European Society for the Study of Coeliac Disease (ESsCD) 2025 updated guidelines on the diagnosis and management of coeliac disease in adults

Part 1: Diagnostic Approach
Part 2: Management, Follow-up, and Complex Disease Courses

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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

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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 ≥ 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 ≥ 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 × 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 ≥ 10 × 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 ≥ 10 × ULN is well established, with high-quality studies consistently demonstrating a positive predictive value of ≥ 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.

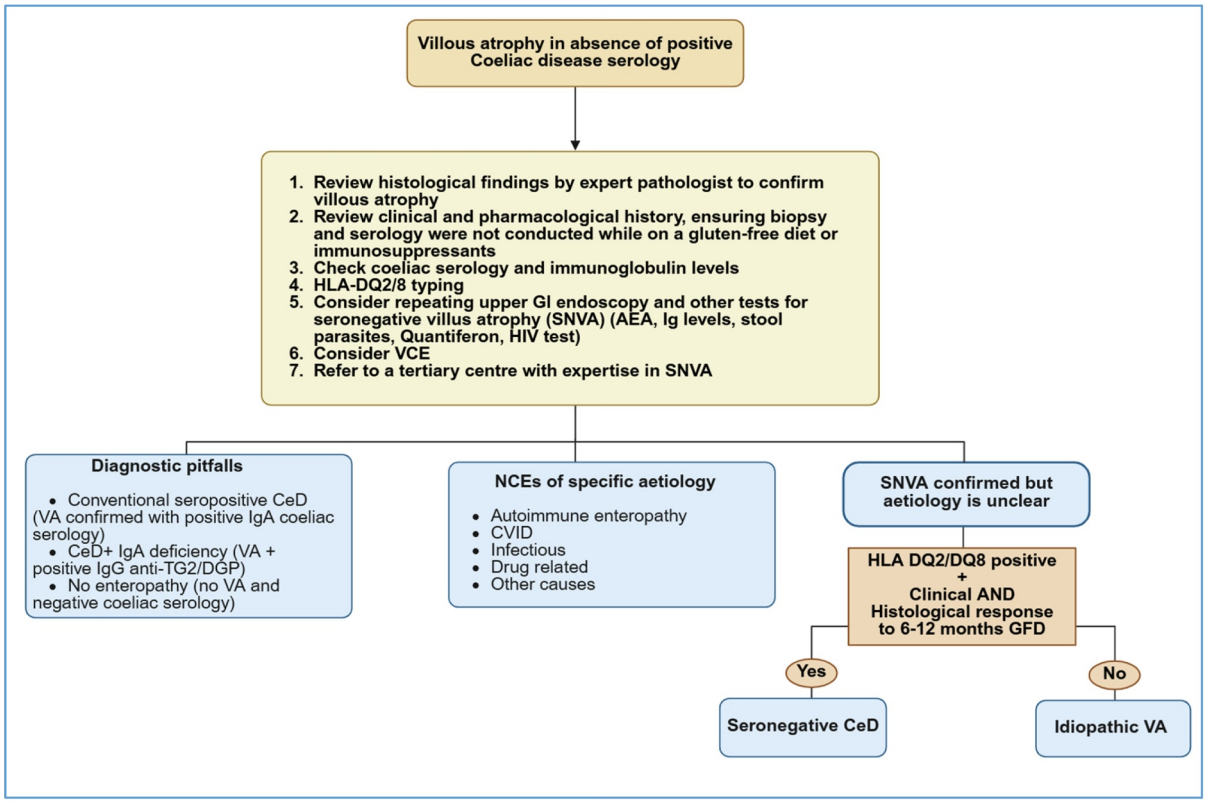

FIGURE 1 | Suggested approach for analysis of villous atrophy in absence of positive CeD serology. AEA, anti-enterocytes antibodies; AEA, Autoimmune enteropathy; CeD, Coeliac disease; CVID, Common variable immunodeficiency; GFD, Gluten-free diet; HIV, Human immune deficiency virus; Ig, immunoglobulins; 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].

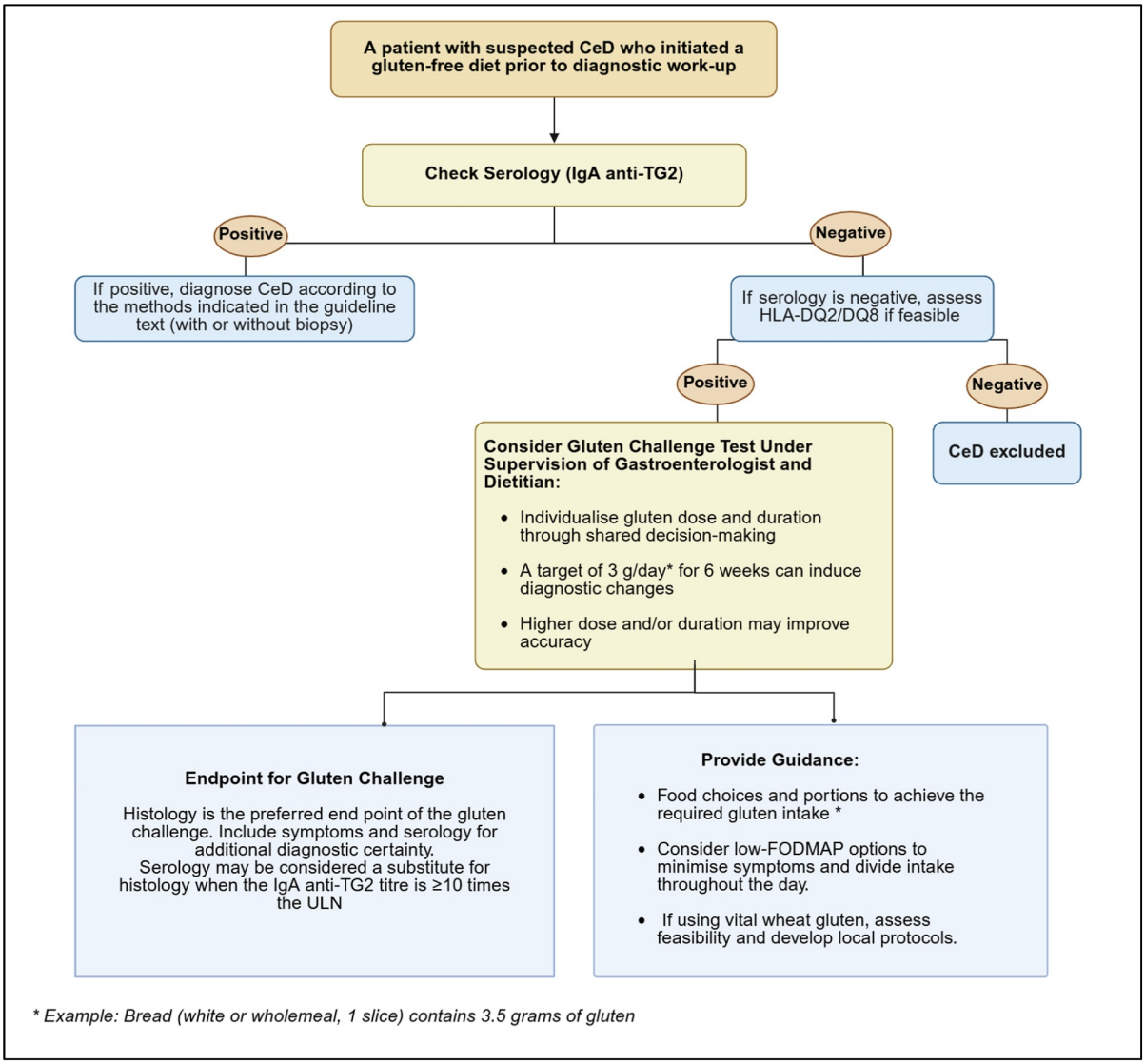

FIGURE 2 | Summarizes the approach to diagnosis of CeD in adults using gluten challenge.

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

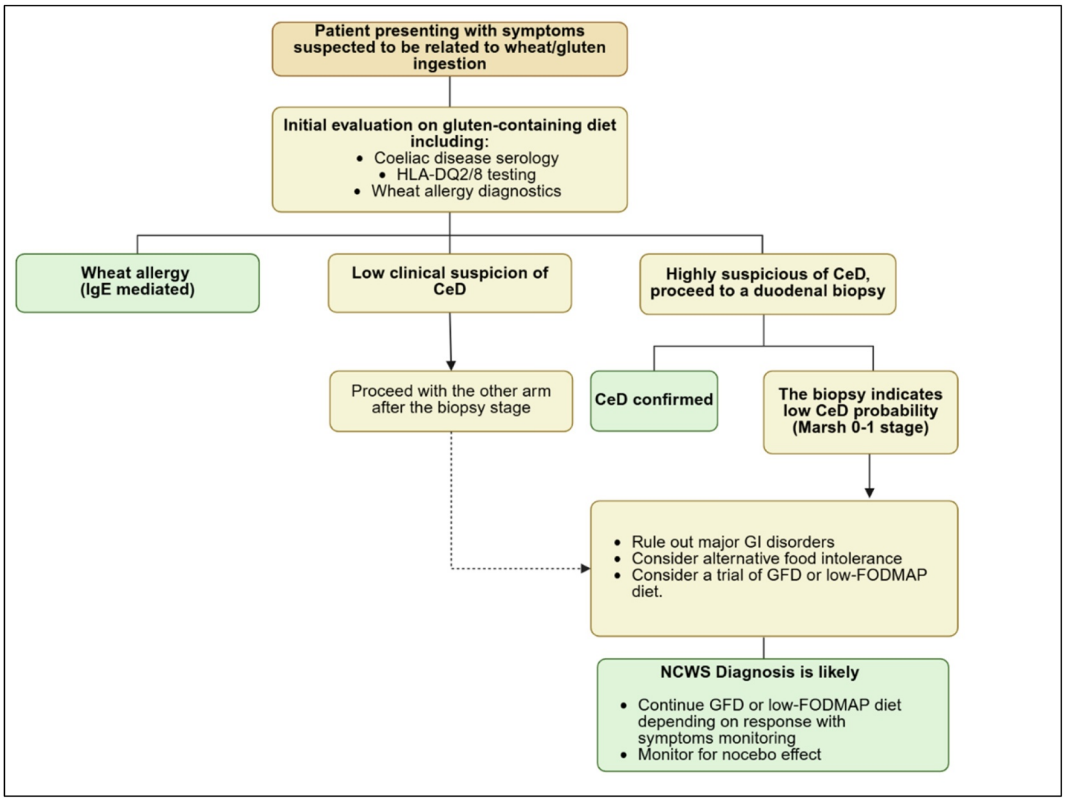

FIGURE 3 | Approach to make the diagnosis of NCWS. CeD, Coeliac disease; FODMAP, Fermentable oligo di-mono-saccharides and polyols; IBS, Irritable bowel syndrome; NCWS, Non-Coeliac Wheat Sensitivity; WA, Wheat allergy.

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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European Society for the Study of Coeliac Disease (ESsCD) 2025 Updated Guidelines on the Diagnosis and Management of Coeliac Disease in Adults. Part 2: Management, Follow-Up, and Complex Disease Courses

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ABSTRACT

Introduction: Since the publication of the first European Society for the Study of Coeliac Disease (ESsCD) guidelines in 2019, substantial advances have been made in understanding the management and complex disease courses of coeliac disease (CeD)

Abbreviations: AGA, Antigliadin Antibodies; AGREE-II, Appraisal of Guidelines for Research and Evaluation II; auto-HSCT, Autologous Hematopoietic Stem Cell Transplantation; BMD, Bone Mineral Density; CeD, Coeliac Disease; CoE, certainty of evidence; DAE, Device-Assisted Enteroscopy; DGP, Deamidated Gluten Peptides; DH, Dermatitis Herpetiformis; DXA, Dual Energy Absorptiometry Measurement; EATL, Enteropathy-associated T cell Lymphoma; ESPGHAN, European Society Paediatric Gastroenterology, Hepatology and Nutrition; ESsCD, European Society for the Study of Coeliac Disease; FODMAPs, fermentable oligo di-mono-saccharides and polyols; GFD, Gluten-Free Diet; GR, grade of recommendation; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HLA, Human Leucocyte Antigen; IBD, Inflammatory Bowel Disease; IBS, Irritable Bowel Syndrome; ICI, immune checkpoint inhibitor; IEL, Intraepithelial Lymphocytes; IgA anti-EMA, anti-Endomysial Antibodies; LE, Level of Evidence; NA, Not Applicable; NCWS, Non-Coeliac Wheat Allergy; NPV, Negative Predictive Value; POCT, Point-of-care testing; PPV, Positive Predictive Value; QoL, Quality of Life; RCD-I, Refractory Coeliac Disease type 1; RCD-II, Refractory Coeliac Disease type 2; 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.

in adults. These 2025 updated guidelines aim to integrate new evidence, refine management strategies, and promote a personalised and multidisciplinary approach to care.

Methods: The ESsCD convened a multidisciplinary panel of experts to revise the 2019 guidelines using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) framework. Evidence was appraised and graded according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology. Statements and recommendations were draughted within working groups and finalised through a structured Delphi consensus process.

Results: The updated guidelines are presented in two parts. *Part 1*, which has already been published, addresses the diagnostic approach to CeD in adults, whereas *Part 2* focuses on disease management, structured follow-up, and the evaluation and treatment of persistent symptoms despite a gluten-free diet or refractory disease. New or expanded sections include guidance on the safe inclusion of oats, use of low-FODMAP diets in patients with persistent symptoms, management of exocrine pancreatic insufficiency, recognition of functional asplenia and related vaccination recommendations, and stratified bone-health screening. The guidelines also discuss nutritional and psychosocial support, digital models of care, and structured transition from paediatric to adult services. Updated therapeutic strategies for refractory CeD are provided, including immunosuppressive and novel pharmacologic options.

Conclusions: These updated guidelines offer a comprehensive, evidence-based framework for the management and follow-up of adults with CeD. By integrating recent scientific advances with pragmatic, patient-centred recommendations, they seek to optimise clinical outcomes, quality of life, and long-term health in individuals with CeD.

1 | Introduction

The 2025 European Society for the Study of Coeliac Disease (ESsCD) guidelines on coeliac disease (CeD) are presented in two complementary parts. Part 1 focuses on the diagnostic approach [1], whilst part 2- the present document-addresses disease management, follow-up, and the approach to patients with persistent or recurrent symptoms despite gluten-free diet (GFD) and refractory CeD (RCD). Together, these updates provide an integrated framework encompassing the full spectrum of adult CeD care.

These guidelines present an update to the 2019 ESsCD guidelines on the Management of CeD and Other Gluten-Related Disorders [2]. Since their publication, emerging evidence has prompted substantial refinements in dietary management, structured follow-up, and the care of patients with complex or treatment-refractory disease. Key developments include:

1. Dietary Management: Maintenance of a lifelong strict GFD remains central to treatment, with new emphasis on nutritional adequacy, metabolic health, prevention of deficiencies and aspects of food labelling. The safety of gluten-free oats is clarified, and a low-FODMAP dietary approach is proposed for patients with persistent gastrointestinal symptoms despite histological remission.
2. Follow-Up & Monitoring: The updated guidance recognises two possible follow-up strategies—a *tailored model* adapted to patient-specific needs and risk profiles, and a *standardised model* with fixed assessment intervals. Both approaches prioritise multidisciplinary evaluation, including telemedicine integration and systematic assessment of adherence, psychosocial wellbeing, and quality of life (QoL).
3. Patient Support Groups are recognized as an integral part of long-term management.
4. Transition from Paediatric to Adult Care: A "coeliac passport" is recommended to facilitate smooth transition and ensuring continuity of care, summarising key medical and dietary information.
5. Management of RCD: Updated recommendations define diagnostic criteria and therapeutic strategies, including the potential use of targeted immunosuppressive therapies such as JAK inhibitors, cladribine or fludarabine, and autologous haematopoietic stem-cell transplantation for selected patients.
6. Newly addressed areas: Management of confirmed exocrine pancreatic insufficiency in CeD, stratified bone-health monitoring, psychosocial support, pregnancy management, risk-based family screening and the potential use of gluten immunogenic peptides (GIPs) as an adjunct tool for monitoring adherence to the GFD.

Collectively, these guideline revisions reflect a paradigm shift towards personalised, proactive, and multidisciplinary care for adults with CeD. The overarching goals are to improve disease control, enhance QoL, and reduce the risk of long-term complications through evidence-based, patient-centred management.

2 | Summary of Recommendations

2.1 | Methodology

We followed the methodology for assessing the quality of evidence and risk of bias as described in Part 1 of these ESsCD guidelines [1].

Whilst maintaining the same approach to grading the overall certainty of evidence according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology, https://www.gradeworkinggroup.org/, we applied the following tools depending on study design: the Cochrane Risk of Bias tool (RoB 2) for randomized controlled trials (RCTs), ROBINS-I for non-randomized studies of interventions,

QUADAS-2 for diagnostic accuracy studies, AMSTAR-2 for systematic reviews, and the NIH Quality Assessment Tool for observational cohort and cross-sectional studies.

3 | Questions, Recommendations and Evidence: Management of Adults With Coeliac Disease

The management of CeD aims to relieve symptoms, promote mucosal healing, restore nutritional status, prevent complications, and optimize quality of life. The cornerstone of treatment is a strict, lifelong GFD, supported by expert dietetic input and ongoing adherence monitoring, whilst emerging dietary approaches, such as low-FODMAP strategies, may be considered in selected cases. Comprehensive care also includes screening for comorbidities, supporting psychosocial well-being, monitoring bone mineral density, providing vaccinations when indicated, and addressing associated conditions, including autoimmune disorders, metabolic syndrome, and extra-intestinal manifestations. Tailored strategies are required for special populations, evolving clinical scenarios such as CeD–like enteropathy during treatment with immune checkpoint inhibitors, and patients with co-existing conditions.

An overview of the key recommendations and statements addressing adult CeD management, follow-up strategies, and complex disease courses is summarised in Table 1. The clinical questions underpinning these recommendations, together with the supporting evidence, are detailed in Supplementary File 1 (PICOs and evidence tables), whilst the corresponding Evidence-to-Decision frameworks are presented in Supplementary File 2. Collectively, these resources provide a framework for holistic, multidisciplinary care that addresses both the biological and psychosocial impact of CeD.

3.1 | Dietary Management: The Gluten-Free Diet

3.1.1 | The Fundamentals of Dietary Management

3.1.1.1 | Q. What Is the Treatment for CeD?. *Recommendation:* The treatment for CeD is a lifelong adherence to a GFD. Strict adherence is essential for controlling symptoms, improving QoL, and reducing the risk of long-term complications.

Certainty of evidence (CoE):moderate; GR: strong; Agreement: 100%

3.1.1.2 | Q. Is There an Established Threshold for Safe Gluten Intake in Patients With CeD?. *Recommendation:* The generally accepted daily threshold of gluten intake for individuals with CeD is no more than 10 mg of gluten per day, as higher intakes over time may induce mucosal injury in some individuals.

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

3.1.1.3 | Q. Are Oats Safe for Patients With CeD?. *Recommendation:* Only certified gluten-free oats are safe and should be recommended for people with CeD and can be included from diagnosis as part of a well-balanced GFD. A small subset may develop intolerance related to avenin-specific CD4+ T cells.

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

Summary of evidence: The only effective treatment for CeD is lifelong, strict adherence to a GFD, requiring complete exclusion of wheat, rye, and barley. Consistent evidence from large observational cohorts and systematic reviews involving more than 30,000 individuals shows that a GFD leads to rapid and sustained symptom improvement, serological normalization, and mucosal healing in most patients [3–5].

Symptomatic relief typically occurs within months, although 10%–20% of adults may experience persistent symptoms despite apparent adherence [6, 7]. Normalization of IgA anti-TG2 antibodies is common correlates fairly well with disease control, but complete histological healing is observed less frequently in adults than in children [4, 5]. Strict adherence improves nutritional status, reduces deficiency-related complications, and is associated with better QoL, although many patients experience social, practical, and psychological burdens in daily life and healthcare settings [6, 8–10].

Professional dietary counselling significantly enhances adherence and patient well-being, and minimizing inadvertent gluten exposure—particularly through cross-contamination in domestic, social, travel, and hospital environments—remains an essential component of long-term management [11]. In hospital settings, unintended gluten exposure remains common; safe management requires clear communication of dietary needs, access to gluten-free meals, and involvement of hospital dietetic services to ensure appropriate food provision and avoidance of contamination [12].

Because eliminating gluten entirely is difficult, *international thresholds* have been established to define ‘safe’ gluten exposure and to regulate gluten-free labelling. The relationship between gluten intake, symptoms, mucosal injury, and long-term outcomes in CeD remains incompletely defined. A well-designed 3-month micro-challenge study showed that 50 mg of gluten per day caused mucosal damage in several participants, whereas 10 mg per day per day was not consistently associated with histological deterioration over the study period [13]. Based on these and other available data, the Codex Alimentarius commission defined ‘gluten-free’ foods as containing no more than 20 mg gluten/kg (20 ppm), a threshold derived using conservative assumptions and clinical evidence indicating that most individuals with CeD tolerate daily gluten intakes below 10 mg without histological damage. Assuming a daily consumption of approximately 500 g of solid food, this corresponds to a maximum gluten exposure of up to ~10 mg/day. This threshold has been adopted into European law (Commission Implementing Regulation (EU) No 828/2014) [14]. Importantly, the 20 ppm gluten-free threshold is currently not under reconsideration [15].

A persistent challenge is the widespread use of ‘may contain gluten’ warnings when unintentional cross-contamination during production cannot be excluded, complicating risk

TABLE 1 | Overview of recommendations and statements regarding management of CeD in adults, follow-up, and complex disease courses.

	Statement/Recommendation	Certainty of evidence	Grade of recommendation	Agreement %
3. Management of adults with CeD				
3.1. Dietary management: thg guten-free diet (GFD)				
3.1.1. The fundamentals of dietary management				
3.1.1.1. Q. What is the treatment for CeD?	The treatment for CeD is a lifelong adherence to a GFD. Strict adherence is essential for controlling symptoms, improving quality of life, and reducing the risk of long-term complications.	*Moderate*	*Strong*	100
3.1.1.2. Q. Is there an established threshold for safe gluten intake in patients with CeD?	The generally accepted daily threshold of gluten intake for individuals with CeD is no more than 10 mg of gluten per day, as higher intakes over time may induce mucosal injury in some individuals.	*Moderate*	*Strong*	100
3.1.1.3. Q. Are oats safe for patients with CeD?	Only certified gluten-free oats are safe and should be recommended for people with CeD and can be included from diagnosis as part of a well-balanced GFD. A small subset may develop intolerance related to avenin-specific CD4+ T cells.	*Moderate*	*Strong*	100
3.1.2. Role of the dietitian at diagnosis and follow-up				
3.1.2.1. Q. What is the role of the dietitian at diagnosis?	At diagnosis, the dietitian should provide education on the lifelong GFD, perform a baseline nutritional assessment, address deficiencies, and offer personalised dietary guidance. Early coordination with the healthcare team and planned follow-up are essential to support treatment initiation.	*Low*	*Strong*	100
3.1.2.2. Q. What is the role of the dietitian in the follow-up of CeD?	1. During follow-up, a CeD-specialised dietitian should monitor nutritional status, reassess deficiencies, and support ongoing adherence to a strict and balanced GFD. 2. Dietetic review is essential for detecting inadvertent gluten exposure and helping evaluate persistent or recurrent symptoms.	*Low*	*Strong*	100
3.1.3. Nutritional assessment and management				
3.1.3.1. Q. How to assess the nutritional status at diagnosis of CeD in adults?	Assessment of nutritional status at diagnosis of CeD in adults should combine clinical evaluation, anthropometric measurements, dietary assessment, and targeted laboratory testing to identify malnutrition and micronutrient deficiencies.	*Low*	*Strong*	100
3.1.3.2. Q. What are the recommendations for a balanced GFD in order to improve the nutritional status, overall health, and well-being?	For patients with CeD, a balanced GFD should be based on naturally gluten-free foods whilst recognising the risk of gluten contamination, particularly in grain products. Vigilant attention to food labelling is important. The diet should include dairy or fortified alternatives, ensure adequate macronutrient intake, and address common nutritional deficiencies, including supplementation when required.	*Low*	*Strong*	100

(Continues)

TABLE 1 | (Continued)

	Statement/Recommendation	Certainty of evidence	Grade of recommendation	Agreement %
3.1.3.3. Q. Can deficiencies of micro- or macro-nutrient arise as a result of the GFD?	When a GFD is poorly balanced, it may lead to macro- and micronutrient deficiencies. Thusly, nutritional monitoring and dietetic support are recommended.	*Low*	*Strong*	100
3.1.4. Assessment of gluten-free Diet adherence				
3.1.4.1. Q. How can adherence to a GFD be assessed in adults with CeD?	• Adherence to a GFD in adults with CeD can be assessed using a combination of clinical evaluation, serology, and structured dietary review by a specialized dietitian. • For an objective measure of recent gluten intake—particularly in cases of persistent symptoms or uncertain adherence—detection of GIPs in stool or urine can be considered. • Duodenal biopsy remains the definitive method for assessing mucosal healing but is not routinely required for adherence monitoring alone.	*Low*	*Strong*	100
3.1.4.2. Q. What are the factors associated with lower rates of adherence to GFD?	Adherence to a GFD varies widely and is reduced by factors such as younger age, lower socioeconomic status, eating outside the home, absence of symptoms, and limited knowledge.	*Low*	*Strong*	95
3.1.5. Other dietary interventions				
3.1.5.1. Q. What is the role of temporary lactose restriction in adults with CeD?	Temporary lactose restriction can play a role in adults with CeD who experience persistent gastrointestinal symptoms at diagnosis due to secondary lactase deficiency. Such intolerance is usually transient and resolves as the intestinal mucosa heals on a GFD.	*Low*	*Conditional*	100
3.1.5.2. Q. For adult patients with CeD with persistent GI symptoms, is there a role for a low-FODMAP diet?	In adults with CeD who have persistent GI symptoms despite a strict GFD and confirmed histological healing, low-FODMAP diet may be considered, provided that other potential causes of symptoms are excluded before starting this additional dietary restriction.	*Moderate*	*Conditional*	100
3.2. Multidisciplinary support				
3.2.1. Q. Does psychosocial support improve well-being, adherence, and QoL?	Psychological assessment and support may be beneficial for a subset of adults with CeD, particularly those experiencing distress or coping difficulties, as it can contribute to improved well-being, dietary adherence, and QoL.	*Low*	*Conditional*	95
3.2.2. Q. How can the transition of care from paediatric to adult services be conducted efficiently?	The guidelines panel suggests a formal transfer of medical care of adolescent with CeD. To facilitate the transfer, a transition letter from paediatricians or a coeliac passport is required, detailing criteria for CeD diagnosis, follow-up, serology, growth data, possible comorbidities, and dietary adherence.	*Low*	*Strong*	100

(Continues)

TABLE 1 | (Continued)

	Statement/Recommendation	Certainty of evidence	Grade of recommendation	Agreement %
3.2.3. Q. What is the role of patient support groups in the management of adults with CeD?	Patient support groups play a valuable role in the management of adults with CeD by providing education, practical guidance, emotional support, and advocacy, all of which can improve dietary adherence and QoL.	*Not applicable (NA)*	*Ungraded good practise statement*	100
3.3. Management of associated conditions & special scenarios				
3.3.1.1. Q. How should thyroid function be assessed in adults with CeD?	Thyroid function should be assessed at the time of CeD diagnosis using a TSH test, with automatic reflex free T4 testing if TSH is abnormal. Consider repeating thyroid function tests periodically, especially in patients with symptoms or risk factors for thyroid disease.	*Low*	*Strong*	100
3.3.1.2. Q. Are there additional dietary recommendations for patients with CeD patients with concomitant type1 diabetes mellitus?	Patients with CeD and concomitant T1DM should follow a dietary plan that integrates gluten-free requirements with the carbohydrate-counting strategies essential for T1DM management. Emphasis on gluten-free carbohydrate sources with a lower glycaemic index may help support more stable glycaemic control.	*Low*	*Strong*	100
3.3.2. Bone mineral density in adults with CeD				
3.3.2.1. Q. Should adults with CeD undergo assessment of bone mineral density, and which individuals require a DXA scan?	Adults with CeD are at increased risk of reduced bone mineral density (BMD) and related fractures. Assessing BMD enables timely interventions to support bone health and prevent osteoporosis, including correction of nutritional deficiencies, lifestyle measures, and optimisation of the GFD. A baseline DXA scan is recommended after 1 year on a GFD for adults with CeD who have additional risk factors for low BMD, including delayed diagnosis, severe malabsorption or marked weight loss at presentation, a history of fragility fractures, other independent osteoporosis risk factors, or down syndrome. For adults without these additional risk factors, routine DXA scanning is not mandatory. However, it may be considered in those approaching midlife (> 35–40 years), where low bone mass is more common. FRAX can support individualised fracture-risk assessment and decision-making.	*Low*	*Strong*	89
3.3.3. Immune dysfunction and vaccination				
3.3.3.1. Q. Which patients with CeD require pneumococcal vaccination?	Pneumococcal vaccination is recommended for adults with CeD with evidence of functional asplenia, concurrent autoimmune disorders or RCD-II, as well as for patients over 65 years.	*NA*	*Ungraded good practise statement*	100
3.3.4. Extra-intestinal manifestations				
See Section 3.3.4	We recommend that significant extra-intestinal manifestations of CeD be managed by a multidisciplinary team. This should include a	*NA*	*Ungraded good practise statement*	100

(Continues)

TABLE 1 | (Continued)

	Statement/Recommendation	Certainty of evidence	Grade of recommendation	Agreement %
	gastroenterologist and dietitian to oversee the GFD and intestinal health, alongside a specialist with expertise in the specific manifestation (i.e., neurologist, dermatologist, dentist) for targeted diagnosis and management.			
3.3.5. Concurrent GI and metabolic issues				
3.3.5.1. Q. Would CeD patients benefit from pancreatic enzyme supplementation?	In adult patients with CeD, pancreatic enzyme replacement therapy (PERT) may be indicated when exocrine pancreatic insufficiency is confirmed. PERT can improve digestive function, relieve symptoms such as steatorrhoea and bloating, enhance nutrient absorption, and improve QoL.	*Moderate*	*Conditional*	89
3.3.5.2. Q. Do probiotics improve symptoms and QoL when added to a GFD?	Current evidence is insufficient to support or oppose the use of probiotics alongside a GFD for improving symptoms and QoL in patients with CeD. Further research may determine their effectiveness.	*NA*	*Ungraded good practise statement*	95
3.3.5.3. Q. Are adults with CeD on a GFD at higher risk of developing metabolic syndrome?	Adults with CeD on a GFD have a higher risk of developing metabolic syndrome compared to individuals with CeD before dietary therapy. A balanced GFD, active lifestyle, and regular monitoring for metabolic risk factors—including obesity, hypertension, dyslipidaemia, and insulin resistance—are recommended.	*Low*	*Strong*	89
3.3.6. Special scenarios				
3.3.6.1. Q. Do pregnant women with CeD require specialized care?	Although evidence is limited, coordinated preconception and perinatal care may help optimize nutritional status in women with CeD and support a healthy environment for early foetal development. Postpartum care should continue to emphasize maintaining the GFD.	*NA*	*Ungraded good practise statement*	95
3.3.6.2. Q. What are the key management considerations for patients diagnosed with CeD at an older age?	In patients diagnosed with CeD at an older age, non-classical symptoms are common, often causing diagnostic delays. These patients have an increased risk of complications, including osteoporosis and malignancy. Although response to a GFD may be slower, it provides substantial clinical benefit and should be strongly considered.	*NA*	*Ungraded good practise statement*	100
3.3.6.3. Q. How to screen family members of patients with CeD?	1. HLA-DQ2/8 genotyping is recommended as the initial screening step primarily in children of patients with CeD —where it can prevent repeated testing—while anti-TG2 serology remains the most cost-effective and widely available initial test for adults and lower-risk relatives. 2. Follow-up: For first-degree relatives who are seronegative at initial assessment, periodic antibody follow-up (e.g., every 4–5 years) may	*Moderate*	*Conditional*	95

(Continues)

TABLE 1 | (Continued)

	Statement/Recommendation	Certainty of evidence	Grade of recommendation	Agreement %
	be considered based on individual risk factors and new symptoms.			
3.3.6.4. Q. How to manage adults presenting with the rare severe presentation 'coeliac crisis'?	Although rare in adults, coeliac crisis—often a manifestation of refractory CeD type 2—requires urgent admission for multidisciplinary care to address dehydration, electrolyte/nutritional deficits, and precipitating factors, whilst promptly initiating a strict GFD.	*NA*	*Ungraded good practise statement*	95
3.3.6.5. Q. What is the recommended management for patients who develop CeD–like enteropathy during treatment with immune checkpoint inhibitors?	In patients receiving immune checkpoint inhibitors (ICI) who develop diarrhoea, coeliac serology should be obtained. If serology is positive, histological confirmation of CeD should be sought. Conversely, if a CeD-like enteropathy is identified histologically in a patient on ICI, coeliac serology should be performed to confirm the diagnosis. First-line management is a strict GFD when CeD is confirmed. Systemic immunosuppression or modification of immunotherapy should be reserved for severe presentations or cases not responding to a GFD, with decisions guided by multidisciplinary discussion.	*Low*	*Conditional*	95
3.4. Pharmacological therapies				
3.4.1. Q. What is the current status of non-dietary drug treatments for CeD?	Non-dietary pharmacological treatments for CeD hold promise for the future but remain experimental and are currently available only within clinical trials.	*Moderate*	*Strong*	100
4. Long-term follow-up and monitoring				
4.1. Q. Why is long-term follow-up recommended for adults with CeD?	Long-term follow-up is recommended to monitor dietary adherence, detect complications and comorbidities, and provide ongoing nutritional and psychosocial support, which helps ensure sustained disease control and optimised long-term outcomes.	*NA*	*Ungraded good practise statement*	95
4.2. Q. What is the most appropriate healthcare setting for the long-term follow-up of adults with CeD, and how should responsibilities be shared between primary and secondary care?	Long-term follow-up of adults with CeD is best coordinated through hospital-based outpatient clinics or specialized coeliac centres, where feasible. For stable patients, follow-up may be conducted in primary care, provided there is clear access to specialist support. Digital tools can be utilised to support remote monitoring and dietary adherence.	*NA*	*Ungraded good practise statement*	95
4.3. Q. Should follow-up of adults with CeD be conducted at fixed-intervals or tailored to the individual through a patient-centred approach?	Both fixed-interval and individualised strategies for follow-up of adults with CeD have advantages; however, follow-up should be individualised and patient-centred, taking into account disease activity, treatment adherence, comorbidities, and individual needs.	*NA*	*Ungraded good practise statement*	100
	The role of IgA anti-TG2 in follow-up is to identify ongoing gluten exposure; a positive	*Moderate*	*Strong*	95

(Continues)

TABLE 1 | (Continued)

	Statement/Recommendation	Certainty of evidence	Grade of recommendation	Agreement %
4.4. Q. What is the role of coeliac serology in follow-up of adult patients with CeD?	IgA anti-TG2 result in patients with CeD on a GFD suggests potential poor dietary adherence or gluten contamination, whilst a negative result does not confirm strict adherence or the absence of gluten exposure and it is not a reliable marker of villous atrophy.			
4.5. Q. Is a follow-up duodenal biopsy necessary in adults with CeD?	A follow-up duodenal biopsy is not routinely necessary for all adults with CeD. It is recommended in a personalized manner, guided by factors such as age at diagnosis, symptom severity, serological status, and clinical response to the GFD. A biopsy should be considered if symptoms persist or worsen.	*Low*	*Conditional*	95
5. Complicated CeD				
5.1. Kinetics of clinical, serologic and histologic response to a GFD in adults with CeD				
5.1.1. Q. When is a clinical response to the diet to be expected in adults with CeD?	Clinical response to a GFD in adults with CeD shows substantial inter-individual variability, with symptom improvement generally expected within 4 weeks to 4–5 months after diet initiation.	*Low*	*Strong*	100
5.1.2. Q. When is a serological response to the diet to be expected in adults with CeD?	A decline in IgA anti-TG2 can be observed as early as 2–4 weeks after starting a GFD, and in the majority, titres normalize within approximately 12 months. There is, however, strong inter-individual variation in this response.	*Moderate*	*Strong*	100
5.1.3. Q. When is a histological response to the GFD to be expected in adult CeD patients?	Healing of the duodenal mucosa is generally expected around 1 year after starting a GFD. However, the proportion of patients achieving full histological recovery ranges widely, from approximately 50%–83% after 1–5 years.	*Low*	*Strong*	100
5.2. Delayed or incomplete response to a GFD				
5.2.1. Q. What are causes of delayed or incomplete response to a gluten-free diet in adult CeD patients?	An incomplete response to a GFD is often due to ongoing gluten exposure but may also indicate slow-responsive disease, RCD, initial misdiagnosis, or concurrent conditions. Persistent symptoms or villous atrophy after ≥ 12 months requires systematic evaluation.	*Moderate*	*Strong*	100
5.2.2. Q. How to evaluate an adult patient with CeD having persistent symptoms despite GFD?	For a symptomatic adult with CeD despite a GFD, first verify the original diagnosis and assess for gluten exposure. If adherence is confirmed, proceed with follow-up histology and evaluate for alternative or overlapping conditions—such as functional disorders, other GI diseases, refractory CeD, or malignancy—using a multidisciplinary approach.	*Moderate*	*Strong*	100
5.3. Refractory coeliac disease				
5.3.1. Q. What is the definition of RCD?	RCD is defined by the persistence or recurrence of symptoms and villous atrophy after at least 12 months on a strict GFD, in the	*Moderate*	*Strong*	100

(Continues)

TABLE 1 | (Continued)

	Statement/Recommendation	Certainty of evidence	Grade of recommendation	Agreement %
	absence of other causes. RCD can be either primary or secondary. Depending on the proportion of aberrant T cells, RCD is further subdivided into: RCD-I and RCD-II.			
5.3.2. Diagnosis of RCD				
5.3.2.1. Q. What is the diagnostic approach to a patient with suspected RCD?	The diagnostic approach involves a systematic workup to confirm the initial CeD diagnosis, ensure strict dietary adherence, and exclude alternative causes of symptoms or an overt EATL. Essential investigations include serology, duodenal biopsies (for histology, IEL flow cytometry, and T-cell receptor clonality analysis), enteroscopy, and cross-sectional imaging. If a strong clinical suspicion for RCD persists, further evaluation and management should be conducted in or in consultation with a tertiary centre experienced in managing RCD.	*Moderate*	*Strong*	100
5.3.2.2. Q. Which molecular diagnostic technology is the gold standard for diagnosis of RCD-II?	Accurate subtyping of RCD requires comprehensive immunophenotyping of small bowel lymphocytes to reliably diagnose or exclude RCD-II. Flow cytometric analysis of isolated IELs after immunostaining is superior to immunohistochemistry for detecting aberrant lymphocyte populations. Additional diagnostic value is provided by PCR-based T-cell receptor clonality assessment and by sequencing of genes in the JAK/STAT pathway to identify relevant somatic mutations.	*Moderate*	*Strong*	100
5.3.3. Treatment of RCD				
5.3.3.1. Q. Is there an evidence-based treatment for RCD-I and RCD-II?	No evidence-based medical treatments supported by controlled trials exist for either RCD-I or RCD-II; current management is based on expert consensus, case series, and observational data.	*Low*	*Conditional*	100
5.3.3.2. Q. What is the treatment for patients with RCD-I?	Based on retrospective and longitudinal evidence, open-capsule budesonide is considered first-line therapy for RCD-I. Conventional immunosuppressant, such as azathioprine, may be added in selected cases. When used, azathioprine should be re-evaluated for possible discontinuation after 2–3 years of clinical, histological and immunophenotypic stability.	*Low*	*Conditional*	100
5.3.3.3. Q. What is the treatment for patients with RCD-II?	Mild-to-moderate RCD-II may be treated with open-capsule budesonide. In selected patients, cladribine (or fludarabine), with or without autologous haematopoietic stem cell transplantation (auto-HSCT), or JAK inhibitors may be considered on an individual basis.	*Low*	*Conditional*	100
6. Coeliac disease and malignancy: Associations and risk of malignant transformation				
		Low	*Strong*	95

(Continues)

TABLE 1 | (Continued)

	Statement/Recommendation	Certainty of evidence	Grade of recommendation	Agreement %
6.1. Q. What is the risk of malignant complications in coeliac disease (non-refractory CeD)?	The risk of malignant complications in non-refractory CeD is only slightly increased, remains low in absolute terms, and decreases with long-term adherence to a strict GFD. Routine malignancy screening beyond general population recommendations is not indicated in the absence of clinical suspicion.			
6.2. Q. What is the risk of malignant transformation in RCD-II?	RCD-II is associated with a substantial risk of malignant transformation, most commonly progression to EATL, which develops in up to half of affected patients and is the major determinant of the markedly reduced 5-year survival seen in this subtype.	*Low*	*Strong*	100

Abbreviations: auto-HSCT, Autologous Hematopoietic Stem Cell Transplantation; BMD, Bone Mineral Density; CeD, Coeliac Disease; CoE, Certainty of Evidence; DXA, Dual Energy Absorptiometry Measurement; EATL, Enteropathy-associated T cell Lymphoma; FODMAPs, Fermentable oligo di-mono-saccharides and polyols; FRAX, Fracture Risk Assessment Tool; GFD, Gluten-Free Diet; GI, Gastrointestinal; HLA, Human Leucocyte Antigen; ICI, immune checkpoint inhibitors; IEL, Intraepithelial Lymphocytes; IgA anti-EMA, anti-Endomysial antibodies; JAK/STAT, Janus kinase/signal transducer and activator of transcription pathway; NA, Not Applicable; PCR, polymerase chain reaction; PERT, pancreatic enzyme replacement therapy; QoL, Quality of Life; RCD-I, Refractory coeliac disease type 1; RCD-II, Refractory coeliac disease type 2; T1DM, Type 1 Diabetes Mellitus; T4, Thyroxine; TG2, Tissue Transglutaminase 2; TSH, Thyroid stimulating hormone.

assessment for patients. Given this uncertainty, most centres pragmatically advise patients to avoid these products to eliminate the possibility of sporadic high-level gluten exposure.

Pharmaceutical excipients must also comply with gluten-labelling rules to prevent inadvertent exposure [16–19].

Emerging evidence indicates that sensitivity to gluten varies amongst individuals and that even very low-level exposure may provoke subtle immune activation without accompanying histological abnormalities [20], challenging the reliance on mucosal healing as the sole marker of dietary safety. Moreover, it is unclear whether histological remission fully reflects long-term risk, as complications such as lymphomagenesis may stem from persistent cytokine activity and mucosal immune dysregulation that are not captured by standard histological assessment [21–23]. Further research incorporating immunologic, molecular, and clinical outcomes is needed to better define what constitutes 'safe' gluten exposure.

However, until newer evidence is validated and incorporated into regulatory frameworks, the $\leq$ 10 mg/day threshold and the 20 ppm labelling standard remain the most evidence-based and operationally feasible definitions of 'gluten-free'.

The safety of oats in the GFD has been a longstanding topic of debate. Standard oats are commonly contaminated with gluten and are unsafe for people with CeD [24–26]. Certified gluten-free oats, however, are nutritionally valuable—providing fibre, vitamins, minerals, and antioxidants—and have been shown to improve dietary variety, GFD acceptability, and long-term gastrointestinal, psychological, and dermatological outcomes [24–26].

Historical concerns about avenin sensitivity [27, 28]. have largely been mitigated by recent studies demonstrating that purified avenin can induce only transient, dose-dependent immune activation in a small minority of adults, without causing enteropathy or serological deterioration [24, 25]. True avenin sensitivity appears to be rare.

Current evidence therefore supports the inclusion of certified gluten-free oats from diagnosis, supported by clear labelling and patient education, although timing may be individualised based on patient preference, symptom burden, or local practise. In patients with symptoms suggestive of avenin intolerance, medical review and dietetic support are recommended; a short, structured trial of oat exclusion may be considered, with subsequent reassessment, to avoid unnecessary long-term restriction if symptoms do not clearly improve [29].

3.1.2 | Role of the Dietitian at Diagnosis and Follow-Up

3.1.2.1 | Q. What Is the Role of the Dietitian at Diagnosis of CeD?. *Recommendation:* At diagnosis, the dietitian should provide education on the lifelong GFD, perform a baseline nutritional assessment, address deficiencies, and offer personalised dietary guidance. Early coordination with the healthcare team and planned follow-up are essential to support treatment initiation.

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

3.1.2.2 | Q. What Is the Role of the Dietitian in the Follow-Up of CeD?. *Recommendation*:

1. During follow-up, a CeD-specialised dietitian should monitor nutritional status, reassess deficiencies, and support ongoing adherence to a strict and balanced GFD.

2. Dietetic review is essential for detecting inadvertent gluten exposure and helping evaluate persistent or recurrent symptoms.

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

Summary of evidence: Given the complexity and lifelong nature of the GFD, referral to an experienced dietitian is essential at diagnosis and throughout follow-up. Dietitians provide personalised counselling that considers the patient's social, cultural, and economic context [30, 31].

At diagnosis: The initial consultation should reaffirm the CeD diagnosis, review comorbidities, and emphasise the need for a strict lifelong GFD. Core components of early education include: clarifying gluten-containing grains and the distinction between contaminated and certified gluten-free oats; [7, 32–35] practical training on label reading and identification of naturally gluten-free foods, suitable substitutes, and processed foods not requiring a gluten-free label; [36] strategies for safe eating outside the home and during travel; [11, 37–39] introduction to patient support organisations; [40] and a baseline nutritional assessment.

During follow-up: Dietitians support ongoing management by monitoring nutritional adequacy, reassessing deficiencies, and providing tailored guidance to maintain a strict but balanced GFD. Education should reinforce healthy dietary patterns, weight maintenance, and avoidance of disordered eating or excessive hypervigilance [41–43].

Structured dietetic assessment is central to evaluating adherence and identifying causes of persistent or recurrent symptoms. Specialist dietitians detect inadvertent gluten exposure or dietary imbalance more reliably than tools such as the Coeliac Dietary Adherence Test (CDAT), showing higher sensitivity and specificity (64% and 80%) for detecting ongoing villous atrophy [44–47].

Despite clear benefits, access to coeliac-specialist dietetic services remains inconsistent, with shortages in dedicated clinics, staffing, and consultation time [48, 49]. Improved investment, defined service standards, and better integration of dietetic care into routine management are needed to ensure equitable long-term support for adults with CeD [50, 51].

3.1.3 | Nutritional Assessment and Management

3.1.3.1 | Q. How to Assess the Nutritional Status at Diagnosis of CeD in Adults?. *Recommendation:* Assessment of nutritional status at diagnosis of CeD in adults should combine clinical evaluation, anthropometric measurements, dietary assessment, and targeted laboratory testing to identify malnutrition and micronutrient deficiencies.

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

3.1.3.2 | Q. What Are the Recommendations for a Balanced GFD in Order to Improve the Nutritional Status, Overall Health, and Well-Being?. *Recommendation:* For patients with CeD, a balanced GFD should be based on naturally gluten-free foods whilst recognising the risk of gluten contamination, particularly in grain products. Vigilant attention to food labelling is important. The diet should include dairy or fortified alternatives, ensure adequate macronutrient intake, and address common nutritional deficiencies, including supplementation when required.

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

3.1.3.3 | Q. Can Deficiencies of Micro- or Macro-Nutrient Arise as a Result of the GFD?. *Recommendation:* When a GFD is poorly balanced, it may lead to macro- and micronutrient deficiencies. Thusly, nutritional monitoring and dietetic support are recommended.

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

Summary of evidence: Nutritional deficiencies are common in adults with CeD at diagnosis, even in those with normal weight or mild symptoms, due to malabsorption from mucosal damage and inadequate intake [52–54]. Iron deficiency affects 7%–80% of newly diagnosed patients, and 2%–5% of individuals with iron-deficiency anaemia are found to have CeD [53, 55]. Fat malabsorption can reduce levels of fat-soluble vitamins—especially vitamin D, which may be further lowered when dairy is restricted for lactose intolerance—and may also lead to deficiencies of vitamins A, E, and K [56, 57]. Additional abnormalities include low albumin, haemoglobin, and trace elements such as zinc and copper; the latter is notable for potentially causing haematological abnormalities and irreversible neurological deficits [54].

Assessment of nutritional status at diagnosis and during follow-up is essential to monitor correction of deficiencies and ensure dietary adequacy [58]. Key components include:

1. History and physical assessment for signs and symptoms suggestive of deficiencies, and screening for other autoimmune disorders.
2. Weight history including BMI, and where appropriate, waist-to-hip ratio and hand-grip strength [59].
3. Laboratory evaluation: haemoglobin, iron studies, fat-soluble vitamins, B12, folate, minerals, electrolytes, and liver function tests [57].
4. Dietary assessment: food and beverage intake, evaluation of nutrients commonly deficient in CeD (iron, calcium, vitamin D, B12, and fibre) [60].

A balanced GFD is central to correcting deficiencies and promoting overall health. Recommended strategies include: [61–64].

- Naturally gluten-free foods: Gluten-free grains (e.g., quinoa, brown rice, millet, amaranth, buckwheat, gluten-free oats), fruits and vegetables, lean proteins, dairy or fortified alternatives, and healthy fats form the foundation of a balanced gluten-free diet. Whilst naturally gluten-free foods are encouraged, it should be recognised that there is a heightened risk of gluten contamination in some food categories.

Evidence indicates that contamination occurs predominantly in oats, other grains, flours, and processed products, whereas fresh fruits and vegetables, unprocessed meats, and unprocessed dairy products are rarely implicated [65, 66]. Accordingly, appropriate sourcing, careful attention to food labelling, and preferential use of certified gluten-free products—particularly for staple grain-based foods—are important to minimise inadvertent gluten exposure.

- Gluten-free substitutes: Breads, pastas, and flours facilitate culturally relevant meals and social participation. Patients should preferentially select fortified products, whilst monitoring for higher saturated fat, sugar, and energy content [67]. Processed foods may be subject to gluten contamination during manufacturing and should therefore be selected with appropriate caution.
- Supplementation tailored to individual needs.
- Education and support: Ongoing support from a specialist dietitian and engagement with patient support groups [44, 68].

Despite clinical improvement on a GFD, nutritional inadequacies may arise from the diet itself [69–78]. Many gluten-free substitutes are nutritionally suboptimal, lower in protein, fibre, iron, vitamin B12, folate, and vitamin D, and higher in saturated fat, sodium, and added sugars [77, 79–82]. A systematic review and meta-analysis showed increased risk of multiple micronutrient deficiencies in treated CeD [78]. Heavy reliance on these products can perpetuate deficiencies, contribute to constipation reduce cardiometabolic benefits, and increase energy intake.

Body-weight changes after initiating a GFD vary with baseline status, and adequate diet quality does not appear to increase long-term obesity risk [83–85].

Overall, a well-balanced GFD—emphasising naturally gluten-free foods, judicious use of fortified substitutes, supplementation when needed, and structured dietetic support—is essential to prevent nutritional deficiencies and support long-term health and wellbeing in adults with CeD [77, 86].

3.1.4 | Assessment of GFD Adherence

3.1.4.1 | Q. How can Adherence to a GFD Be Assessed in Adults With CeD?. *Recommendations:*

- Adherence to a GFD in adults with CeD can be assessed using a combination of clinical evaluation, serology, and structured dietary review by a specialized dietitian.
- For an objective measure of recent gluten intake—particularly in cases of persistent symptoms or uncertain adherence—detection of gluten immunogenic peptides (GIPs) in stool or urine can be considered.
- Duodenal biopsy remains the definitive method for assessing mucosal healing but is not routinely required for adherence monitoring alone.

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

3.1.4.2 | Q. What Are the Factors Associated With Lower Rates of Adherence to GFD?. *Statement:* Adherence to a GFD varies widely and is reduced by factors such as younger age, lower socioeconomic status, eating outside the home, absence of symptoms, and limited knowledge.

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

Summary of evidence: Assessment of adherence to a GFD in adults with CeD should employ a combination of methods, including clinical evaluation, serology, structured dietary review by a specialist dietitian, and, when appropriate, direct detection of gluten ingestion. Table 2 provides an overview of methods for assessing adherence to the GFD.

Factors Affecting Adherence to GFD:

Adherence to a GFD varies widely, with reported rates ranging from 42% to 91%, depending on assessment method [100]. Lower adherence is associated with younger age at diagnosis, particularly adolescence, lower socioeconomic status, local food cultures, frequent eating outside the home, absence of symptoms, and limited disease knowledge or motivation [101, 102].

Gluten-free foods remain more expensive than standard equivalents, creating a financial barrier, particularly in lower-income households, which is linked to poorer adherence [103].

Targeted support—such as prioritizing dietetic resources for at-risk individuals, providing additional consultations, improving health literacy, and addressing perceived dietary burden—can enhance adherence and long-term outcomes [104].

3.1.5 | Other Dietary Interventions

3.1.5.1 | Q. What Is the Role of Temporary Lactose Restriction in Adults With CeD?. *Recommendation:* Temporary lactose restriction can play a role in adults with CeD who experience persistent gastrointestinal symptoms at diagnosis due to secondary lactase deficiency. Such intolerance is usually transient and resolves as the intestinal mucosa heals on a GFD.

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

3.1.5.2 | Q. For Adult Patients With CeD With Persistent Gastrointestinal Symptoms, Is There a Role for a Low-FODMAP Diet?. *Recommendation:* In adults with CeD who have persistent GI symptoms despite a strict GFD and confirmed histological healing, low-FODMAP diet may be considered, provided that other potential causes of symptoms are excluded before starting this additional dietary restriction.

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

Summary of evidence: Persistent GI symptoms in adult patients with CeD are common, even in those adhering strictly to a GFD. Whilst inadequate dietary adherence and CeD-

TABLE 2 | Overview of methods for assessing adherence to the gluten-free diet.

Method	Details
Dietary assessment and adherence questionnaires	Validated tools evaluate self-reported compliance and understanding of the GFD. They are simple, inexpensive, and widely available, but are subjective and may miss inadvertent gluten exposure [87, 88]. structured dietetic assessment is often more sensitive than questionnaires or serology alone in detecting ongoing dietary transgressions and guiding interventions [87, 89].
CeD serology (e.g., IgA anti-TG2)	Reflects ongoing autoimmune response to gluten. Serology is routinely available and useful for long-term follow-up, but slow normalisation and occasional gluten exposure may not be detected, and negative results do not guarantee mucosal recovery. [90]
Testing for GIPs in stool or urine	GIPs are gluten fragments detectable for up to 4 days in stool and 48 h in urine. When available, GIP testing provides a moderately sensitive and specific real-time measure of recent gluten ingestion and is particularly useful when symptoms persist or adherence is uncertain. Nevertheless, GIPs do not provide a fully reliable measure of inadvertent gluten exposure [91–93].
Other biomarkers	Intestinal fatty acid-binding protein (I-FABP) reflects recent enterocyte injury and correlates with villous atrophy; however, its use remains investigational pending validation in larger studies [94–97]. Faecal calprotectin has inconsistent utility in CeD monitoring [98, 99].
Duodenal biopsy	Remains the gold standard for assessing mucosal healing but is not routinely required for adherence monitoring. See Section 4.5.

Abbreviations: CeD, Coeliac disease; GFD, Gluten-free diet; GIPs, Gluten Immunogenic peptides; I-FABP, Intestinal fatty acid-binding protein; TG2, Transglutaminase 2.

related complications—such as refractory CeD (RCD) or ongoing mucosal inflammation—are important considerations, a substantial proportion of patients may experience symptoms due to coexisting functional GI disorders, particularly irritable bowel syndrome (IBS) [105–108].

Secondary lactose intolerance is frequent at CeD diagnosis due to villous atrophy and reduced lactase activity, affecting up to 50%–70% of untreated patients [109]. Symptoms usually improve with mucosal healing on a GFD. Temporary lactose restriction may be considered in symptomatic patients, with gradual reintroduction once tolerance is restored [110]. Dietitian guidance is essential to ensure adequate calcium and vitamin D intake.

In patients with persistent IBS-type symptoms despite strict GFD adherence and confirmed histological healing, a structured low-fermentable oligo-, di-, mono-saccharides and polyols (low-FODMAP) diet may reduce bloating, abdominal pain, and altered bowel habits [105, 106, 111–113].

A systematic review and meta-analysis found that, when implemented for a minimum of 4 weeks, a low-FODMAP diet was significantly more effective than a standard GFD alone in reducing GI symptoms, particularly bloating, abdominal pain, and altered bowel habits [113].

Before initiating a low-FODMAP diet, other potential causes of persistent symptoms should be systematically excluded, including secondary lactose intolerance, fructose malabsorption, or other food intolerances. Recognition and targeted management of these conditions—through structured dietary assessment, breath testing when appropriate, and specialist dietetic input—can improve symptom control, QoL, and dietary adequacy whilst avoiding unnecessary broader FODMAP dietary exclusions.

The low-FODMAP diet is complex and highly restrictive and without appropriate guidance, there is a risk of nutritional inadequacy, disordered eating behaviours, and increased food-related anxiety. Therefore, it is strongly recommended that any implementation of the low-FODMAP diet in patients with CeD be undertaken only after excluding other potential causes of symptoms—including histological confirmation of remission of gluten-related inflammation—and under the supervision of a dietitian with expertise in both gluten-free and low-FODMAP dietary protocols. Individualized dietary reintroduction and symptom tracking are also essential components of this approach to avoid unnecessary long-term restrictions and hypervigilance [105].

3.2 | Multidisciplinary Support

3.2.1 | Q. Does Psychosocial Support in Patients With CeD Improve Well-Being, Dietary Adherence, and QoL?

Recommendation: Psychological assessment and support may be beneficial for a subset of adults with CeD, particularly those experiencing distress or coping difficulties, as it can contribute to improved well-being, dietary adherence, and QoL.

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

Summary of evidence: Adults with CeD do not always adjust easily to the GFD [114]. Beyond the physical implications of the disease, adherence to the GFD can have profound psychological and behavioural consequences. Many individuals experience lasting changes in mood, food-related behaviours, attitudes towards eating, and even their sense of identity [115]. The need for lifelong dietary restrictions may lead to feelings of frustration, social isolation, and emotional distress, particularly in

situations where access to gluten-free options is limited or where individuals feel excluded from shared meals and cultural traditions [77, 86].

Psychological distress in CeD is common, with strong evidence of increased anxiety and depression post-diagnosis, which are both associated with reduced QoL and resilience [71, 116, 117]. Moreover, there is strong evidence of an increased risk of eating disorders in patients with CeD [118, 119]. The strict requirements of a GFD, constant vigilance around food, and anxiety about inadvertent gluten exposure may contribute to restrictive or maladaptive eating behaviours. The risk is higher in women and in those diagnosed during adolescence or early adulthood. Early recognition and multidisciplinary management—including psychological support alongside dietary counselling—are essential to improve adherence, nutritional status, and overall well-being [120–123].

In patients with CeD with affective disorders, psychological support seems to be able to reduce depression and to increase GFD compliance [124]. Furthermore, psychological wellbeing is a predictor of adherence to the GFD [125], so that it appears important to provide psychological support to patients with CeD showing signs of distress in order to ensure good QoL [117, 124, 126, 127].

Whilst current evidence indicates that psychological support can be beneficial—and may even be necessary—for achieving optimal outcomes, this applies only to a subset of CeD patients and should be reserved for those with the psychological sequelae described above.

3.2.2 | How can the Transition of Care for Children or Adolescents With CeD to Adult Care Be Conducted Efficiently?

Recommendation: The guidelines panel suggests a formal transfer of medical care of adolescent with CeD. To facilitate the transfer, a transition letter from paediatricians or a coeliac passport is required, detailing criteria for CeD diagnosis, follow-up, serology, growth data, possible comorbidities, and dietary adherence.

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

Summary of evidence: Structured transition from paediatric to adult care is recommended to ensure continuity, prevent gaps in follow-up, and support self-management in adolescents with CeD. Expert consensus statements advocate a planned, individualised transition process incorporating preparatory education, assessment of transition readiness, and a formal transfer of essential clinical information through a transition letter or 'coeliac passport' [128, 129].

Observational studies suggest improved attendance and self-management with multidisciplinary support and structured transition programmes, although the evidence is heterogeneous and largely non-interventional [130].

Data linking structured transition to long-term outcomes are limited, and current recommendations are mainly consensus-based and extrapolated from other chronic disease models [131].

Practical tools such as transition checklists and coeliac passports are feasible in clinical practise, but further research is needed to identify which components most effectively improve adherence and long-term outcomes [132, 133].

Coeliac Passport—Checklist: [129]

- Main clinical presentation at diagnosis
- Coeliac disease diagnostic criteria (Serology and histology at diagnosis)
- Growth and anthropometric data
- Important lab findings
- Current medications
- Nutritional supplements
- Dietary adherence and education status
- Relevant comorbidities
- Serology and important lab at transition

3.2.3 | Q. What Is the Role of Patient Support Groups in the Management of Adults With CeD?

Recommendation: Patient support groups play a valuable role in the management of adults with CeD by providing education, practical guidance, emotional support, and advocacy, all of which can improve dietary adherence and QoL.

CoE: Not applicable (NA); GR: ungraded good clinical practise statement (UGPS); Agreement: 100%

Summary of evidence: The management of CeD extends far beyond the simple removal of gluten from the diet. It is a lifelong journey with substantial practical, emotional, and social challenges. Patient support groups play an indispensable and multi-faceted role in this journey. They provide the essential education, emotional scaffolding, and collective advocacy that empower individuals to manage their condition effectively, improve their dietary adherence, and enhance their overall QoL. As such, healthcare professionals should actively encourage newly diagnosed and existing CeD patients to engage with a reputable support group as a standard component of comprehensive care [134, 135].

3.3 | Management of Associated Conditions and Special Scenarios

3.3.1 | Associated Autoimmune Diseases

3.3.1.1 | Q. How Should Thyroid Function Be Assessed in Adults With CeD?. *Recommendation:* Thyroid function should be assessed at the time of CeD diagnosis using a TSH

test, with automatic reflex free T4 testing if TSH is abnormal. Consider repeating thyroid function tests periodically, especially in patients with symptoms or risk factors for thyroid disease.

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

Summary of evidence: Autoimmune thyroid disorders occur more frequently in individuals with CeD than in the general population, with reported prevalence rates ranging from 2% to 10% for overt thyroid disease and up to 20%–30% for thyroid autoantibody positivity [136, 137]. Untreated thyroid dysfunction can worsen symptoms such as fatigue and weight changes, complicating assessment of response to a GFD.

It is recommended that thyroid function, including serum TSH with reflex free T4 if abnormal, be assessed at CeD diagnosis [129, 138]. Periodic reassessment is strongly advised, especially for symptomatic patients or those with a personal or family history of autoimmune disease.

Although thyroid autoantibodies are frequently positive in CeD, routine antibody testing is not required, as positivity alone does not reliably predict progression to overt thyroid disease. However, selective testing, such as, antibodies against thyroid peroxidase (anti-TPO) and thyroglobulin (anti-TG) may be useful in individuals with abnormal thyroid function tests, symptoms suggestive of thyroid disease, or strong autoimmune predisposition [139]. Any abnormal findings warrant further evaluation, ideally in collaboration with an endocrinologist.

This proactive approach to monitoring is critical, as untreated thyroid dysfunction can exacerbate symptoms like fatigue and weight changes, potentially obscuring the clinical response to a GFD [140]. Early detection and management, ideally with endocrinology input, support overall metabolic stability and patient wellbeing.

3.3.1.2 | Q. Are Additional Dietary Considerations Needed for Patients With CeD Who Also Have Type 1 Diabetes Mellitus?.

Recommendation: Patients with CeD and concomitant type 1 diabetes mellitus (T1DM) should follow a dietary plan that integrates gluten-free requirements with the carbohydrate-counting strategies essential for T1DM management. Emphasis on gluten-free carbohydrate sources with a lower glycaemic index may help support more stable glycaemic control.

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

Summary of evidence: Patients with CeD and T1DM require specific and coordinated dietary support to address the needs of both conditions [141]. Evidence, particularly in younger patients, indicates that adherence to a GFD supports normal growth and stable BMI without adverse effects on HbA1c or insulin requirements [142, 143]. However, evidence on the impact of a GFD on T1DM-specific outcomes is mixed and varies by population. Meta-analyses and larger trials show no consistent improvement in HbA1c, although smaller studies suggest potential benefits in selected subgroups, such as preservation of residual beta-cell function in newly diagnosed children [144–146].

Overall, a GFD does not appear to negatively affect growth, with studies confirming stable BMI and height outcomes [147, 148]. The relationship between GFD adherence and QoL is complex, with reports of both improved and reduced QoL, highlighting the psychosocial burden and need for strong support [149, 150]. Patients with coexisting CeD and T1DM may have increased micro- and macrovascular risk, and emerging evidence suggests that GFD adherence may be protective, though data remain limited [151, 152]. Further research is needed to clarify the long-term impact of GFD therapy on diabetes-related complications [143].

Key management considerations include:

- Accurate carbohydrate counting, selection of lower–glycaemic index gluten-free foods, and ensuring nutritional adequacy [153].
- Regular monitoring of glycaemic control and nutritional status is essential, ideally within a multidisciplinary care model involving gastroenterology, endocrinology, and dietitians [154] The involvement of dietitians with expertise in both CeD and T1DM is highly desirable but may not be universally accessible. This recommendation sets an optimal standard of care, though implementation may depend on available local resources.
- Adherence to a GFD is often suboptimal in this population, underscoring the importance of strengthened follow-up and targeted dietary support [155–157].

3.3.2 | Bone Mineral Density in Adults With CeD

3.3.2.1 | Q. Should Adults With CeD Undergo Assessment of Bone Mineral Density, and Which Individuals Require a DXA Scan?.

Recommendation: Adults with CeD are at increased risk of reduced bone mineral density (BMD) and related fractures. Assessing BMD enables timely interventions to support bone health and prevent osteoporosis, including correction of nutritional deficiencies, lifestyle measures, and optimisation of the GFD.

A baseline DXA scan is recommended after 1 year on a GFD for adults with CeD who have additional risk factors for low BMD, including delayed diagnosis, severe malabsorption or marked weight loss at presentation, a history of fragility fractures, other independent osteoporosis risk factors, or Down syndrome.

For adults without these additional risk factors, routine baseline DXA scanning is not mandatory. However, it may be considered in those approaching midlife (> 35–40 years), where low bone mass is more common. FRAX can support individualised fracture-risk assessment and decision-making.

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

Summary of evidence: A decrease in bone mineral density (BMD) is reported in over 50% of adults with newly diagnosed CeD, and osteoporosis may be the sole presentation or develop later in the disease course [158, 159]. Osteoporosis and osteopenia have been reported in approximately 14% and 39% of patients, respectively, with an increased risk of osteoporotic fractures [160, 161]. CeD-related osteoporosis is associated with underweight, age over 45 years, severity of intestinal damage, and possibly male sex [160, 162, 163]. BMD often improves during the first year of a GFD, although recovery is variable and incomplete in many patients, and fracture risk remains increased compared with the general population [164, 165]. The fracture risk in CeD patients varies from 1.3 to 10-fold more than that in the general population [166–169].

Assessment of bone health should include evaluation of clinical risk factors and biochemical testing, including serum calcium, albumin, alkaline phosphatase, and 25-hydroxyvitamin D, with further investigations in those with low BMD to exclude secondary causes such as osteomalacia [170–173]. DXA and vertebral fracture assessment are useful for fracture risk prediction and monitoring, with minimal radiation exposure [171, 174]. Exposure from a DXA scan is comparable to only a few days of natural background radiation [175].

Although evidence on optimal timing is limited, baseline DXA may be considered at diagnosis or after 1 year of GFD in adults at high risk, including those with delayed diagnosis, malabsorption, significant weight loss, prior fragility fractures, or other osteoporosis risk factors. FRAX may help identify low-risk patients who would benefit from DXA, although further validation in CeD is needed given potential confounding from disease duration, adherence to the GFD, time to resolution of malabsorption, and presence of RCD [176].

Management of osteopenia includes strict adherence to a GFD, correction of vitamin D and calcium deficiency, and lifestyle measures such as weight-bearing exercise, smoking cessation, and moderation of alcohol intake. Pragmatically, many adults with CeD may benefit from ensuring a daily intake of approximately 1000 IU of vitamin D and achieving a calcium intake of around 1000 mg/day (preferably through diet, with supplementation when dietary intake is insufficient), in line with general bone-health recommendations. Repeat DXA should be considered based on individual risk profile.

Drug therapy should be reserved for patients with progressive bone loss or high fracture risk, following standard osteoporosis guidelines and individual risk assessment. Importantly, a low T-score alone—particularly in younger adults—should not automatically trigger pharmacotherapy; conversely, some older adults with osteopenia may warrant treatment based on overall fracture risk. Treatment strategies may differ between males and females, and premenopausal women require special consideration [177, 178]. In individuals with persistent diarrhoea, parenteral medication may be necessary [179].

Specialist referral is recommended when bone loss is unexplained, comorbid endocrine or musculoskeletal disorders are present, or management decisions are uncertain.

Key Points:

- Low bone mineral density is common in adults with CeD, and fracture risk is increased.
- Assess clinical risk factors and check calcium, vitamin D, and related biochemical markers.
- DXA is indicated in high-risk adults and may be considered in those > 35–40 years depending on individual risk.
- FRAX can help guide DXA decisions in low-risk patients, though further validation in CeD is needed.
- Management includes strict GFD, adequate calcium/vitamin D, and regular weight-bearing/resistance exercise.
- Correct vitamin D and calcium deficiency to avoid osteomalacia before considering osteoporosis therapy.
- Pharmacotherapy should follow country-specific guidelines and individual fracture risk—not T-score alone.
- Refer to an osteoporosis specialist when bone loss is unexplained or comorbidities complicate management.

3.3.3 | Immune Dysfunction and Vaccination

3.3.3.1 | Q. Which Patients With CeD Require Pneumococcal Vaccination?. *Recommendation:* Pneumococcal vaccination is recommended for adults with CeD with evidence of functional asplenia, concurrent autoimmune disorders or RCD-II, as well as for patients over 65 years.

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

Summary of evidence: Functional asplenia or hyposplenism is diagnosed by the presence of Howell-Jolly bodies and pitted erythrocytes in the peripheral blood smear or radiological conformation of splenic atrophy.

Functional asplenia and/or radiological evidence of splenic atrophy is observed in 19%–43% of uncomplicated CeD cases, in 59% of those with associated autoimmune disorders, and in over 80% of patients with RCD-II or enteropathy-associated T-cell lymphoma (EATL) [180–183]. The duration of gluten exposure before diagnosis and older age at diagnosis are key prognostic factors for developing functional asplenia [184].

Because of hyposplenism, patients with CeD have a higher risk of sepsis, particularly from encapsulated bacteria such as *Streptococcus pneumoniae*, compared with the general population [185, 186]. Up to 61% of patients with CeD—including

those adhering to a GFD and those without Howell–Jolly bodies or pitted erythrocytes—show functional defects in IgM memory B cells [187]. Although a GFD can reverse functional asplenia, it does not restore structural splenic atrophy [188, 189].

Adherence to vaccination guidelines markedly reduces the incidence of severe infections and contributes to improved overall health and QoL [190–193].

3.3.4 | Management of Specific Extra-Intestinal Manifestations

Recommendation: We recommend that significant extra-intestinal manifestations of CeD be managed by a multidisciplinary team. This should include a gastroenterologist and dietitian to oversee the GFD and intestinal health, alongside a specialist with expertise in the specific manifestation (i.e., neurologist, dermatologist, dentist) for targeted diagnosis and management.

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

Summary of Evidence: A multidisciplinary approach is the standard of care for specific extra-intestinal manifestations of CeD, as these conditions require specialized diagnostic and therapeutic expertise beyond the scope of gastroenterology alone. The GFD remains the foundational, shared treatment goal, but collaboration is essential for optimal patient outcomes. The management of specific extra-Intestinal manifestations is summarised in Table 3.

3.3.5 | Concurrent GI and Metabolic Issues

3.3.5.1 | Q. Would CeD Patients Benefit From Pancreatic Enzyme Supplementation?. *Recommendation:* In adult patients with CeD, pancreatic enzyme replacement therapy (PERT) may be indicated when exocrine pancreatic insufficiency is confirmed. PERT can improve digestive function, relieve symptoms such as steatorrhoea and bloating, enhance nutrient absorption, and improve QoL.

TABLE 3 | Management of specific extra-intestinal manifestations.

3.3.4.1. Neuro-Coeliac
The management of neurological manifestations (e.g., gluten ataxia, peripheral neuropathy) in CeD necessitates a strict GFD, involving a multidisciplinary team (gastroenterology, neurology, dietetics). Neurological assessment to define deficits, exclude alternative causes, monitor progression, and manage symptoms. Early establishment of a gluten-related aetiology is important, as recovery may be only partial [194, 195].
3.3.4.2. Dermatitis herpetiformis (DH) and other dermatological associations
DH: Lifelong strict GFD (cornerstone therapy); dermatology-led diagnosis (skin biopsy) and short-term pharmacologic treatment (e.g., dapsone) [196–198]. multidisciplinary care with gastroenterology to assess enteropathy, monitor treatment-related adverse effects, and reinforce GFD adherence [196]. Other dermatological associations: Higher prevalence in CeD (e.g. psoriasis, atopic dermatitis, alopecia areata, chronic urticaria); not primarily gluten-dependent, though partial improvement with GFD reported in some patients [199, 200]. Management is primarily dermatology-led, with gastroenterology involvement when CeD is suspected or confirmed.
3.3.4.3. Oro-Dental care
Recurrent aphthous stomatitis and other oral lesions may occur in adult CeD [201]. Dental involvement to identify suggestive oral signs, manage oral lesions, and reinforce GFD adherence. Address oral complications related to nutrient deficiencies and associated autoimmune conditions [202, 203].
3.3.4.4. Chronic fatigue
Fatigue is a common extra-intestinal manifestation of CeD. Management includes strict GFD adherence, assessment and correction of micronutrient deficiencies (e.g. iron, folate, B12), and evaluation for comorbid conditions (e.g. thyroid disease, depression). Psychological support may be beneficial to address behavioural and lifestyle factors. [204, 205]
3.3.4.5. Coeliac hepatitis/Autoimmune hepatitis
Coeliac hepatitis presents with abnormal liver tests and/or histology that resolve with a strict GFD after exclusion of other causes [206, 207]. Coexisting autoimmune liver diseases (e.g. AIH, PBC, PSC) are not GFD-responsive and require appropriate hepatology-led evaluation. Coexistent AIH in CeD requires a GFD alongside corticosteroids and, when required, longer-term immunosuppressive therapy. Shared care ensures that GFD adherence is optimized, the liver disease is accurately characterized, and timely treatment is provided to improve long-term hepatic and systemic outcomes [207, 208].
3.3.4.6. IgA nephropathy
Association with CeD remains uncertain [209, 210]. Nephrology-led management is recommended, with gastroenterology involvement when CeD is confirmed or strongly suspected. A GFD may be considered in confirmed CeD, with possible improvement in renal parameters reported in some patients.

Abbreviations: AIH, autoimmune hepatitis; CeD, Coeliac disease; DH, Dermatitis herpetiformis; GFD, gluten-free diet; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

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

Summary of evidence: Exocrine pancreatic insufficiency (EPI) is a recognized cause of persistent GI symptoms in patients with CeD, particularly those who do not respond fully to a GFD [211]. In newly diagnosed CeD, EPI prevalence can reach 26%, likely from enterocyte damage and pancreatic hypostimulation [212]. However, in those patients with persistent GI symptoms despite adherence to a GFD, the prevalence of EPI remains high (28%) [212].

The pathophysiology of PEI in CeD is complex. Proposed mechanisms include mucosal damage and a reduction in the absorbing surface due to duodenal intestinal villi atrophy in CeD, which reduce the secretion of the gastrointestinal hormone CCK-pancreozymin and thusly prejudice intraluminal fat digestion because the secretory and motor functions of the target organs, the pancreas and the gallbladder, are impaired [213].

When EPI is confirmed, pancreatic enzyme replacement therapy (PERT) significantly improve digestive function. PERT alleviates symptoms, particularly steatorrhoea and bloating, enhances nutrient absorption, and improve QoL [214]. European PEI guidelines recommend considering PEI testing in CeD patients with significant malnutrition at diagnosis or persistent symptoms despite a GFD, although supporting evidence remains limited, highlighting an important knowledge gap [215].

3.3.5.2 | Q. In Patients With CeD, Do Probiotics Improve Symptoms and QoL When Added to a GFD?. *Statement:* Current evidence is insufficient to support or oppose the use of probiotics alongside a GFD for improving symptoms and QoL in patients with CeD. Further research may determine their effectiveness.

CoE: NA; GR: UGPS; Agreement: 95%

Summary of evidence: In general, there is no consensus on the role of various probiotics, and there is still controversy about the safety of probiotics. A systematic review and meta-analysis found that probiotics significantly improved GI symptoms in patients with CeD. However, there was no significant improvement in QoL due to insufficient data [216].

Another meta-analysis reported that probiotics increased the abundance of beneficial bacteria and noted that probiotics might alleviate GI symptoms and improve immune response in CeD [217] Small sample sizes, varying probiotic strains, variable periods of GFD, differing methodologies and absence of well-designed, large-scale studies often contribute to the inconsistency of the results.

3.3.5.3 | Q. Are Adults With CeD on a GFD at Higher Risk of Developing Metabolic Syndrome?. *Recommendation:* adults with CeD on a GFD have a higher risk of developing metabolic syndrome compared to individuals with CeD before dietary therapy. A balanced GFD, active lifestyle, and regular monitoring for metabolic risk factors—including obesity, hypertension, dyslipidaemia, and insulin resistance—are recommended.

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

Summary of evidence: Evidence suggests that patients with CeD are not at increased risk of metabolic syndrome at diagnosis compared with the general population. In fact, the prevalence of metabolic syndrome in newly diagnosed, treatment-naïve CeD patients is substantially lower (approximately 3%–4%) than in the general adult population, where reported metabolic syndrome prevalence ranges from 26% in Canada to 38%–42% in the United States, and 24%–33% across Europe, depending on population age and diagnostic criteria. Similarly, and metabolic dysfunction-associated fatty liver disease (MASLD) is uncommon at CeD diagnosis, with reported rates around 1.7% [218–220].

However, after initiation of a GFD, both metabolic syndrome and MASLD become more prevalent. A study demonstrated that the prevalence of metabolic syndrome and MASLD increased after GFD [218]. A systematic review of 11 studies (n = 2578) revealed that patients with CeD have a 18.2% prevalence of MASLD and 4% prevalence of metabolic syndrome at diagnosis [219]. These prevalence rates are actually lower than those reported in the general population in Western countries, but increase to 28.2% and 21.3%, respectively, after initiating a GFD, approaching the prevalence in the general population [221].

The increase in prevalence of metabolic syndrome following GFD initiation is thought to reflect improved nutrient absorption, weight gain, and changes in body composition, which occur as intestinal healing progresses. Regular clinical evaluation, metabolic monitoring, dietary counselling, and encouragement of physical activity are essential to mitigate these risks [207, 219, 222–225].

3.3.6 | Special Scenarios

3.3.6.1 | Q. Do Pregnant Women With CeD Require Specialized Care?. *Recommendation*: Although evidence is limited, coordinated preconception and perinatal care may help optimize nutritional status in women with CeD and support a healthy environment for early foetal development. Postpartum care should continue to emphasize maintaining the GFD.

CoE: NA; GR: UGPS; Agreement: 95%

Summary of evidence: Available data, although limited, suggest that women with CeD may be at increased risk of adverse pregnancy outcomes. A systemic review reported that women with CeD are at significantly higher risk of developing preterm birth, intrauterine growth retardation, stillbirth, low birth weight, and being small for gestational age [226]. Malnutrition and the autoimmune mechanism are considered two possible causes [227].

Maternal CeD may be a risk factor for deficiency of nutrients during pregnancy [228]. In women with CeD planning pregnancy, strict adherence to a GFD is essential, together with resolution of disease-related symptoms and adequate supplementation of folate and other vitamins, to optimise nutritional

status and create a favourable environment for preimplantation, early foetal development, and placental formation [229]. Additionally, during pregnancy, care is needed to optimize nutrient needed of both the mother and the infant to protect them from complications [230]. Adherence to a GFD has been associated with improved reproductive outcomes [230–232].

3.3.6.2 | Q. What Are the Key Management Considerations for Patients Diagnosed With CeD at an Older Age?.

Recommendation: In patients diagnosed with CeD at an older age, non-classical symptoms are common, often causing diagnostic delays. These patients have an increased risk of complications, including osteoporosis and malignancy. Although response to a GFD may be slower, it provides substantial clinical benefit and should be strongly considered.

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

Summary of evidence: CeD in the elderly (typically > 65 years) frequently presents with non-classical features such as iron-deficiency anaemia, fatigue, and bloating, rather than classic diarrhoea, often leading to a significant diagnostic delay [233–237]. This often leads to a significant diagnostic delay in diagnosis.

The diagnostic criteria for CeD in the elderly are the same as for other adults. The severity of villous atrophy at diagnosis is generally comparable to that in younger adults. Clinicians should have a low threshold for testing for CeD in elderly individuals with suggestive symptoms or associated conditions.

Patients diagnosed with CeD at an older age have a higher burden of specific complications:

- Metabolic Bone Disease: A high prevalence of osteopenia and osteoporosis, necessitating BMD assessment.
- Malignancy: A significantly increased risk of EATL and other malignancies.
- Functional Hyposplenism: This is more common in elderly CeD patients, with implications for vaccination.
- Other Autoimmune Diseases: A higher prevalence of associated autoimmune conditions is often seen.

A strict, lifelong GFD is the primary treatment. Whilst elderly patients may experience a slower or incomplete clinical and histological response due to long disease duration and practical challenges, the initiation of a GFD leads to significant symptomatic improvement, enhanced QoL, and correction of nutrient deficiencies. Therefore, diagnosis and dietary treatment are strongly recommended and beneficial, regardless of age.

3.3.6.3 | Q. How to Screen Family Members of Patients With CeD Patients?.

Recommendations:

1. HLA-DQ2/8 genotyping is recommended as the initial screening step primarily in children of patients with CeD —where it can prevent repeated testing—while anti-TG2 serology remains the most cost-effective and widely available initial test for adults and lower-risk relatives.
2. Follow-up: For first-degree relatives who are seronegative at initial assessment, periodic antibody follow-up (e.g., every 4–5 years) may be considered based on individual risk factors and new symptoms.

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

Summary of evidence: The recommendations for screening family members of patients with CeD, including cost-effectiveness across family relative groups, are summarised in Table 4.

First-degree relatives (FDRs) of CeD patients have a 5%–10% disease risk, highlighting a need for targeted screening [238–240]. Genetic susceptibility, primarily conferred by HLA-DQ2 and/or HLA-DQ8 haplotypes, plays a central role in disease development. HLA genotyping is therefore a useful first-line risk stratification tool, particularly in children, as the absence of HLA-DQ2/8 effectively excludes CeD [241]. Rare cases linked to alleles like HLA-DQ7.5 carry a residual risk below 1% [242, 243].

Amongst genetically susceptible individuals, HLA-DQ2 homozygosity is associated with a substantially increased risk of developing CeD and with earlier disease onset [244]. Prospective cohort studies and recently developed risk prediction models suggest that combining HLA genotype with age, sex, and serological data may help individualise decisions regarding the timing and frequency of serological re-screening in at-risk relatives. These emerging data indicate that such personalised approaches may be preferable to uniform re-screening intervals [245].

Twin studies further support a strong genetic contribution, with concordance rates of approximately 70% in monozygotic twins compared with around 9% in dizygotic twins within 5 years of follow-up [246]. These findings justify periodic monitoring of genetically susceptible relatives.

In children who are FDRs of patients with CeD, initial HLA genotyping can avoid unnecessary long-term follow-up in those who are HLA-DQ2/8 negative. DQ2/8-positive children should undergo periodic serological screening, as disease presentation is frequently asymptomatic [241].

In adult relatives of patients with CeD, serological testing—specifically IgA anti-TG2 with total serum IgA—is recommended as the primary screening approach [247]. Early identification may prevent complications such as nutritional deficiencies, metabolic bone disease, and the development of associated autoimmune conditions.

Second-degree relatives of patients with CeD have a lower, but still increased, risk compared with the general population [239, 244]. Whilst universal screening of second-degree relatives is not recommended, serological testing should be considered in the presence of suggestive symptoms, associated autoimmune conditions (e.g., T1DM or autoimmune thyroid disease), or

TABLE 4 | Summary of the screening methods across family relative groups together with cost-effectiveness considerations.

Family relative group	Recommended approach	Cost-effectiveness rationale
Children (FDR)	*HLA-DQ2/8 genotyping* is preferred when it is accessible and affordable, as a first-line risk stratification tool. HLA-negative children do not require further follow-up.	The pre-test probability is *high*. The upfront cost of HLA testing is offset by eliminating decades of repeated serology in HLA-negative children, making it cost-saving over the long term.
Adults (FDR)	*Serology* is preferred in most adult FDRs due to lower cost and broad availability. *HLA-DQ2/8 genotyping* is reserved for selected situations, such as equivocal serology, IgA deficiency, individuals already on a GFD, or complex family histories.	The pre-test probability of CeD is moderately elevated. Adults have already passed much of the highest-risk period; repeated long-term screening is less likely. Serology is cheaper and widely available.
Second-degree relatives	*No universal screening is recommended.* Serological testing (IgA anti-TG2 with total IgA) should be considered selectively, particularly in the presence of symptoms suggestive of CeD or associated autoimmune diseases (e.g., T1DM, autoimmune thyroid disease).	The pre-test probability of CeD is low. Universal screening is not cost-effective due to low disease prevalence; HLA testing adds little value and increases cost.
Families with multiple CeD cases	*Screening should follow age- and genotype-based principles*, rather than family history alone. In children, HLA-DQ2/8 genotyping may help stratify individual risk and guide follow-up. In adults, serology remains the first-line screening test.	Recent large cohort studies indicate that multiple affected family members do not constitute an independent risk factor once HLA genotype is accounted for. Cost-effectiveness depends on individual genetic risk and anticipated need for future screening, rather than family history alone.

Abbreviations: CeD, Coeliac disease; FDR, First-degree relatives; GFD, Gluten-free diet; HLA, Human Leucocyte antigen; T1DM, Type 1 diabetes mellitus.

other clinical indications [239, 248]. Recent large cohort studies indicate that the presence of multiple affected family members alone does not constitute an independent risk factor once HLA genotype is taken into account, and should therefore not be used as a sole criterion for screening [244, 245].

Finally, consider serological follow-up every 4–5 years for initially negative FDRs with persistent symptoms or strong family history, accounting for possible later-onset disease.

3.3.6.4 | Q. How to Manage Adults Presenting With the Rare Severe Presentation 'Coeliac Crisis'?. *Recommendation:* Although rare in adults, coeliac crisis—often a manifestation of refractory CeD type 2—requires urgent admission for multidisciplinary care to address dehydration, electrolyte/nutritional deficits, and precipitating factors, whilst promptly initiating a strict GFD.

CoE: NA; GR: UGPS; Agreement: 95%

Summary of Evidence: In adults, CeD may rarely present as a severe condition known as a 'coeliac crisis', which can be life-threatening if not promptly recognized and managed [249]. This is usually in the context of refractory CeD type 2.

Clinically, patients have a severe malabsorption with electrolyte disturbances, metabolic acidosis, dehydration, hypoalbuminemia and anaemia [250, 251]. A systematic review showed that amongst 42 adults with CeD crisis, the median age was 50 years (range 23–83), with a 2:1 female to male ratio. In the majority of cases (88%), the coeliac crisis most often presents as the initial manifestation of CeD, whilst the remaining were previously diagnosed CeD cases reporting non-adherence to a GFD [250]. Precipitating factors (such as: trauma, surgery, infections) are present in about 25% of cases [250].

Management is multidisciplinary and includes in-hospital supportive care, with intravenous fluid administration, correction of electrolyte imbalances and nutritional deficiencies [251, 252]. The GFD should be started promptly [249, 250].

3.3.6.5 | Q. What Is the Recommended Management for Patients Who Develop CeD–like Enteropathy in Association With Immune Checkpoint Inhibitors?. *Recommendation:* In patients receiving immune checkpoint inhibitors (ICI) who develop diarrhoea, coeliac serology should be obtained. If serology is positive, histological confirmation of CeD should be sought. Conversely, if a CeD-like enteropathy is identified histologically in a patient on ICI, coeliac serology should be performed to confirm the diagnosis.

First-line management is a strict GFD when CeD is confirmed. Systemic immunosuppression or modification of immunotherapy should be reserved for severe presentations or cases not responding to a GFD, with decisions guided by multidisciplinary discussion.

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

Summary of Evidence: ICI-CeD is a rare immune-related adverse event from immunotherapy, supported mainly by case reports and small studies [253–255]. ICIs can unmask or trigger CeD as

a rare immune-related adverse event (irAE). Patients typically present with diarrhoea, weight loss, and malabsorption, with histology showing villous atrophy similar to classic CeD. Whilst serology is often positive, seronegative cases require duodenal biopsy and exclusion of other causes [253].

Most patients respond significantly to a strict GFD, often avoiding systemic steroids. This response helps distinguish it from other ICI-related enteropathies (e.g., colitis), which typically require immunosuppression [253, 256]. Accurate diagnosis is crucial to prevent unnecessary interruption of cancer therapy.

Due to sparse, low-certainty evidence, firm recommendations are limited. However, a GFD is consistently effective first-line therapy for both seropositive and carefully evaluated seronegative cases. Immunosuppression should be reserved for dietary failure or suspected overlapping immune-related toxicity [254, 257].

3.4 | Pharmacological Therapies

3.4.1 | Q. What Is the Current Status of Non-dietary Medical Treatments for CeD?

Statement: Non-dietary pharmacological treatments for CeD hold promise for the future but remain experimental and are currently available only within clinical trials.

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

Summary of evidence: Since adherence to a GFD can be difficult and some patients have persistent symptoms or mucosal damage despite a GFD, there is growing interest in non-dietary medical treatments for CeD.

Several therapeutic approaches target various aspects of CeD pathophysiology are under investigation [258, 259]. However, broader validation through phase III trials is still necessary.

Clinical trials often reveal discrepancies between symptoms, serological markers, and mucosal biopsy results, highlighting the need for further research. Additionally, many results and potential pitfalls remain unpublished. Existing studies also have methodological limitations, particularly regarding patient selection. Most trials have enroled patients with CeD with GI symptoms and duodenal mucosal damage, often linked to poor GFD adherence, which may persist throughout the trial [260–262].

Enzyme-based over-the-counter supplements that claim to degrade gluten are not approved therapies for CeD and should not replace a strict GFD; their efficacy and safety have not been established in rigorous clinical trials [263, 264].

In conclusion, non-dietary treatments for CeD hold promise for the future but remain experimental and are currently available only within clinical trials.

4 | Long-Term Follow-Up and Monitoring of CeD in Adults

4.1 | Q. Why Is Long-Term Follow-Up Recommended for Adults With CeD?

Recommendation: Long-term follow-up is recommended to monitor dietary adherence, detect complications and comorbidities, and provide ongoing nutritional and psychosocial support, which helps ensure sustained disease control and optimised long-term outcomes.

CoE: NA; GR: UGPS; Agreement: 95%

Summary of evidence: For patients with CeD, a lifelong GFD is not a voluntary lifestyle choice, it is a necessity and simply avoiding gluten-containing products after diagnosis is not enough. Follow-up is relevant in the long-term, given that persistent symptoms and mucosal changes occur in 20%–40% of adult patients with CeD [219, 265, 266].

Strict GFD is expected to reduce symptoms and normalize biomarkers (biochemical, serological and histological) that were abnormal at diagnosis. However, neither symptom improvement nor biochemical or serological testing may reliably predict CeD activity or histological recovery [23, 267].

Dietary adherence improves with regular follow-up in a specialist coeliac clinic, where structured dietetic support is a key component of care [268–270] Patients should be encouraged to join national coeliac societies or other disease-specific patient support groups.

Follow-up presents a valuable opportunity to proactively detect and manage associated autoimmune disorders, address complications like bone disease, and recognize warning signs that may suggest the development of RCD or malignancies [269].

Key endpoints at follow-up include the resolution of symptoms and evidence of disease remission. Mucosal healing—defined as normalization of villous architecture, absence of intraepithelial lymphocytosis, and resolution of crypt hyperplasia (Marsh 0–I)—is an important therapeutic goal, as it is associated with improved long-term outcomes. However, histological reassessment is not required in all patients and should be individualized based on clinical status, serological response, and risk factors for persistent disease activity [271]. By maintaining a strict GFD and regular follow-up with healthcare providers, most patients can achieve sustained health and good QoL [272].

4.2 | Q. What Is the Most Appropriate Healthcare Setting for the Long-Term Follow-Up of Adults With CeD, and How Should Responsibilities Be Shared Between Primary and Secondary Care?

Recommendation: Long-term follow-up of adults with CeD is best coordinated through hospital-based outpatient clinics or

specialized coeliac centres, where feasible. For stable patients, follow-up may be conducted in primary care, provided there is clear access to specialist support. Digital tools can be utilised to support remote monitoring and dietary adherence.

CoE: NA; GR: UGPS; Agreement: 95%

Summary of evidence: No universal consensus exists on who should provide long-term care for adults with CeD [269]. Creating international standards is difficult due to differing healthcare systems, resources, and access.

Follow-up has traditionally been based in hospital clinics or specialized centres. However, these centres often lack the capacity to meet the growing demand associated with the increasing prevalence of CeD.

For clinically stable, patient with good dietary adherent, primary care can manage follow-up if specialist and dietitian support is available [68, 273]. Dietitian-led care with physician oversight is effective and cost-efficient [68, 273]. Telemedicine and digital tools can aid monitoring and adherence without overburdening hospitals [274, 275].

In several European countries, primary care commonly handles long-term follow-up, supported by higher patient volumes. Successful decentralization requires adequate provider training and easy access to specialist consultation The hospital team must clearly communicate to primary care providers the management plan, including key follow-up points, recognition of red flags for complications, and criteria for referral back to specialist care [268].

4.3 | Q. Should Follow-Up of Adults With CeD Be Conducted at Fixed-Intervals or Tailored to the Individual Through a Patient-Centred Approach?

Recommendation: Both fixed-interval and individualised strategies for follow-up of adults with CeD have advantages; however, follow-up should be individualised and patient-centred, taking into account disease activity, treatment adherence, comorbidities, and individual needs.

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

Summary of evidence: The optimal interval between follow-up visits for adults with CeD remains unclear and has not been systematically studied [269]. Whilst a strictly structured follow-up at fixed intervals may not always be feasible in routine clinical practise, it provides a valuable framework tostandardize care and ensure consistent monitoring. Conversely, an individualized, patient-centred approach—considering factors such as the patient's risk profile, serological response, dietary adherence, symptom evolution, and personal preferences—is both reasonable and practical. Both strategies have their merits and may be applied flexibly based on clinical context.

A structured follow-up framework as outlined in Table 5 may be implemented.

Tailored follow-up is necessary to address individual needs and comorbidities, ensuring optimized health outcomes [4, 269]. Key factors for successful implantation of this strategy are outlined in Table 6.

4.4 | Q. What Is the Role of Coeliac Serology in Follow-Up of Adult Patients With CeD?

Statement: The role of IgA anti-TG2 in follow-up is to identify ongoing gluten exposure; a positive IgA anti-TG2 result in patients with CeD on a GFD suggests potential poor dietary adherence or gluten contamination, whilst a negative result does not confirm strict adherence or the absence of gluten exposure and it is not a reliable marker of villous atrophy.

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

Summary of evidence: CeD-specific antibodies, particularly IgA anti-TG2, typically decline within months of starting a GFD and often normalize within the first year [281–284].

Persistently positive, or not decreasing, IgA anti-TG2 levels are predictive of some degree of gluten intake. The sensitivity of IgA anti-TG2 for the detection of diet transgressions evaluated by patient self-reports or dietitian-led assessments was low (52%–57%) [282, 285]. This illustrates that negative IgA anti-TG2 levels should not be considered a marker of strict dietary compliance, nor do they reflect histological recovery [23, 267, 286]. IgA anti-EMA and IgG anti-DGP perform similarly to IgA anti-TG2 detection in this setting [281]. With regard to patients with CeD and IgA deficiency, IgG anti-TG2 levels also decline slowly over time on a GFD but fail to reach normalization in up to 80% of cases despite long-term strict diet adherence, limiting its utility as a standalone marker of compliance [287, 288].

4.5 | Q. Is a Follow-Up Duodenal Biopsy Necessary in Adults With CeD?

Recommendation: A follow-up duodenal biopsy is not routinely necessary for all adults with CeD. It is recommended in a personalized manner, guided by factors such as age at diagnosis, symptom severity, serological status, and clinical response to the GFD. A biopsy should be considered if symptoms persist or worsen.

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

Summary of evidence: In adults, neither symptoms nor serology is reliable to predict small-bowel damage. The need for routine follow-up duodenal biopsies to monitor CeD is debatable, as there is insufficient evidence that this practise impacts clinical outcomes [267, 289]. Studies on mucosal healing after a GFD show that the process can be slow or incomplete, with some studies reporting healing in only 30% of patients after 3–5 years [46, 290].

Currently, there are no studies indicating an absolute necessity for performing routine follow-up biopsy for all patients.

TABLE 5 | Suggested follow-up scheme for adults with CeD.

Contact (timing, provider, mode)[a]	Assessments and interventions
At diagnosis (physician and dietitian), face-to-face consultation	• Physical examination including body mass index (BMI) • Coeliac serology (if not previously obtained at diagnosis)[b] • Routine tests (complete blood count, iron status, folate, B12, thyroid function tests, liver enzymes, albumin, calcium, phosphate, vitamin D, blood glucose) • Education on CeD and dietary counselling by a CeD dietitian • Discuss family screening • Advise membership of a coeliac national society or support group • Check the indication for bone densitometry and decide on future timing
At 4–6 months (physician and dietitian), face-to-face consultation	• Assess symptoms and coping strategies • Repeat routine tests (if previously abnormal) • Dietary review • Offer referral to a psychologist (in case of evident coping issues)
At 12 months (physician and dietitian), face-to-face, telephone, video consultation or via digital app (if available)	• Assess symptoms • Physical examination (as indicated) • Coeliac serology • Repeat routine tests (if previously abnormal) • Dietary review
At 24 months (physician or dietitian), by telephone, video consultation or digital app (if available), thereafter every 1–2 years, depending on dietary adherence, level of education, and patient confidence in self-management	• Assess symptoms • Dietary review (optional) • Coeliac serology (if negative seroconversion is already achieved then it is optional) • Thyroid function tests • Other tests as clinically indicated (e.g., deficiencies, testing for GIPs when indicated and if available)

Abbreviations: BMI, body mass index; CeD, Coeliac disease; GIPs, Gluten Immunogenic Peptides.
[a]Methods of contact depend on local resources.
[b]Serology does not need to be routinely repeated within the first year of a gluten-free diet.

However, there is a need for distinguishing asymptomatic patients with negative serology from symptomatic patients who need repeated biopsies to rule out RCD or malignancy [291] . There are data suggesting a more personalized follow-up, wherein the follow-up biopsy is conducted after a few years and only for a selected group based on age, initial disease severity and response to the GFD [292].

The indication for a follow-up biopsy in patients with CeD adhering to a strict GFD should be discussed with the patient, taking into consideration their preferences and choices. Common indications for a follow-up biopsy include:

- Persisting or worsening symptoms and/or biochemical or laboratory evidence of malabsorption.
- Development of new red flag symptoms raising suspicion of complications.
- In adults diagnosed with CeD after the age of 45 or those with initially severe presentation, a follow-up biopsy after 1–2 years on a GFD may be reasonable to assess mucosal healing.
- In seronegative CeD, follow-up biopsies are essential for accurate diagnosis and monitoring recovery.

TABLE 6 | Key Factors Influencing tailored follow-up in Adults with CeD.

Factor	Consideration
1. Symptom severity and presentation	Patients with persistent symptoms or nutritional deficiencies may require more frequent follow-up and additional testing. Asymptomatic individuals may need fewer visits but still require periodic assessments to ensure adherence to a GFD and to monitor for silent complications.
2. Serological testing and intestinal healing	Patients with persistently elevated CeD antibodies may require more frequent monitoring to evaluate adherence or identify ongoing gluten exposure and may benefit from dietary counselling or psychological support to help maintain a strict GFD. Those who have achieved serological remission and demonstrated intestinal healing may benefit from less frequent follow-ups.
3. Age and comorbidities	Older adults or those with coexisting conditions may require integrated management of non–CeD–specific health risks, including cardiovascular disease. Whilst CeD has been associated with a modestly increased relative cardiovascular risk in some studies, absolute risk in treated disease is low and is largely driven by traditional cardiovascular risk factors and dietary quality [276, 277]. Accordingly, cardiovascular health should be addressed as part of holistic long-term follow-up, focussing on optimisation of nutrition, promotion of physical activity, and management of conventional risk factors in line with general population recommendations. Younger patients without comorbidities may benefit from less frequent visits focussed on education and prevention. Monitoring for the development of comorbidities during follow-up remains important.
4. Dietary quality	An unhealthy and nutritionally unbalanced GFD may be harmful, leading to micronutrient deficiencies, undesirable weight gain, and the development of metabolic syndrome, MAFLD, and cardiovascular complications [218, 219]. Current evidence does not demonstrate a clear, direct effect of a GFD per se on reducing cardiovascular outcomes [278, 279]. The impact of a GFD on cardiovascular risk factors is heterogeneous and does not consistently translate into improved cardiovascular outcomes [278, 279]. Dietary counselling should therefore emphasise not only gluten exclusion, but also overall dietary quality, nutritional adequacy, and a balanced dietary pattern, alongside encouragement of regular physical activity.
5. Coexistence of autoimmune conditions	The presence of autoimmune conditions (e.g., autoimmune thyroid disease, T1DM, Addison's disease, vitiligo, alopecia, hypogonadism, chronic autoimmune gastritis, systemic lupus erythematosus) requires integrated management and input from relevant specialists such as endocrinologists [138, 248, 280].
6. Individual preferences	Preferences regarding visit frequency and level of support should be considered. Some patients may prefer regular follow-up for reassurance, whilst others may opt for a more independent approach.

Abbreviations: CeD, Coeliac disease; GFD, gluten-free diet; MAFLD, metabolic dysfunction–associated fatty liver disease; T1DM, type 1 diabetes mellitus.

- A biopsy may be performed at the patient's request for reassurance that mucosal healing has been achieved.

5 | Complicated CeD

5.1 | Kinetics of Clinical, Serologic and Histologic Response to a GFD in Adults With CeD

5.1.1 | Q. When Is a Clinical Response to the Diet to Be Expected in Adults With CeD?

Statement: Clinical response to a GFD in adults with CeD shows substantial inter-individual variability, with symptom improvement generally expected within 4 weeks to 4–5 months after diet initiation.

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

Summary of evidence: Evidence describing the symptomatic course after initiating a GFD in adults with CeD is limited, as few studies have prospectively evaluated the kinetics of clinical response. Available prospective data largely support clinical experience. Symptomatic improvement shows marked interindividual variability: some adults experience relief within 4 weeks of starting a GFD, whereas others may require 4–5 months before a clear response becomes evident [284]. In a cohort evaluated at the time of follow-up biopsy—performed after highly variable intervals averaging 2–3 years—82% reported good symptomatic improvement, independent of histological recovery [293]. This highlights that clinical response does not reliably predict mucosal healing. Additionally, a minority of patients may show a delayed symptomatic response 'late responders', sometimes occurring more than 1 year after starting the GFD [294, 295].

5.1.2 | Q. When Is a Serological Response to the Diet to Be Expected in Adults With CeD?

Statement: A decline in IgA anti-TG2 can be observed as early as 2–4 weeks after starting a GFD, and in the majority, titres normalize within approximately 12 months. There is, however, strong inter-individual variation in this response.

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

Summary of evidence: Once a GFD is initiated, a reduction in IgA anti-TG2 titres is expected. Some prospective studies have investigated the time course of IgA anti-TG2 normalization, but the limited follow-up in most studies precludes precise conclusions. A decline in IgA anti-TG2 can be observed as early as 2–4 weeks after starting a GFD, and in many patients, titres usually normalize within approximately 12 months [281, 284] Considerable inter-individual variability exists, however, in the time required to reach normal levels. In one study, 47% of adults with CeD still had nominally positive IgA anti-TG2 titres 1 year after starting a GFD, although titres were significantly lower than at baseline [164].

5.1.3 | Q. When Is a Histological Response to the GFD to Be Expected in Adult CeD Patients?

Statement: Healing of the duodenal mucosa is generally expected around 1 year after starting a GFD. However, the proportion of patients achieving full histological recovery ranges widely, from approximately 50%–83% after 1–5 years.

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

Summary of evidence: Histological healing of the duodenal mucosa represents a key milestone in the successful management of CeD, as it underpins restoration of normal intestinal absorption. Whilst Marsh criteria are commonly used in clinical practise to assess the severity of mucosal lesions, they are semi-quantitative and, in research contexts, less precise than measurements of the villous-to-crypt (Vh:Cd) ratio. A Vh:Cd ratio above 2.0–2.5 is generally considered indicative of mucosal recovery [296].

Available studies show considerable variability in the timing and proportion of patients achieving histological healing. In the Risnes study, nearly all patients had recovered a Vh:Cd ratio ≥ 2.0 1 year after starting a GFD [284]. Another study reported that 83% of patients reached a Vh:Cd ratio ≥ 2.0 after an average of 4 years on a GFD [297]. In contrast, Lebwohl et al. observed that only 50% of adults achieved mucosal healing within 6 months–1 year of GFD initiation, increasing to 62% at 1–2 years [265] Wahab and colleagues reported 65% mucosal recovery after 2 years and 85.3% after 2–5 years, highlighting the existence of a subset of 'slow responders' [266]. Data from the US suggest even slower recovery in some cohorts, with only 34% of patients showing full mucosal healing at 2 years and 66% at 5 years after starting a GFD [293].

Overall, these findings underscore both the variability in histological recovery amongst adults with CeD and the importance of long-term follow-up, as a significant proportion of patients may require several years to achieve full mucosal healing.

5.2 | Delayed or Incomplete Response to a GFD

5.2.1 | What Are the Causes of Delayed or Incomplete Response to a GFD in Adults With CeD?

Statement: An incomplete response to a GFD is often due to ongoing gluten exposure but may also indicate slow-responsive disease, RCD, initial misdiagnosis, or concurrent conditions. Persistent symptoms or villous atrophy after ≥ 12 months requires systematic evaluation.

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

5.2.2 | Q. How to Evaluate an Adult Patient With CeD Having Persistent Symptoms Despite GFD?

Recommendation: For a symptomatic adult with CeD despite a GFD, first verify the original diagnosis and assess for gluten exposure. If adherence is confirmed, proceed with follow-up histology and evaluate for alternative or overlapping conditions—such as functional disorders, other GI diseases, refractory CeD, or malignancy—using a multidisciplinary approach.

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

Summary of evidence: Up to 30%–40% of adults with CeD may have persistent symptoms or villous atrophy despite a GFD, although rates vary by definitions, follow-up duration, and clinical setting [265, 298, 299]. The optimal timing for assessing response remains uncertain and is typically based on expert opinion (12–24 months) [2, 265, 300].

Based on a combination of clinical, serological, histopathological, and immunological features, patients who continue to experience symptoms and/or show incomplete mucosal healing despite presumed adherence to a strict GFD are classified into one of the following categories:

1. Continued gluten exposure: Gluten exposure, whether intentional and inadvertent, accounts for up to 80% of persistent symptoms [299, 301, 302]. Intentional gluten intake is reported in up to 40% of adult patients, [303] and it is multifactorial, and may depend on poor self-efficacy, lower symptom burden, scarce knowledge of CeD, social-economic barriers and low educational level [265].
2. Delayed or slow-responsive CeD: Some patients show slow clinical, serological, or histological recovery despite confirmed adherence. Improvement occurs gradually and may take months to years, especially in those with longstanding disease or severe baseline mucosal damage [266].
3. RCD: See Section 4.3 for detailed discussion.

4. Misdiagnosis of CeD. See part 1 of the guidelines, section Q.IV.4. What Is the Approach to Villous Atrophy in the Absence of CeD-Specific Serology? [1].
5. Other conditions unrelated to gluten exposure. these include:
   - Associated or concomitant disorders—other food intolerances (e.g., lactose, fructose), microscopic colitis, inflammatory bowel disease [304], bile acid diarrhoea [305], exocrine pancreatic insufficiency, IBS, medication effects [306, 307], or other autoimmune diseases.
   - Malignant complications—EATL or small-bowel adenocarcinoma [308, 309].
   - Functional or psychosomatic disorders—functional gastrointestinal symptoms, difficulty adapting to a chronic diagnosis, or health-related anxiety, particularly in younger patients.

Structured, stepwise approach to evaluate persistent symptoms despite a GFD includes:

1. *Re-assessment of the original CeD diagnosis* to confirm it was appropriately established before GFD initiation [310, 311].
2. *Exclusion of ongoing gluten exposure* through expert dietary review and, where appropriate, GIPs testing; [91, 312–315] if excluded, alternative gastrointestinal, functional, or psychological causes should be considered [308, 309]. Empirical approaches such as a low-FODMAP diet or pancreatic enzymes may be used when clinically indicated [113, 212].
3. *Assessment of persistent villous atrophy* should be performed with follow-up biopsy, as mucosal healing may be delayed despite symptom resolution, particularly in older adults [265].
4. *Evaluate for and exclude RCD and malignant complications* in patients with persistent villous atrophy persists despite confirmed dietary adherence. This evaluation should be conducted in specialised centres (Figure 1).

5.3 | Refractory Coeliac Disease

5.3.1 | Definition of RCD

5.3.1.1 | Q. What Is the Definition of RCD?. *Statement:* RCD is defined by the persistence or recurrence of symptoms and villous atrophy after at least 12 months on a strict GFD, in the absence of other causes. RCD can be either primary or secondary. Depending on the proportion of aberrant T cells, RCD is further subdivided into: RCD-I and RCD-II.

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

Summary of evidence: RCD is defined by the persistence or recurrence of symptoms and villous atrophy after at least 12 months on a strict GFD, despite negative coeliac serology. This 12-month duration accounts for the fact that some patients may be slow-responders, extending beyond the 6-month period used in earlier studies [316–318].

From the clinical point of view, RCD can be either primary, when there is no clinical or histological response to a strict GFD from the outset of disease, or secondary, when symptoms and villous atrophy recur after an initial period of response to the GFD, once ongoing gluten exposure has been reliably excluded.

RCD is a rare complication of CeD, affecting approximately 0.3%–2% of adult patients, with most population-based studies suggesting a prevalence closer to 1% or less [319]. RCD-I accounts for the majority of cases, whilst RCD-II represents a minority (around 20%–30% of RCD cases) and is exceedingly rare in the general coeliac population. In referral and tertiary care centres, the reported prevalence of RCD—particularly type II—has been estimated at 1%–4% of all CeD cases; however, this likely reflects referral bias and overestimates true community prevalence [320, 321].

RCD is further subdivided into:

- RCD-I: The immunophenotype of IELs is normal. Thusly, it requires the observation of the clinical course of the patient to differentiate RCD-1 from slow-responsive CeD. PCR-based amplification of the variable region of the T-cell receptor (TCR) gene in duodenal mucosal biopsies (molecular pathology) reveals a poly- or oligoclonal T-cell population.
- RCD-II: Is defined by the presence of an aberrant IEL population characterised by loss of surface CD3 and CD8, with expression of intracytoplasmic CD3. Flow cytometry typically demonstrates ≥ 20% aberrant IELs, and clonality is confirmed by T-cell receptor (TCR) gene rearrangement analysis [322, 323]. RCD-II is considered a pre-lymphomatous state with a high risk of transforming into EATL, accounting for its poor prognosis. Complications such as ulcerative jejunitis and subsequent small bowel stenoses are also common in this subtype [324].

The classification of RCD into types 1 and 2 is based on immunological criteria and may not fully encompass the spectrum of clinical presentations. Incorporating both immunological and clinical criteria into the classification system enhances diagnostic accuracy [322, 325]. The two RCD subtypes represent biologically and prognostically distinct entities. RCD-I is typically characterised by less severe malabsorptive symptoms and relatively preserved nutritional status. In contrast, RCD-II is associated with more severe malabsorption, frequent hypoalbuminaemia, and ulceration or stenosis of the small bowel. These differences underpin the markedly divergent clinical outcomes, with RCD-I generally following a benign course with excellent long-term survival, whereas RCD-II carries a high risk of progression to EATL and a poor prognosis.

Notably, a subset of patients presents with clonal or aberrant IELs in the absence of significant clinical symptoms, biochemical abnormalities, or histological damage, raising uncertainty about their classification as RCD-II. These cases are challenging to categorize and may not warrant immediate aggressive therapy; instead, they require careful monitoring. Importantly, the clonal T cell population in such individuals may remain stable over time or even regress during follow-up. Recognizing this intermediate subset has meaningful clinical implications,

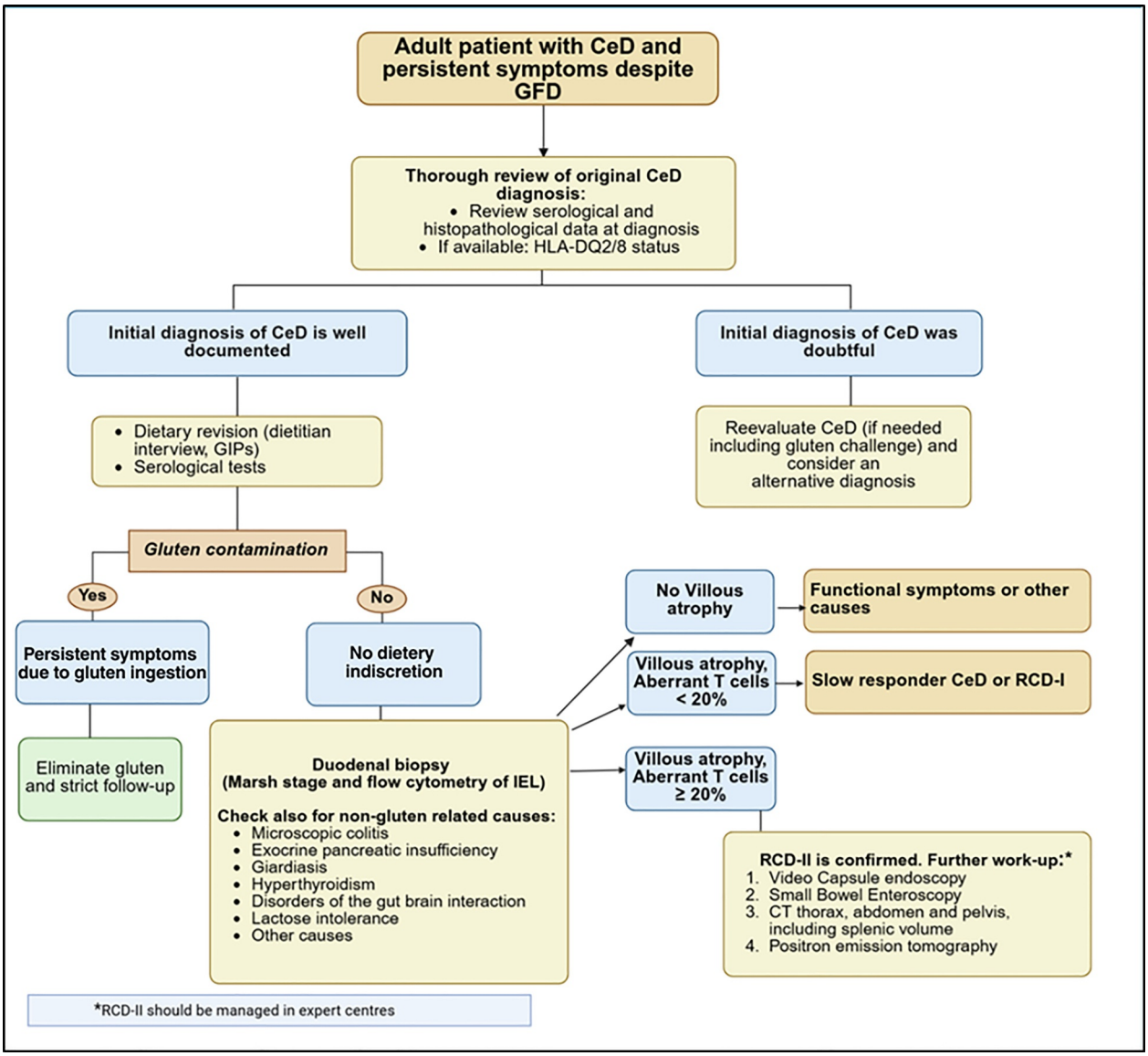

FIGURE 1 | Summarises the approach to adult patients with CeD having persistent symptoms despite GFD. CeD, Coeliac disease; CT scan, Computed tomography; GIPs, Gluten Immunogenic Peptides; GFD, Gluten-Free Diet; HLA-DQ2/8, Human leucocyte antigen; IEL, Intraepithelial lymphocytes; RCD, Refractory Coeliac Disease, RCD-I, refractory coeliac disease type 1; RCD-II, refractory coeliac disease type 2.

potentially preventing overtreatment and supporting more individualized management strategies. Further research is essential to validate these observations and refine existing classification frameworks [322, 326].

If a strong clinical suspicion for RCD persists, further evaluation and management should be conducted in or in consultation with a tertiary centre experienced in managing RCD.

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

5.3.2 | Diagnosis of RCD

5.3.2.1 | Q. What Is the Diagnostic Approach to a Patient With Suspected RCD?. *Recommendation:* The diagnostic approach involves a systematic workup to confirm the initial CeD diagnosis, ensure strict dietary adherence, and exclude alternative causes of symptoms or an overt EATL. Essential investigations include serology, duodenal biopsies (for histology, IEL flow cytometry, and T-cell receptor clonality analysis), enteroscopy, and cross-sectional imaging.

5.3.2.2 | Q. Which Molecular Diagnostic Technology Is the Gold Standard for Diagnosis of RCD-II?. *Recommendation:* Accurate subtyping of RCD requires comprehensive immunophenotyping of small bowel lymphocytes to reliably diagnose or exclude RCD-II. Flow cytometric analysis of isolated IELs after immunostaining is superior to immunohistochemistry for detecting aberrant lymphocyte populations. Additional diagnostic value is provided by PCR-based T-cell receptor clonality assessment and by sequencing of genes in the JAK/STAT pathway to identify relevant somatic mutations.

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

Summary of evidence: The diagnostic workup of RCD is summarised in Table 7:

5.3.3 | Treatment of RCD

5.3.3.1 | Q. Is There an Evidence-Based Treatment for RCD-I and RCD-II?. *Recommendation:* No evidence-based medical treatments supported by controlled trials exist for either RCD-I or RCD-II; current management is based on expert consensus, case series, and observational data.

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

5.3.3.2 | Q. What Is the Treatment for Patients With RCD-I?. *Recommendation:* Based on retrospective and longitudinal evidence, open-capsule budesonide is considered first-line therapy for RCD-I. Conventional immunosuppressants, such as thiopurines, may be added in selected cases. When used, thiopurines should be re-evaluated for possible discontinuation after 2–3 years of clinical, histological and immunophenotypic stability.

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

5.3.3.3 | Q. What Is the Treatment for Patients With RCD-II?. *Recommendation:* Mild-to-moderate RCD-II may be treated with open-capsule budesonide. In selected patients, cladribine (or fludarabine), with or without autologous haematopoietic stem cell transplantation (auto-HSCT), or JAK inhibitors may be considered on an individual basis.

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

Summary of evidence: Prospectively designed, randomized controlled trials (RCTs) in RCD are exceedingly scarce. To date, the only prospective controlled study evaluated anti-IL-15 therapy (AMG 714) and did not meet its primary endpoint, which was a reduction in aberrant IELs. However, secondary endpoints—such as clinical improvement in chronic diarrhoea and a reduction in T-cell clonality—were achieved [350].

All other available studies are retrospective and typically longitudinal in design. Their conclusions rely on interpreting clinical, histological, and immunological changes after initiating a medical intervention. Because these studies lack appropriate control groups (e.g., placebo or equivalent comparator), it is not possible to determine with certainty whether the observed outcomes are attributable to the intervention itself [342, 346, 356–362].

Treatment of RCD-I:

In an open-label study including 43 patients with RCD-I, budesonide administered as an open-capsule, induced clinical response and histologic improvement in approximately 90% of patients with RCD-I [356]. This treatment is based on the hypothesis that opening the gelatine capsule followed by grinding the drug will allow the release of budesonide from polymer matrix, providing more immediate action in the proximal small-bowel. Another retrospective study concluded that open-capsule budesonide was well-tolerated and associated with improvements in enteropathy (83%) and symptoms (90%) in CeD patients with persistent symptoms and RCD [357].

Escalation therapy to immunosuppressants is not standardized and is also not supported by firm data from clinical trials. Nevertheless, it can be considered in cases of steroid refractoriness or dependency on higher steroid doses. In RCD-1, the addition of thiopurines, such as, azathioprine or 6-mercaptopurine to steroids was effective in inducing a clinical response in some cases [316, 360, 363]. When used, thiopurines should be re-evaluated for possible discontinuation after 2–3 years of clinical, histological and immunophenotypic stability. The options for pharmacological treatment of RCD-I are summarized in Table 8.

Treatment of RCD-II:

Summary of evidence: Several therapies have been attempted for RCD-II, including cladribine (2-chlorodeoxyadenosine (2-CdA) [358, 360], open-capsule budesonide [356], 6-thioguanine [364], alemtuzumab [316], infliximab [365, 366], auto-HSCT [330, 342, 346, 359, 367, 368], and mesenchymal stem cell infusion [369]. Whilst some treatments showed positive results, there is still a risk of progression to EATL [360, 368, 370].

In a study, including 13 RCD-II, budesonide administered as an open-capsule, induced clinical response and histologic improvement in 77% and 55% of cases, respectively [356]. Moreover, in 7 patients, the clonal TCR rearrangement observed at diagnosis was not detected in the follow-up biopsies and the number of abnormal IELs were reduced.

The use of azathioprine in patients with RCD-II is not currently recommended due to the potential risk of increasing the likelihood of developing EATL [318, 361]. Treatment with biologicals, such as infliximab, may induce responses, but only a few cases have been reported [371].

In an open-label study, including 13 patients with RCD-II unresponsive to cladribine and treated with auto-HSCT, most showed clinical improvement, with a 4-year survival rate of 66% [346, 359].

The anti-IL-15 monoclonal antibody AMG714 was tested in a phase-2 trial but did not meet the primary endpoint of reducing aberrant IELs [350]. However, it did improve diarrhoea and reduce T-cell receptor clonality.

Due to the presence of JAK/STAT pathway mutations in RCD-II, tofacitinib, a JAK 1/3 inhibitor, may offer promising therapeutic potential [372]. In a small study, tofacitinib induced clinical and histological improvement in six patients with RCD-II but did not reduce abnormal IELs [362]. Further research is needed to confirm the safety and effectiveness of this approach, with the goal of reducing inflammation and limiting the risk of EATL [361]. The options for pharmacological treatment of RCD-II are summarized in Table 8.

TABLE 7 | The diagnostic workup of refractory coeliac disease.

Domain	Key points
1. Clinical assessment	Common manifestations: Chronic diarrhoea, weight loss, abdominal pain, and malnutrition. RCD typically presents in adults, often after a long-standing CeD diagnosis, and may include systemic features such as fever or signs of protein-losing enteropathy [323, 327]. in severe cases with widespread bowel involvement, a 'functional' short bowel syndrome may occur, complicated by D-lactic acidosis in the context of carbohydrate malabsorption or bacterial overgrowth [328, 329]. Clinical suspicion should also be raised in newly diagnosed CeD with severe symptoms and extensive villous atrophy. Rarely, extra-intestinal localisation of aberrant T cells (skin, sinuses, lungs, liver, CNS) may cause atypical presentations [330–332].
2. Endoscopy and histology	Endoscopic features may resemble active CeD; adequate duodenal biopsies must be collected in formalin and for IEL immunophenotyping. Exclude collagenous sprue, characterised by thickened subepithelial collagen bands [333–335]. Mucosal ulcers raise suspicion for RCD-II. VCE is useful for assessing extent of mucosal damage and guiding device-assisted enteroscopy to rule out EATL [333–338].
3. Immunophenotyping of IELs	Essential to differentiate RCD-I from RCD-II. RCD-I shows normal cytotoxic T-lymphocytes phenotype (CD103+, sCD3+, CD8+). RCD-II shows aberrant IELs with intracellular CD3 but lacking surface CD3 and CD8 [339]. These aberrant T cells represent a clonal, pre-malignant population with potential progression to EATL. Flow cytometry is regarded as the most sensitive and specific technique for detecting these aberrant IEL populations, as it allows precise differentiation between cytoplasmic and membranous CD3 expression and quantifies the proportion of aberrant cells [340]. It is also valuable for excluding other indolent small-bowel lymphoproliferative disorders [322, 323, 341]. However, the availability of flow cytometry with expertise in IEL phenotyping remains limited to specialised centres, and sample transport and tissue handling requirements further constrain its routine use. Immunohistochemistry (IHC), in contrast, is more widely available and can provide reliable information when performed by experienced laboratories. IHC allows assessment of CD3 and CD8 expression patterns and, when combined with TCR gene rearrangement studies, can support the diagnosis in most cases. Although less quantitative than flow cytometry, IHC remains a practical first-line approach for many institutions, reserving flow cytometry for cases where IHC findings are inconclusive or where RCD-II is strongly suspected [322]. Overall, both techniques contribute to accurate classification of RCD subtypes. Flow cytometry remains the reference standard for identifying aberrant IELs, but immunohistochemistry—with or without TCR clonality testing—offers a feasible and informative alternative in settings where flow cytometry is unavailable.
4. T-cell clonality analysis	Assesses TCR rearrangements. RCD-II shows monoclonal/oligoclonal populations; RCD-I remains polyclonal [327, 339, 342]. If TCR-γ is absent, TCR-δ may be detected [316, 343]. TCR analysis allows diagnosis of extra-intestinal locations of RCD-II such as skin, lung, brain or in peripheral blood by identification of the same TCR rearrangement found in duodenum [344–346].
5. Genetic analysis	Screening for germline mutations and constitutive (primary) immune disorders aids in differentiating RCD-I from autoimmune enteropathy [347].
6. Somatic mutation analysis	Somatic mutations may guide therapy. JAK1–STAT3 gain-of-function mutations found in up to 80% of RCD-II cases and 90% of EATL cases [348–350]. Other mutations (TNFAIP3/A20, TET2, KMT2D) may explain poor response to anti-IL-15 therapy [348, 350, 351].
7. Radiological imaging	Findings may include marked small-bowel wall thickening, strictures, ulceration or ulcerative jejunitis, mass-like changes, and atypical or necrotic mesenteric lymph nodes. Reduced spleen volume may also be present. PET can assist in excluding overt EATL and detecting metabolically active complications [183, 352–354].
8. Nutritional assessment	Wasting and hypoalbuminaemia are suggestive of RCD-II or EATL [322, 355].
9. Exclusion of EATL	All diagnostic modalities should be used to exclude EATL before confirming RCD.

Abbreviations: CeD, coeliac disease; CNS, central nervous system; EATL, enteropathy-associated T-cell lymphoma; IEL, intraepithelial lymphocytes; IHC, immunohistochemistry; PET, positron emission tomography; RCD, refractory coeliac disease; sCD3, surface CD3; TCR, T-cell receptor (TCR-γ, gamma, TCR-δ delta); VCE, video capsule endoscopy.

TABLE 8 | Options for pharmacological treatment in RCD-I and RCD-II.[a]

RCD-I	
Nutritional support	Enteral or parenteral nutrition, as needed.
Open-capsule budesonide	9 mg daily for 6 weeks, followed by 6 mg daily for an additional 6 weeks, then 3 mg daily thereafter. 9 mg dose: open two budesonide capsules and grind the contents; swallow with plenty of water. Swallow the third capsule whole. 6 and 3 mg doses: Open the capsule(s) and grind the contents; swallow with plenty of water.
Oral prednisone	0.5–1 mg/kg body weight may be needed for few weeks in cases of no response to budesonide. Following a response, thiopurines, such as azathioprine or 6-thioguanine may be initiated and continued for up to 2 years. Careful monitoring is required to detect potential complications.
Thiopurines, such as azathioprine	Azathioprine 2.5 mg/kg body weight to maintain remission after tapering of steroids. Re-evaluated for possible discontinuation after 2–3 years of clinical histological and immunophenotypic stability.
RCD-II	
Nutritional support	Enteral or parenteral nutrition, as needed.
Open capsule budesonide	Dosage and capsule handling are described in the RCD-I section. Seriously ill patients might require alternative treatment including parenteral steroids.
Cladribine (2-CdA)	A dose of 0.15 mg/kg/day administered intravenously for 5 consecutive days, repeated in 1–3 treatment courses at intervals of 6 months.
Autologous haematopoietic stem cell transplantation (Auto-HSCT)	A conditioning regimen with fludarabine and melphalan followed by Auto-HSCT.
JAK inhibitors, such as, tofacitinib	10 mg twice daily for 12 weeks, followed by a reduced maintenance dose of 5 mg twice daily.

Abbreviations: Auto-HSCT, autologous haematopoietic stem cell transplantation; 2-CdA, 2-chlorodeoxyadenosine; EATL, enteropathy-associated T-cell lymphoma; JAK, Janus kinase; RCD, refractory coeliac disease; RCD-I, refractory coeliac disease type 1; RCD-II, refractory coeliac disease type 2.

[a]Important notes: (1) Dosages are indicative and should be individualised based on clinical response, tolerability, and comorbidities. (2) Patients with RCD-II should be managed in specialised referral centres with expertise in complicated coeliac disease, including dedicated gastroenterology, immunology, and haematology services. Whenever possible, treatment within clinical trials is strongly recommended. (3) Enteropathy-associated T-cell lymphoma (EATL) must be confidently excluded before initiating immunosuppressive or cytotoxic therapy. (4) In a subset of patients with RCD-II complicated by ulcerative jejunitis and significant small-bowel stenosis, surgical resection prior to pharmacological therapy may improve survival [324].

5.3.4 | Prognosis of RCD

Summary of evidence: The prognosis of RCD is influenced by multiple factors, including disease subtype, nutritional status, and development of complications such as ulcerative jejunitis, EATL, and small bowel adenocarcinoma [308]. The most important prognostic determinant is the distinction between RCD-I and RCD-II. RCD-I generally follows a benign course with a 5-year survival rate exceeding 90%, whereas RCD-II carries a significantly higher risk of progression to EATL and has a 5-year survival of approximately 44%–58% [342, 373].

Other poor prognostic indicators in RCD include severe malabsorption, weight loss, hypoalbuminemia, and persistent inflammation despite treatment [355, 373]. Nutritional deficits in patients with EATL are usually profound, driven by severe malabsorption and systemic disease burden, and are associated with poorer tolerance to chemotherapy and worse overall survival rates [342, 373, 374].

Additionally, patients with RCD who develop ulcerative jejunitis, strictures, or infections have a worse prognosis [342].

6 | Coeliac Disease and Malignancy: Associations and Risk of Malignant Transformation

6.1 | Q. What Is the Risk of Malignant Complications in Coeliac Disease (Non-refractory CeD)?

Statement: The risk of malignant complications in non-refractory CeD is only slightly increased, remains low in absolute terms, and decreases with long-term adherence to a strict GFD. Routine malignancy screening beyond general population recommendations is not indicated in the absence of clinical suspicion.

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

6.2 | Q. What Is the Risk of Malignant Transformation in RCD-II?

Statement: RCD-II is associated with a substantial risk of malignant transformation, most commonly progression to EATL,

which develops in up to half of affected patients and is the major determinant of the markedly reduced 5-year survival seen in this subtype.

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

Summary of Evidence: Patients with CeD who are responsive to GFD and do not develop refractory disease have a modestly increased risk of certain malignancies compared with the general population; however, the absolute risk remains low [308]. Large population-based studies demonstrate a small increase in overall cancer risk, particularly during the first years following diagnosis, likely reflecting prolonged untreated disease prior to diagnosis rather than the effect of treated CeD [375, 376].

Specific malignancies reported at increased relative risk include lymphoproliferative malignancies, small bowel adenocarcinoma, and oesophageal cancer, but these remain rare events in absolute terms [308]. Importantly, the risk of malignancy appears to decline over time with sustained adherence to a strict GFD and may approach that of the general population during long-term follow-up. Development of EATL in patients without RCD is exceedingly uncommon. Accordingly, in patients with non-refractory CeD who are clinically stable and adherent to a GFD, routine cancer surveillance beyond age- and risk-appropriate population screening is not recommended. Long-term follow-up should focus on assessment of dietary adherence, symptom review, nutritional status, and vigilance for alarm features.

In contrast, RCD-particularly RCD-II- carries a substantially increased risk of malignant transformation, most notably progression to EATL. RCD-II is widely regarded as a pre-lymphomatous condition [342]. The cumulative risk of EATL in RCD-II is high, and malignant transformation may occur despite dietary adherence. The risk of malignant transformation in RCD-I is considerably lower, though still higher than in uncomplicated CeD.

Patients with RCD should therefore undergo close clinical follow-up, including regular assessment for symptoms suggestive of lymphoma (e.g., persistent abdominal pain, unexplained weight loss, fevers, bowel obstruction), and appropriate use of imaging, endoscopy, and histological reassessment where indicated.

In patients who progress to EATL, prognosis is particularly poor. EATL often presents late, with nonspecific symptoms or complications such as bowel perforation, bleeding, or obstruction [374, 377]. Median survival after diagnosis is less than 1 year, even with treatment. The survival in EATL is negatively affected by: profound malnutrition and catabolic state, poor performance status at diagnosis and delayed or incomplete response to therapy [342].

Two types of EATL are recognised. Type I EATL accounts for approximately 80%–90% of cases and is exclusively associated with pre-existing CeD, often following RCD-II. Type II EATL (de novo) is usually not associated with pre-existing CeD and may occur independently of CeD [378].

Management of EATL typically involves multi-agent chemotherapy, but outcomes are limited by chemotherapy toxicity, particularly in patients with malnutrition. Recent protocols incorporate pre-emptive debulking surgery with resection of the affected bowel segment, and auto-HSCT as consolidation therapy in selected fit patients, which may improve survival [379]. Combination chemotherapy followed by auto-HSCT has shown improved progression-free survival in highly selected patients, with 2-year survival rates up to 60%–70% in some series. However, many patients are ineligible for intensive regimens due to poor functional status or advanced disease at presentation.

Early identification of RCD-II and close surveillance for transformation to EATL is critical. A multidisciplinary approach involving gastroenterologists, dietitians, haematologists/oncologists, and pathologists is essential to optimize diagnosis, supportive care, and treatment planning [380]. Advances in targeted therapies offer hope for improving survival rates and QoL in affected individuals.

Small bowel adenocarcinoma, although less common than EATL, is a recognized and serious complication that also confers a poor prognosis [308]. Small bowel adenocarcinoma often presents with obstructive symptoms, bleeding, or perforation, typically in the jejunum. Diagnosis is usually made via capsule endoscopy, CT/MRI enterography, or enteroscopy with biopsy. Treatment involves surgical resection, which is the only curative option [381–383].

7 | Conclusions, Limitations of These Guidelines and Future Perspectives

These 2025 ESsCD guidelines, presented in two parts, update the 2019 recommendations on the diagnosis and management of CeD in adults [2], incorporating new evidence from multidisciplinary expert consensus using the AGREE II and GRADE methodologies. Part 1, which has been already published, refines diagnostic strategies, including serological testing, biopsy protocols, and the no-biopsy approach for high-titre IgA anti-TG2 cases [1].

The current Part 2 of the ESsCD guidelines provides a comprehensive, evidence-based framework for the management and follow-up of adult CeD. This update transforms the standard of care from a sole emphasis on dietary exclusion to a more sophisticated, personalised, proactive, and multidisciplinary paradigm. Central to these advancements are refined strategies for complex disease courses such as RCD, a strengthened focus on the metabolic health and nutritional quality of the GFD, and the formal integration of innovative care models leveraging telemedicine and dietitian-led services.

The guidelines specifically address dietary management—including the GFD, safe consumption of oats, and the use of a low-FODMAP diet for persistent symptoms—alongside the management of associated and documented exocrine pancreatic insufficiency. Furthermore, it introduces critical new topics: expanded strategies for nutritional and psychosocial monitoring, metabolic risk management, the use of digital

communication tools, and updated recommendations for family screening and pregnancy care. It also details systematic approaches to patients with persistent symptoms despite GFD and RCD, clarifying the RCD-I/II subtypes and the associated risk of EATL.

Despite the significant progress in the management of adults with CeD, several challenges and knowledge gaps remain. The certainty of evidence supporting guideline recommendations is limited, largely because many clinical situations have not been studied prospectively or in controlled settings. As a result, we often lack the opportunity to propose algorithms supported by robust evidence. Key limitations include the absence of a unified framework for long-term follow-up and the lack of standardized approaches for managing patients with persistent symptoms. Consensus is also lacking on optimal strategies for monitoring and maintaining bone mineral health specifically in CeD. There is a clear need for high-quality data on the indications, timing, and frequency of DXA testing in adults with CeD, rather than relying on extrapolation from other disease populations.

In addition, whilst non-dietary pharmacological therapies represent a promising and much-needed avenue for treatment, their efficacy and safety require validation through rigorously designed clinical trials. Addressing these gaps will be critical to improving evidence-based, individualized care and long-term outcomes for adults with CeD.

Furthermore, the practical implementation of these recommendations faces hurdles, especially in low-resource settings where equitable access to specialised diagnostics, dietetic expertise, the local or national policies and novel treatments may be constrained.

Looking ahead, future efforts must focus on bridging these gaps through high-quality basic science and robust clinical trials. A critical priority is the development of pragmatic, context-sensitive guidance that can be adapted to diverse healthcare systems, ensuring that all patients with CeD, regardless of location, can benefit from advancing standards of care. Widespread dissemination and flexible application of these guidelines are essential to elevate the QoL and long-term health outcomes for adults living with this condition globally.

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.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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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 three 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.

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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.

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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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