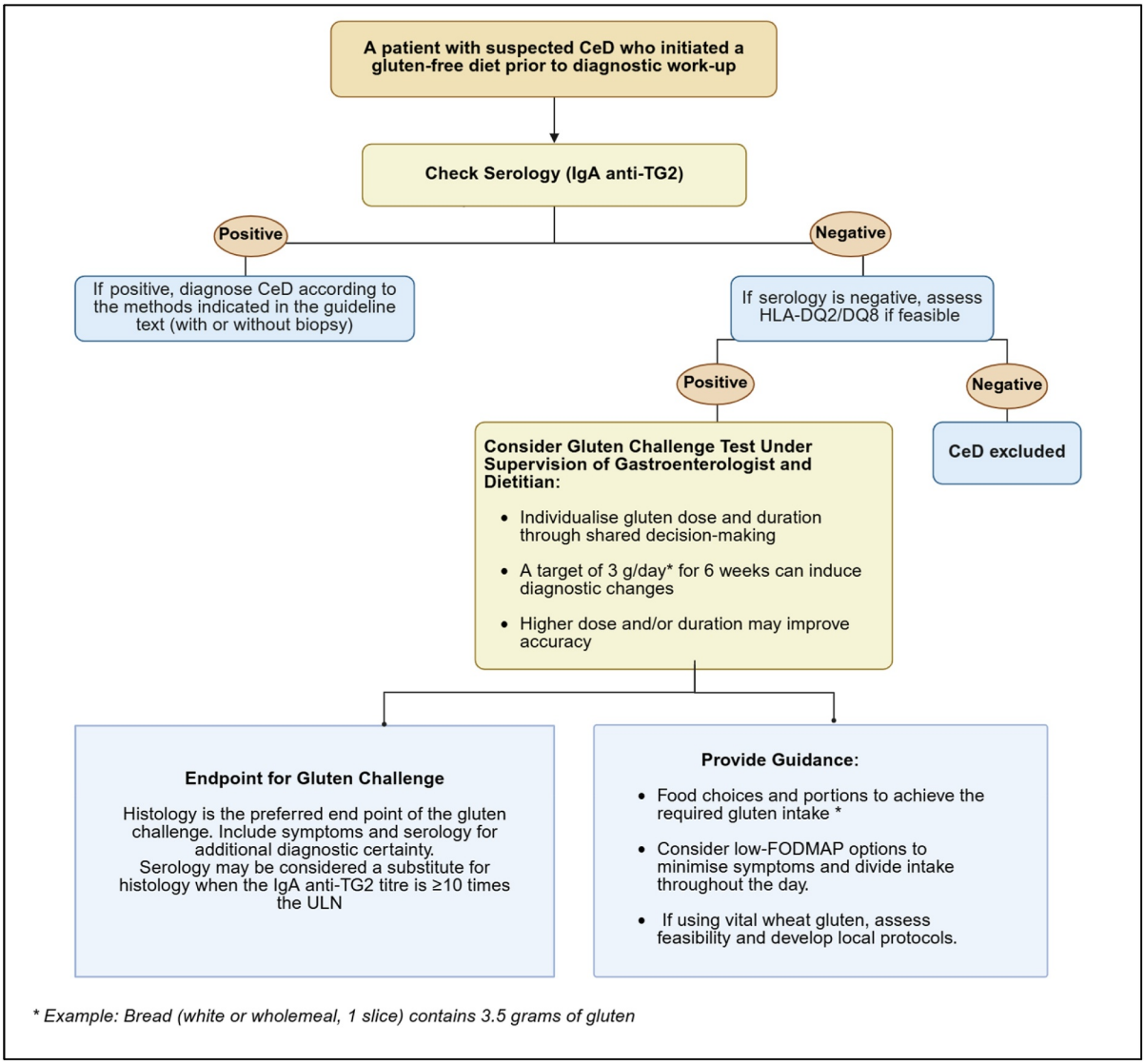

FIGURE 2 | Summarizes the approach to diagnosis of CeD in adults using gluten challenge.

A multi-step approach is suggested to make the diagnosis of NCWS, as shown in Figure 3:

6 | Conclusions, Limitations of These Guidelines and Future Perspectives

These Part 1 of the updated ESSCD guidelines on coeliac disease provide evidence-based statements and recommendations focussed on key aspects of diagnosing coeliac disease in adults. Management aspects, including approaches to non-responsive coeliac disease and refractory coeliac disease, will be addressed in the upcoming Part 2 of the guidelines. Some recommendations in Part 1 are designated good practice statements where high-quality evidence is lacking but clinical consensus supports the proposed approach. The overarching aim is to enhance the quality of care, increase awareness of this often under-recognised condition, and ultimately improve outcomes for patients with coeliac disease.

Despite considerable advances, particularly in our understanding of coeliac disease immunopathology, important knowledge gaps persist. These include challenges in diagnosing specific patient subgroups, such as those with seronegative disease, IgA deficiency, or potential coeliac disease. Additional unresolved issues include the validation of biopsy-free diagnostic thresholds across diverse populations, the clinical significance of Marsh III subclassifications, and the absence of reliable biomarkers to distinguish coeliac disease from non-coeliac enteropathies. Further research is also needed to optimize gluten challenge protocols, better define the role of HLA-DQ typing in risk stratification, and improve diagnostic tools for conditions such as non-coeliac wheat sensitivity.

As the guideline development process and the appraisal of existing evidence revealed, there is an urgent need for further research, particularly prospective diagnostic studies, to strengthen the foundation for future recommendations. Key priorities include refining biopsy-free diagnostic approaches, identifying biomarkers that differentiate patients at higher risk

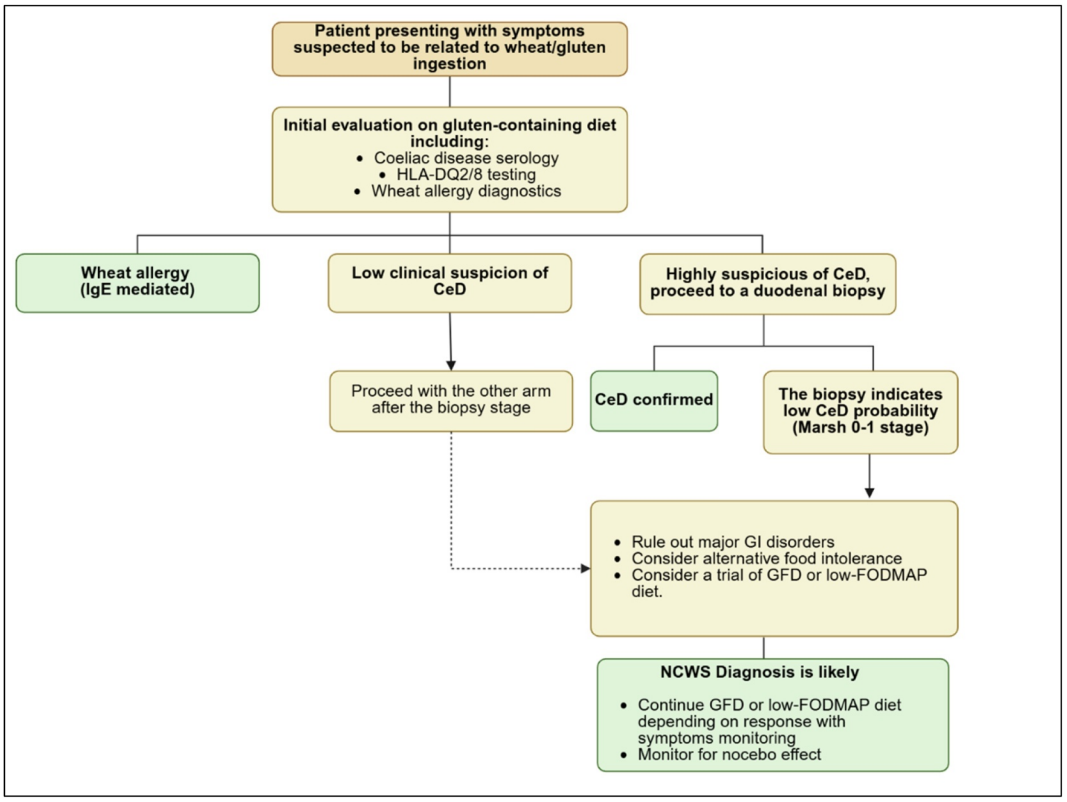

FIGURE 3 | Approach to make the diagnosis of NCWS. CeD, Coeliac disease; FODMAP, Fermentable oligo di-mono-saccharides and polyols; IBS, Irritable bowel syndrome; NCWS, Non-Coeliac Wheat Sensitivity; WA, Wheat allergy.

for complications from those likely to follow a benign course, and validating tools omitting the need for longer gluten exposures but also non-invasive screening tools such as optimized point-of-care tests. Such efforts will be essential for enabling risk stratification, guiding individualised care, and optimizing the allocation of healthcare resources.

Bridging these knowledge gaps will require sustained investment in both basic science and high-quality clinical trials to ensure future guidelines are grounded in robust and clinically meaningful evidence. At the same time, translating recommendations into practice demands effective implementation strategies and widespread dissemination. While the guidelines are designed to be broadly applicable across different healthcare systems, practical challenges remain—particularly in low-resource settings, where diagnostic infrastructure, test availability, and local policies may be limited. Rather than imposing rigid diagnostic criteria, the guideline emphasizes flexibility and advocate for locally adapted approaches based on available resources.

Looking ahead, future efforts should prioritize the development of pragmatic, context-sensitive guidance to support clinicians working in resource-limited environments, while continuing to advance research in key areas such as diagnostic thresholds, improved strategies for diagnosing patients with subtle histological or serological abnormalities (the 'grey zone' in CeD diagnosis), patients with non-coeliac enteropathies mimicing CeD, AI-assisted endoscopic techniques, and the long-term outcomes of patients diagnosed without biopsy confirmation.

Author Contributions

The ESsCD board (A.A., A.P., L.E., C.G., N.T., R.A., K.L., L.M.S., M.S.) organised the working groups and designed the preliminary list of topics to be covered. C.C., I.R., and H.O. conducted the assessment of the evidence and applied the GRADE approach. All authors (A.A., F.Z., G.M., A.S., N.T., F.B., L.E., A.P., C.G., R.A., A.B., D.S, C.S., C.M., G.B., K.E.A.L., L.M.S., M.S.) systematically reviewed the literature and draughted the statements and recommendations and provided GRADE evaluations. All authors and members of the guidelines working group voted on the statements and recommendations. The subgroups then draughted the initial manuscript, which was reviewed, revised and approved by all members of the guidelines working group. Subsequently, it was made available to all members for final comments prior to submission for publication.

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These guidelines have been developed with reasonable care and with the best of knowledge available to the authors at the time of preparation. They are intended to assist healthcare professionals and allied healthcare professionals as an educational tool to provide information that may support them in providing care to patients. Patients or other community members using these guidelines shall do so only after consultation with a health professional and shall not mistake these guidelines as professional medical advice. These guidelines must not substitute seeking professional medical and health advice from a health professional. These guidelines may not apply to all situations and should be interpreted in the light of specific clinical situations and resource availability.

It is up to every clinician to adapt these guidelines to local regulations and to each patient's individual circumstances and needs. The information in these guidelines shall not be relied upon as being complete, current or accurate, nor shall it be considered as inclusive of all proper treatments or methods of care or as a legal standard of care.

Conflicts of Interest

Before appointment to the panel, individuals disclosed financial and nonfinancial interests. No industry or government affiliations influenced this guideline. *Fabiana Zingone* has received speaker fees from Werfen, EG Stada Group, Fresenius Kabi, Kedrion, Janssen, Pfizer, Takeda, Unifarco, Malesci, and Galapagos; and has consulted for Galapagos, Takeda, and Tillotts. *Ludvig M. Sollid* has served as a consultant in the past 3 years for Falk, GSK, Precigen ActoBio, Sanofi, Takeda, and Topas Therapeutics. *Knut Lundin* has had confidentiality agreements, consultancy roles, or speaker honorariums with Allero, Alimentiv, Anokion, Amyra, Chugai, GenXBioscience, Falk, Takeda, Topas, and Tillotts. *David S. Sanders* has received an educational grant from Dr Schaer, serves as a board member of Nemysis, and has received consulting fees from Tillotts and Takeda. *Michael Schumann* has had confidentiality agreements, consultancy roles, or speaker honorariums with Falk, Takeda, Topas, Dr. Schär and Tillotts. All other authors declared no conflict of interest.

Data Availability Statement

The data that supports the findings of this study are available in the supplementary material of this article.

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