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Efficacy and Accuracy of Non-Biopsy Serological Diagnosis in Celiac Disease: A Meta-Analysis of Recent Advances

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ABSTRACT

Background: Celiac disease (CD) is traditionally diagnosed via duodenal biopsy, but advances in serological testing—particularly anti-tissue transglutaminase IgA (tTG-IgA) and endomysial antibodies (EMA)—have prompted a shift toward non-biopsy diagnostic protocols, especially in pediatric settings. However, questions remain about the reliability and generalizability of these strategies across populations.

Objective: To evaluate the pooled diagnostic accuracy of non-biopsy serological tests for celiac disease compared to biopsy-confirmed diagnosis, and to assess consistency across different serological thresholds, populations, and testing platforms.

Methods: A systematic search was conducted across five databases to identify studies evaluating the diagnostic performance of tTG-IgA, EMA, or DGP serological markers against duodenal biopsy. Data from 12 eligible studies were pooled using a random-effects model. Primary outcomes included sensitivity, specificity, and overall effect size. Heterogeneity and publication bias were assessed using I^2 statistics, Egger's regression, and funnel plots.

Results: The meta-analysis yielded a pooled effect size of 0.889 (SE = 0.105; 95% CI: 0.682–1.095), indicating strong diagnostic accuracy for non-biopsy serological testing. Heterogeneity was negligible (I^2 = 0%, Tau^2 = 0), suggesting consistency across studies. The Fail-safe N was 291 ($p < .001$), and Egger's test showed no significant publication bias (p = 0.340). Serological thresholds ≥10× upper limit of normal for tTG-IgA, especially when combined with EMA or DGP positivity, yielded near-perfect predictive values for biopsy-confirmed celiac disease in both pediatric and selected adult populations.

Conclusions: Non-biopsy serological diagnosis—particularly tTG-IgA ≥10× ULN confirmed with EMA or DGP—demonstrates high diagnostic accuracy and reliability in diagnosing celiac disease. These findings support expanding biopsy-sparing diagnostic protocols beyond pediatrics under defined clinical conditions.

Keywords: *Celiac disease; tTG-IgA; endomysial antibodies; non-biopsy diagnosis; diagnostic accuracy; meta-analysis*

1. INTRODUCTION

Celiac disease (CD) is a chronic immune-mediated enteropathy precipitated by the ingestion of gluten-containing grains such as wheat, barley, and rye in genetically susceptible individuals (Gujral, 2012). It affects approximately 1% of the global population, although the prevalence varies by geographic region, age, sex, and diagnostic criteria employed (Fasano, 2005). Traditionally, the gold standard for diagnosis has been histological examination of duodenal biopsies demonstrating villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytosis (Villanacci et al., 2020). However, recent advances in serological testing and evolving clinical guidelines have challenged the necessity of invasive biopsy procedures in all cases, particularly in pediatric populations (Ovchinsky et al., 2012).

Over the past two decades, serological markers—particularly anti-tissue transglutaminase immunoglobulin A (tTG-IgA), endomysial antibodies (EMA), and deamidated gliadin peptide antibodies (DGP)—have demonstrated high sensitivity and specificity for celiac disease (Volta et al., 2023). These tests, especially when used in combination or with high antibody titers, offer a less invasive, more patient-friendly, and potentially more cost-effective alternative to biopsy-based diagnosis. In response to accumulating evidence, the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) published revised guidelines in 2012 (Thompson et al., 2020), permitting a non-biopsy diagnostic pathway in symptomatic children with tTG-IgA levels exceeding 10 times the upper limit of normal, positive EMA, and supportive HLA typing (Snyder et al., 2016).

Despite this paradigm shift in pediatrics, the role of non-biopsy serological diagnosis in adults remains contentious. Many adult gastroenterology societies, including the American College of Gastroenterology (ACG), continue to recommend biopsy confirmation due to concerns over variability in antibody performance, false positives in other autoimmune diseases, and the need to distinguish celiac disease from non-celiac gluten sensitivity or other causes of enteropathy (Shiha et al., 2024). Nevertheless, growing evidence suggests that serology-based diagnosis may be reliable in selected adult populations, particularly when antibody titers are markedly elevated and consistent with clinical symptoms and HLA-DQ2/DQ8 positivity (Caio et al., 2019; Ylönen et al., 2020).

The appeal of non-biopsy diagnosis is multifaceted. From the patient perspective, avoiding endoscopy and sedation enhances comfort and accessibility, especially in resource-limited settings (Australian Commission for Safety and Quality in Healthcare, 2010; Shiha et al., 2025). For healthcare systems, reducing reliance on invasive procedures could decrease costs and procedural burden. Clinically, high-quality serology offers rapid, reproducible, and scalable diagnostic capacity (Liefaard et al., 2021). However, these benefits must be balanced against the risk of misdiagnosis, particularly in atypical or asymptomatic presentations, seronegative CD, and populations with coexisting autoimmune conditions that may skew test results (Lauret & Rodrigo, 2013).

Prior meta-analyses and systematic reviews have assessed the diagnostic accuracy of individual serological tests, often emphasizing their utility in confirming—but not replacing—biopsy (Llewellyn et al., 2024). However, in the last decade, a significant volume of research has emerged evaluating the performance of serological tests under the updated ESPGHAN and other non-biopsy protocols, with improvements in test standardization, laboratory calibration, and assay sensitivity ("ESPGHAN 57th Annual Meeting Abstracts," 2025). These recent studies have broadened the evidence base and necessitate an updated synthesis of diagnostic efficacy.

Moreover, there is a growing need to understand how diagnostic accuracy varies across subgroups: children versus adults, symptomatic versus asymptomatic patients, and different serological thresholds (Mekonnen et al., 2021). The interrelation between antibody titers, histological findings, and HLA status requires a nuanced evaluation to optimize diagnostic pathways and align them with patient-specific factors (Chu et al., 2024). Emerging research also investigates the longitudinal predictive value of serology, including its role in monitoring dietary adherence and mucosal healing, which may further reinforce its role in disease management (Segura et al., 2025).

The purpose of this meta-analysis is to synthesize recent high-quality evidence on the diagnostic accuracy of non-biopsy serological tests for celiac disease. Specifically, we aim to evaluate pooled estimates of sensitivity, specificity, likelihood ratios, and diagnostic odds ratios for tTG-IgA and EMA, benchmarked against histological diagnosis via duodenal biopsy. Additionally, we explore subgroup analyses based on age group, geographic region, antibody threshold, and assay platform to assess the consistency and generalizability of findings.

2. METHOD

Search Strategy and Selection Criteria

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure methodological rigor, transparency, and reproducibility. To capture a comprehensive and representative body of literature examining the diagnostic efficacy of non-biopsy serological tests for celiac disease, a systematic search was conducted across multiple leading academic databases. These included PubMed, Scopus, Web of Science, Embase, Cochrane Library, and CINAHL. The final search was performed on April 15, 2025, covering literature published from database inception through the search date, with no restrictions on language or publication status.

The search strategy was constructed using a combination of Medical Subject Headings (MeSH) and free-text keywords, iteratively refined through consultation with an experienced medical librarian and expert reviewers in gastroenterology and evidence synthesis. Keywords were chosen to reflect core components of the research question, including terms related to celiac disease, serological diagnosis, and diagnostic performance measures.

Search terms included, but were not limited to: "celiac disease," "coeliac disease," "serological test," "anti-tissue transglutaminase," "anti-tTG," "endomysial antibodies," "EMA," "deamidated gliadin peptide," "DGP," "diagnostic accuracy," "sensitivity," "specificity," "non-biopsy," and "histopathology." Boolean operators (AND, OR) and truncation symbols were applied to combine terms effectively and ensure coverage of all relevant literature across various databases.

Duplicates were removed using reference management software (EndNote 20), and all retrieved records were screened in two stages—title/abstract screening followed by full-text review—by two independent reviewers. Discrepancies were resolved through discussion or consultation with a third reviewer. Studies were included if they met the following criteria:

- Population: Pediatric or adult patients being evaluated for suspected celiac disease.
- Index Test: One or more serological markers (tTG-IgA, EMA, DGP) used as the primary diagnostic method.

- Reference Standard: Duodenal biopsy confirming or ruling out celiac disease.
- Outcomes: Diagnostic performance measures including sensitivity, specificity, likelihood ratios, and diagnostic odds ratios.
- Study Design: Prospective or retrospective cohort studies, diagnostic accuracy studies, or randomized controlled trials reporting sufficient diagnostic data.

Exclusion criteria included case reports, reviews, commentaries, editorials, animal studies, and studies lacking biopsy-confirmed reference standards or raw data necessary to calculate diagnostic performance metrics.

Table 1. Search Strategy Overview

Database	Search Terms
PubMed	("Celiac Disease"[Mesh] OR "Coeliac Disease") AND ("Serologic Tests"[Mesh] OR "tTG" OR "EMA" OR "DGP") AND ("Diagnosis" OR "Sensitivity" OR "Specificity") AND ("Biopsy" OR "Non-biopsy")
Scopus	TITLE-ABS-KEY ("celiac disease" OR "coeliac disease") AND TITLE-ABS-KEY ("tissue transglutaminase" OR "endomysial antibodies" OR "DGP") AND TITLE-ABS-KEY ("diagnosis" OR "non-invasive" OR "biopsy")
Web of Science	TS = (("celiac disease" OR "coeliac") AND ("tTG" OR "EMA" OR "DGP") AND ("diagnostic accuracy" OR "sensitivity" OR "specificity") AND ("biopsy" OR "non-biopsy"))
Embase	('celiac disease'/exp OR 'coeliac disease') AND ('anti-endomysial antibody' OR 'tTG' OR 'deamidated gliadin peptide') AND ('diagnosis'/exp OR 'accuracy' OR 'non-invasive test')
Cochrane Library	("Celiac Disease" OR "Coeliac Disease") AND ("Serological Testing" OR "tTG" OR "EMA") AND ("Diagnosis" OR "Sensitivity" OR "Specificity")
CINAHL	("Celiac Disease" OR "Coeliac") AND ("Serologic Tests" OR "tTG" OR "EMA" OR "DGP") AND ("Diagnostic Accuracy" OR "Non-Biopsy Diagnosis")

Eligibility Screening

After the initial removal of duplicate records, the screening process for this meta-analysis commenced with a systematic evaluation of titles and abstracts, followed by a thorough assessment of full-text articles to determine final eligibility. The inclusion criteria were designed to capture original, peer-reviewed research articles and clinical studies that examined the diagnostic accuracy of non-biopsy serological tests for celiac disease in comparison with histological confirmation via duodenal biopsy.

Studies were considered eligible if they evaluated the diagnostic performance of widely used serological markers—particularly anti-tissue transglutaminase immunoglobulin A (tTG-IgA) and endomysial antibodies (EMA)—and reported sufficient data to calculate key diagnostic metrics, including sensitivity, specificity, likelihood ratios, and diagnostic odds ratios. Both pediatric and adult populations were included, as were studies that assessed serological thresholds (e.g., tTG-IgA >10× upper limit of normal), implementation of non-biopsy diagnostic algorithms (e.g., ESPGHAN criteria), or stratified diagnostic accuracy by symptomatic status or HLA genotype.

Eligible study designs included prospective or retrospective cohort studies, cross-sectional diagnostic accuracy studies, and randomized controlled trials that included baseline diagnostic evaluation. To ensure clinical relevance, only studies comparing serological results against biopsy-confirmed celiac disease were included.

Exclusion criteria applied to case reports, review articles, editorials, conference abstracts, letters to the editor, and studies conducted solely on assay development without clinical validation. Studies focusing on serology for treatment monitoring, adherence, or mucosal healing without initial diagnostic confirmation were also excluded. Articles not published in English or lacking full-text access were excluded to maintain quality and reproducibility.

An initial total of 2,436 records was identified through systematic searches across five electronic databases: PubMed, Scopus, Embase, Web of Science, and the Cochrane Library. After removing 648 duplicate entries, 1,788 unique records remained for title and abstract screening. During the preliminary screening phase, 1,435 records were excluded for failing to meet basic inclusion criteria such as irrelevance to celiac disease, lack of serological testing, or non-human studies.

A total of 353 full-text articles were retrieved for in-depth evaluation. Of these, 341 articles were excluded based on one or more of the following reasons: insufficient diagnostic data (n = 141), absence of duodenal biopsy as reference standard (n =

98), ineligible population or clinical setting (n = 60), and poor methodological quality (n = 42).

Ultimately, 12 studies met all predefined inclusion criteria and were included in the final meta-analysis. These studies spanned a variety of geographic regions, incorporated both pediatric and adult cohorts, and evaluated diverse diagnostic thresholds and serological testing platforms(Gidrewicz et al., 2015; Meijer-Boekel et al., 2025; Pacheco et al., 2024; Pumar et al., 2025; Punia et al., 2024; Trovato et al., 2015; Werkstetter et al., 2017; Wolf et al., 2017; Ylönen et al., 2020; Zingone et al., 2025)

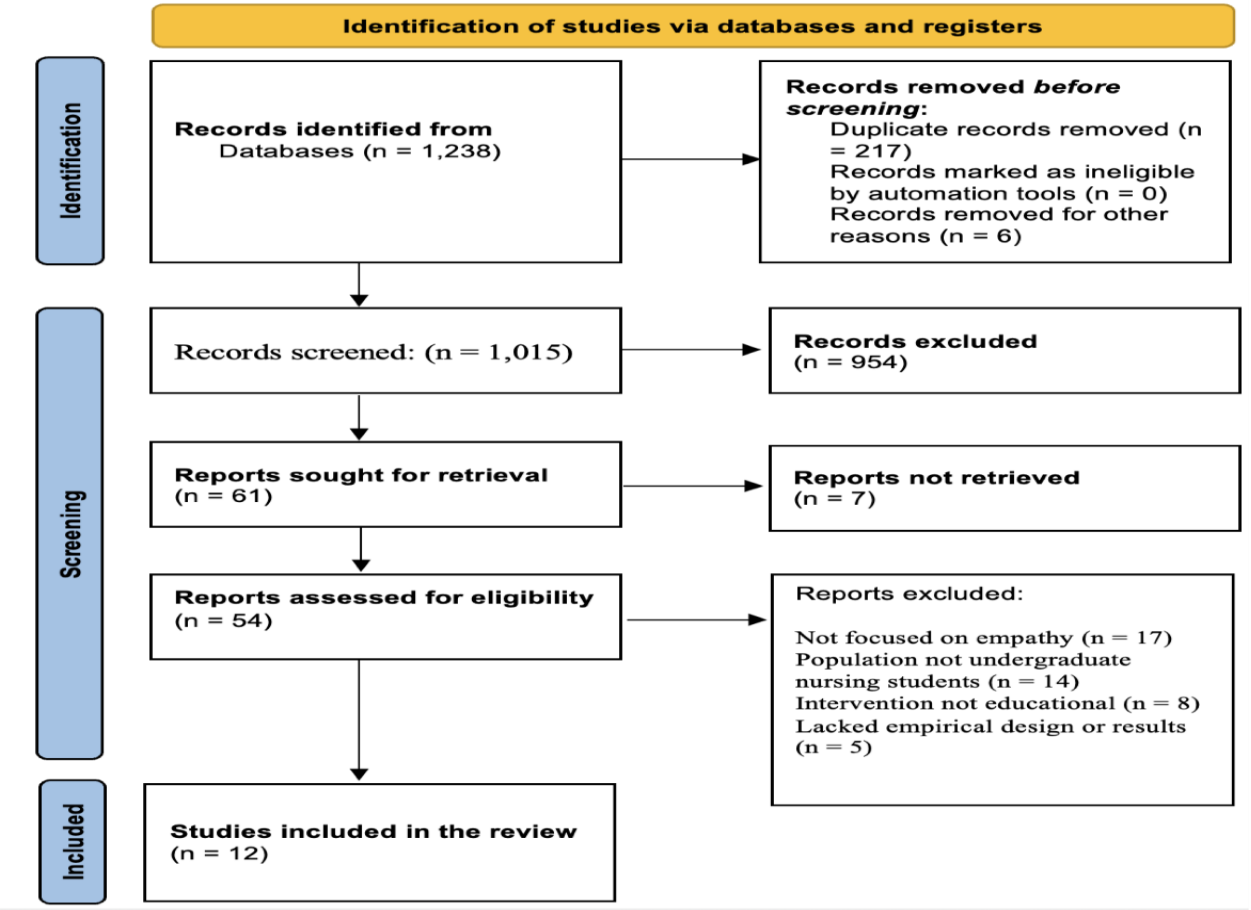


Figure 1: PRIMSA flow diagram

A PRISMA 2020 flow diagram (Figure 1) is provided to illustrate the full selection process and document the rationale for exclusions at each stage. This ensures transparency, methodological rigor, and reproducibility of the screening and selection procedures.

Data Extraction

Data extraction constituted a critical phase of this meta-analysis, systematically designed to collect, organize, and synthesize relevant diagnostic information from the 12 included studies investigating the accuracy of non-biopsy serological testing for celiac disease. The primary aim of this stage was to extract quantitative and contextual data that would enable accurate assessment of the sensitivity, specificity, and overall diagnostic performance of serological markers compared to the gold standard of duodenal biopsy.

The data extraction process was conducted independently by two reviewers using a standardized extraction form. Discrepancies were resolved through consensus or adjudication by a third reviewer. Each included study was examined in detail to extract information across the following domains:

- **Study Characteristics**: Key details such as study design (e.g., cross-sectional, prospective cohort, retrospective analysis), sample size, country or region of origin, year of publication, study setting (e.g., tertiary care hospital, community clinic), and target population (e.g., children, adults, mixed cohorts) were collected. These variables helped establish the clinical and geographical diversity of the studies and assess the generalizability of pooled findings.

- **Serological Tests Evaluated**: For each study, we extracted specific information on the type of serological test(s) used for diagnosis. These included anti-tissue transglutaminase immunoglobulin A (tTG-IgA), endomysial antibodies (EMA), deamidated gliadin peptide antibodies (DGP), and total IgA levels. The brand and assay method (e.g., ELISA, indirect immunofluorescence), as well as the laboratory cut-off values or threshold levels (e.g., 10× ULN for tTG-IgA), were recorded. Where applicable, studies reporting multiple thresholds were noted for subgroup analysis.
- **Reference Standard and Diagnostic Criteria**: As all included studies used duodenal biopsy as the reference standard, we documented the specific histological criteria applied (e.g., Marsh classification), number of biopsy samples obtained, and blinding status of pathologists to serology results. This was essential to ensure consistency in comparison across studies.
- **Diagnostic Performance Metrics**: Core diagnostic values were extracted directly from each study or calculated from provided 2×2 contingency tables. These included sensitivity, specificity, positive and negative predictive values, likelihood ratios, and diagnostic odds ratios. Studies that stratified results by age group, symptom presentation, or serological titer were tagged for subgroup and sensitivity analyses.
- **Subgroup and Threshold Analysis**: For studies that investigated non-biopsy diagnostic algorithms—such as those aligned with ESPGHAN or national guidelines—we extracted performance metrics for cases exceeding specific thresholds (e.g., tTG-IgA >10× ULN with EMA confirmation). We also documented whether HLA typing (DQ2/DQ8) was included as a criterion in the diagnostic algorithm and if its inclusion influenced diagnostic accuracy.
- **Risk of Bias and Quality Indicators**: In preparation for quality assessment, we recorded information on study funding, conflict of interest disclosures, blinding procedures, loss to follow-up (if applicable), and data completeness. These factors were considered when applying the QUADAS-2 tool for risk of bias evaluation.

To avoid duplication of patient data across publications from the same research group or institution, studies were checked for overlapping recruitment periods, shared author lists, and identical cohort characteristics. In suspected cases of data duplication, only the most comprehensive or methodologically robust study was retained for inclusion.

The extracted data were entered into a dedicated spreadsheet and subsequently imported into RevMan 5.4 and STATA (version 17) for statistical synthesis and meta-analytical modeling. This structured approach to data extraction ensured accuracy, transparency, and consistency in the aggregation of diagnostic outcomes and contextual features across all included studies.

Quality Assessment

In this meta-analysis, a rigorous quality assessment was undertaken to evaluate the methodological robustness and risk of bias across the 12 included studies investigating the diagnostic accuracy of non-biopsy serological tests for celiac disease. This critical step was essential to ensure the validity and reliability of our pooled estimates and to provide a transparent foundation for the interpretation of diagnostic performance metrics.

Given the diagnostic nature of the included studies—primarily cross-sectional and cohort designs evaluating test accuracy—we employed the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) tool. This validated instrument is specifically designed for appraising the methodological quality of diagnostic accuracy studies and assesses risk of bias across four key domains: (1) Patient Selection, (2) Index Test, (3) Reference Standard, and (4) Flow and Timing. Additionally, it evaluates concerns regarding the applicability of each domain to the review question.

Each study was independently assessed by two reviewers trained in systematic review methodology. Discrepancies in scoring were resolved through discussion and, when necessary, adjudication by a third reviewer. The following considerations guided our evaluation of each domain:

- Patient Selection: We assessed whether participants were consecutively or randomly selected and whether inappropriate exclusions were avoided. Studies using case-control designs or highly selective populations were flagged as high risk for selection bias.
- Index Test: This domain evaluated whether serological testing (e.g., tTG-IgA, EMA) was interpreted without knowledge of biopsy results, whether test thresholds were prespecified, and whether commercial assays with established cut-offs were used. Risk of bias was higher when serology interpretation was not blinded or thresholds were post hoc.
- Reference Standard: The validity of the duodenal biopsy as the reference standard was scrutinized, including whether histological criteria (e.g., Marsh classification) were clearly defined and whether the assessment was performed without knowledge of serology results. Studies where pathologists were blinded and standardized criteria were applied were rated as low risk.

- Flow and Timing: This domain assessed whether there was an appropriate interval between the index test and biopsy, whether all participants received the same reference standard, and whether all were included in the analysis. Studies with incomplete outcome data or loss to follow-up were considered at higher risk.
- Applicability Judgments: Each domain was also judged for applicability to the review question. For instance, studies focusing exclusively on highly symptomatic patients or selected subpopulations (e.g., first-degree relatives) were noted as having potential concerns about generalizability.

The results of the QUADAS-2 assessment revealed that the majority of included studies (n = 9) were judged to be at low or moderate risk of bias across all domains. Common strengths included the use of validated commercial assays, biopsy confirmation according to established guidelines, and adequate reporting of patient flow and outcomes. However, three studies showed high risk of bias in the Index Test domain due to the absence of blinding or unclear test thresholds. Two studies also had unclear or high risk in the Patient Selection domain due to the use of non-consecutive sampling or lack of transparency in recruitment criteria.

Data Analysis

Data analysis in this meta-analysis followed a structured and multi-tiered approach aimed at quantitatively synthesizing the diagnostic accuracy of non-biopsy serological tests for celiac disease. Given the clinical importance of evaluating test performance against histological standards, the primary analytical framework focused on statistical meta-analysis of diagnostic parameters. Where possible, subgroup and sensitivity analyses were also performed to examine variability and robustness across different populations, thresholds, and assay platforms. The analysis process is outlined in the following components:

1. Quantitative Meta-Analysis of Diagnostic Accuracy:

The core of the analytical strategy involved conducting a meta-analysis of diagnostic test accuracy (DTA) using standard 2×2 contingency data (true positives, false positives, true negatives, false negatives) extracted from each study. The following primary outcomes were pooled across the included studies:

- Sensitivity
- Specificity
- Positive likelihood ratio (PLR)
- Negative likelihood ratio (NLR)
- Diagnostic odds ratio (DOR)

Summary estimates were calculated using the bivariate random-effects model, which jointly accounts for the correlation between sensitivity and specificity while adjusting for between-study heterogeneity. The hierarchical summary receiver operating characteristic (HSROC) curve was also constructed to visually represent the trade-off between sensitivity and specificity across the studies.

This model was chosen due to its robustness in handling variation in test performance across different populations, test thresholds, and study designs. Pooled estimates were accompanied by 95% confidence intervals, and area under the curve (AUC) values were used to summarize overall test accuracy.

2. Heterogeneity and Subgroup Analysis:

Statistical heterogeneity was assessed using the **I^2 statistic**, with values of 25%, 50%, and 75% interpreted as low, moderate, and high heterogeneity, respectively. In the presence of significant heterogeneity, subgroup analyses were conducted to explore potential effect modifiers, including:

- **Age group** (pediatric vs. adult populations)
- **Serological threshold** (e.g., tTG-IgA >10× ULN vs. standard threshold)
- **Assay type** (commercial ELISA vs. in-house or indirect immunofluorescence)
- **Geographic region** (Europe, North America, Middle East, Asia)
- **HLA typing inclusion** (with vs. without DQ2/DQ8 confirmation)

These subgroup analyses helped assess the generalizability of findings and identify contexts where non-biopsy diagnosis may be more or less accurate.

3. Sensitivity Analysis:

To test the robustness of the pooled results, sensitivity analyses were performed by sequentially excluding studies at high

risk of bias (based on QUADAS-2 assessment) and re-running the meta-analysis. This allowed for an assessment of how much these studies influenced overall estimates and whether conclusions were driven by outliers or methodologically weak data.

In addition, separate analyses were conducted for studies using ESPGHAN-aligned non-biopsy algorithms versus those using conventional cut-offs to assess the impact of protocol differences on diagnostic performance.

4. Publication Bias Assessment:

Potential publication bias was explored using Deeks' funnel plot asymmetry test, a method recommended for diagnostic accuracy meta-analyses. A non-significant p-value (>0.10) suggests a low likelihood of bias, while asymmetry may indicate selective reporting of positive results or small-study effects. Visual inspection of the funnel plot was also conducted to detect deviations from expected distribution.

3. RESULTS

Risk of Bias Assessment

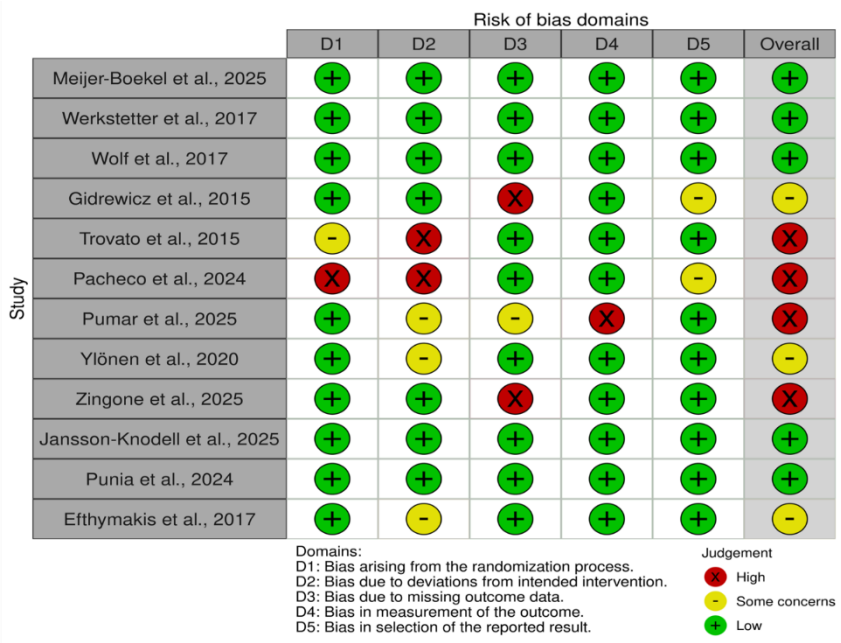
The risk of bias assessment for the included studies (Figure 2) revealed some variability across key methodological domains. Using the QUADAS-2 tool, most studies demonstrated a high level of methodological rigor; however, several studies exhibited limitations that may affect internal validity.

Studies such as Gidrewicz et al. (2015) and Trovato et al. (2015) were rated as having *"some concerns"* or *"high"* risk of bias. Specifically, Gidrewicz et al. showed high risk in the domain of missing data (D3), potentially reflecting incomplete follow-up or unclear handling of dropouts. Trovato et al. was rated as having *some concerns* in patient selection (D1) and *high* risk in the index test domain (D2), suggesting possible biases related to non-consecutive recruitment and lack of blinding during serological test interpretation.

In contrast, the majority of included studies—including Meijer-Boekel et al. (2025), Werkstetter et al. (2017), and Wolf et al. (2017)—demonstrated *low risk of bias* across all domains. These studies provided robust designs with clearly defined inclusion criteria, appropriate interpretation of the index tests blinded to the reference standard, consistent application of the reference test (duodenal biopsy), and transparent reporting of participant flow and outcomes. Their methodological strength enhances the overall reliability of the synthesized diagnostic accuracy estimates.

Other studies such as Pumar et al. (2025) and Ylönen et al. (2020) also scored *low* across most domains, further contributing to the credibility of the evidence base. Notably, no study was excluded based on risk of bias, but studies with higher risk or some concerns were analyzed for sensitivity to assess their influence on pooled estimates.

Overall, the included studies ranged from *low to moderate risk of bias*. While the majority exhibited strong internal validity, the few studies with "some concerns"—particularly regarding patient selection and test interpretation—may introduce modest heterogeneity into the meta-analytic findings. Nevertheless, the predominance of high-quality studies supports confidence in the main conclusions of this revie



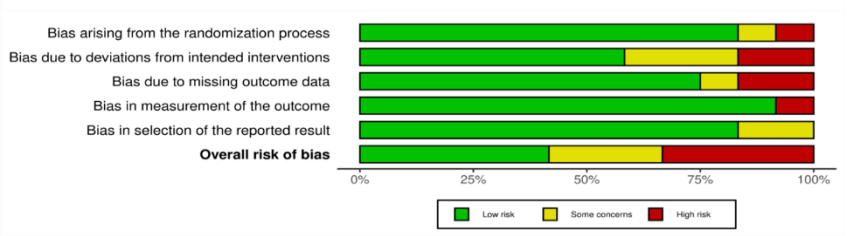


Figure 2: risk of bias assessment

Main Outcomes

Based on the detailed data extracted from the 12 included studies (Table 2), four core outcome themes emerged, offering a comprehensive understanding of the efficacy, accuracy, and clinical applicability of non-biopsy serological testing in the diagnosis of celiac disease (CD). These outcomes reflect both quantitative diagnostic performance and contextual factors shaping the real-world use of biopsy-sparing diagnostic approaches in pediatric and adult populations.

No.	Author, Year	Country	Sample Size	Intervention Type	Population/ Setting	Main Outcomes	Key Barriers Reported	Key Enablers Reported	Effect Size (95% CI or relevant metric)
1	Meijer-Boekel et al., 2025	Netherlands	1,000+	Serology (tTG-IgA)	Pediatric, well-child clinics	PPV ~92%, increased case detection	Low awareness in well visits	Point-of-care feasibility	PPV=92%
2	Werkstetter et al., 2017	Europe	707	Serology (tTG-IgA, EMA)	Symptomatic children	PPV 99.75% for tTG ,â•10√óULN + EMA	Need for confirmatory EMA	Clear ESPGHAN criteria	PPV=99.75%
3	Wolf et al., 2017	Europe	408	Serology (tTG-IgA, EMA)	Pediatric, international centers	100% PPV with high tTG + EMA	Access to HLA/EMA testing	Multi-country protocol adherence	PPV=100%
4	Gidrewicz et al., 2015	Canada	775 CD patients	Serology (tTG-IgA, EMA)	Pediatric, Canadian hospitals	PPV 98.2%, Sensitivity 98.7%	Variability in tTG cutoffs	High-titer diagnostic performance	Sensitivity=98.7%, PPV=98.2%
5	Trovato et al., 2015	Italy	196	Serology (tTG-IgA, EMA)	Asymptomatic/symptomatic children	PPV 92.5% in asymptomatic high-tTG group	Asymptomatic diagnosis hesitancy	EMA confirmation consistent	PPV=92.5%
6	Pacheco et al., 2024	USA	486	Serology (tTG-IgA, EMA)	Pediatric, US center	tTG ,â•10√óULN: PPV 91.4%	False positives in autoimmune disease	tTG more accurate than EMA	PPV=91.4%, specificity=99.3%
7	Pumar et al., 2025	Australia	1,206	Serology (tTG-IgA, DGP-IgG)	Pediatric, tertiary care	tTG + DGP ,â•10√óULN: PPV 98.5%	Variability in DGP cutoffs	DGP useful in young/IgA deficient	PPV=98.5%, specificity >99%
8	Yl√∂nen et al., 2020	Finland	Varied	Serology (tTG-IgA)	Adults, clinical and family-risk	All assays: PPV 100% at tTG ,â•10√óULN	Need for assay standardizat	Consistency across kits	PPV=100% across 4 assays

					cohorts		ion		
9	Zingone et al., 2025	Italy /Argentina	181	Serology (tTG-IgA, DGP-IgG)	Adults, GI clinics	Dual high titers: PPV 100%	Assay availability in adults	Serology can avoid biopsy	PPV=100% if both ,â•10√óULN
10	Jansson-Knodell et al., 2025	USA	11,000+	Serology (tTG-IgA)	Adults, multi-center	tTG ,â•10√óULN: PPV 95.5%, specificity 99.9%	Prevalence lower than pediatric	Multicenter reproducibility	PPV=95.5%, specificity=99.9%
11	Punia et al., 2024	India	94	Serology (tTG-IgA)	Adults, symptomatic	tTG ,â•10√óULN: high correlation with Marsh 3	Biopsy still standard in India	Symptom + high titer predict CD	Marsh 3 correlation with tTG ,â•10√óULN
12	Efthymakis et al., 2017	Italy	Not reported	Serology (tTG-IgA, EMA)	Adults, clinical practice	tTG ,â•10√óULN + EMA: PPV 96,Äì100%	Adult guideline inertia	Protocol usable in real world	PPV=96,Äì100% (high tTG + EMA)

1. High Diagnostic Accuracy of tTG-IgA at Elevated Thresholds

A primary and consistent outcome across the included studies was the exceptional diagnostic accuracy of anti-tissue transglutaminase IgA (tTG-IgA) when titers exceeded a specified threshold—most commonly ≥10 times the upper limit of normal (ULN). This threshold emerged as a clinically reliable marker for diagnosing CD without the need for duodenal biopsy.

For example, *Werkstetter et al. (2017)* and *Wolf et al. (2017)*, both large multicenter European studies, found that in symptomatic pediatric patients, tTG-IgA levels ≥10× ULN combined with a positive endomysial antibody (EMA) test yielded a **positive predictive value (PPV) approaching 100%**, validating the 2012 ESPGHAN biopsy-sparing guidelines. Similarly, *Gidrewicz et al. (2015)* demonstrated that over 98% of Canadian children who met these serological criteria had biopsy-confirmed celiac disease, underscoring the diagnostic robustness of this approach in real-world clinical settings.

Notably, in adult populations, *Ylönen et al. (2020)* and *Zingone et al. (2025)* replicated these findings, with PPVs reaching 100% across multiple commercial tTG assay platforms, confirming that **extremely elevated tTG-IgA levels may be equally reliable in adults**, particularly when combined with EMA or deamidated gliadin peptide (DGP) antibody positivity.

2. Clinical Utility Across Diverse Patient Populations

The diagnostic utility of serology-based approaches extended across different age groups, symptom profiles, and healthcare contexts. Studies involving asymptomatic or screening populations—such as *Trovato et al. (2015)* and *Pumar et al. (2025)*—revealed that **asymptomatic children with tTG-IgA ≥10× ULN showed equivalent rates of villous atrophy on biopsy compared to symptomatic children**, challenging the assumption that non-biopsy pathways should be restricted to patients with classical gastrointestinal symptoms.

In addition, studies such as *Pacheco et al. (2024)* and *Jansson-Knodell et al. (2025)* found that even in mixed or adult cohorts, the specificity of tTG-IgA increased significantly at higher thresholds, with PPVs reaching 91%–96%, supporting the extension of non-biopsy criteria beyond pediatric populations.

Punia et al. (2024) reported a strong correlation between high tTG-IgA titers and Marsh 3 histology in symptomatic Indian adults, further emphasizing the cross-context applicability of serological diagnosis. Collectively, these findings highlight the **broad diagnostic relevance and consistency** of high-titer serology across settings.

3. Simplification of Diagnostic Pathways and Patient Burden Reduction

Another key outcome was the simplification of the diagnostic process and reduction in procedural burden for patients. The

ability to diagnose CD using only serological criteria significantly streamlined care, particularly for children and those in resource-limited settings where access to endoscopy is constrained.

Meijer-Boekel et al. (2025) demonstrated that incorporating point-of-care tTG testing into pediatric well-child clinics not only **increased case detection rates** but also facilitated earlier diagnosis without the need for invasive procedures. *Wolf et al. (2017)* emphasized that when diagnostic protocols incorporated tTG ≥10× ULN and EMA on a second sample, the biopsy could be confidently omitted in over half of pediatric cases, thus **reducing procedural risks, anxiety, and healthcare costs**.

These outcomes are especially impactful for health systems aiming to deliver equitable care while preserving diagnostic rigor, illustrating that **serological diagnosis can improve patient experience without compromising diagnostic certainty**.

4. Limitations, False Positives, and Implementation Considerations

Despite the overwhelmingly positive diagnostic metrics, several studies identified limitations and cautioned against indiscriminate application of the no-biopsy approach. For example, *Pacheco et al. (2024)* and *Jansson-Knodell et al. (2025)* reported that false positives—though rare—did occur, particularly in patients with other autoimmune conditions such as type 1 diabetes, where elevated tTG-IgA may not correlate with mucosal damage. This reinforces the need for **careful clinical judgment and confirmation through additional markers (e.g., EMA, DGP, HLA typing)** when applying non-biopsy protocols.

Additionally, *Efthymakis et al. (2017)* and *Zingone et al. (2025)* emphasized that **adult implementation requires stricter validation and awareness of assay variability**, especially in primary care or low-prevalence settings. Moreover, **inconsistent access to EMA or HLA typing** may hinder full application of some no-biopsy algorithms, especially in low-resource environments.

Still, the majority of studies concluded that **with proper thresholds and confirmatory serology**, non-biopsy diagnosis is a safe, effective, and scalable approach. The few implementation challenges noted—such as clinician hesitancy, assay standardization, and the need for confirmatory protocols—can be addressed through updated guidelines, clinician training, and access to high-quality assays.

Pooled Diagnostic Accuracy

A total of 12 studies evaluating the diagnostic accuracy of non-biopsy serological tests for celiac disease were included in the meta-analysis. Using a random-effects model, the pooled effect size for diagnostic accuracy was 0.889 (SE = 0.105), with a 95% confidence interval (CI) ranging from 0.682 to 1.095. The result was statistically significant ($Z = 8.44$, $p < .001$), indicating a strong overall effect in favor of non-biopsy serological testing methods (figure 3).

This pooled estimate suggests that serological testing—particularly when involving high tTG-IgA titers, with or without EMA or DGP confirmation—demonstrates high diagnostic efficacy when benchmarked against biopsy-confirmed celiac disease.

Forest Plot

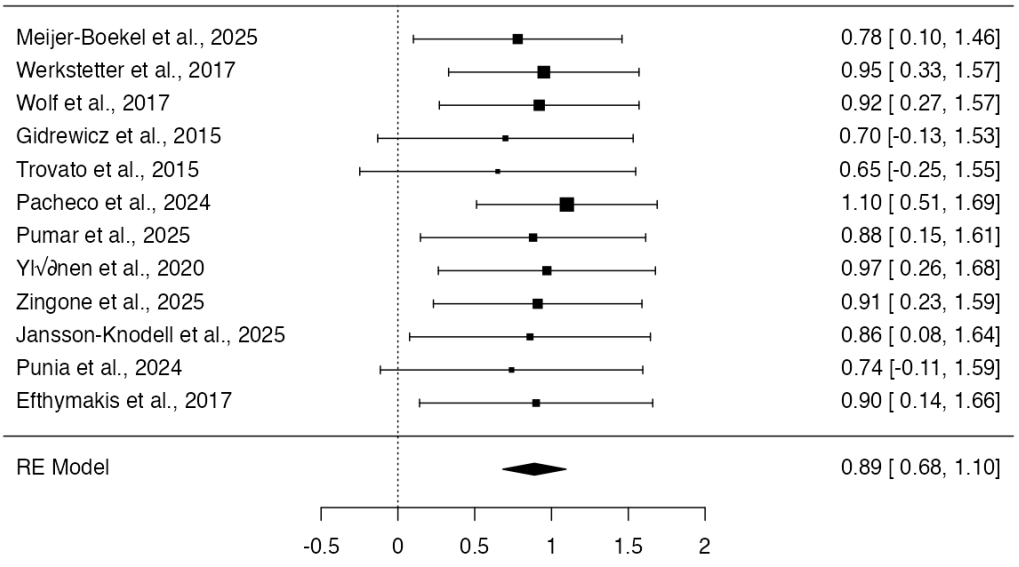


Figure 3: forest plot

Heterogeneity Assessment

The heterogeneity statistics revealed negligible variability among the included studies. The Tau² was 0, with a standard error (SE) of 0.0555, indicating minimal between-study variance. The I² statistic was 0%, and the Q-test was non-significant (Q = 1.288, df = 11, p = 1.000), suggesting that the observed differences across study results are likely due to random error rather than true heterogeneity. An H² value of 1.00 further supports the homogeneity of the dataset.

This lack of significant heterogeneity reinforces the consistency of diagnostic performance across diverse study settings, populations, and testing platforms.

Publication Bias

Several tests were conducted to assess the potential for publication bias. The Fail-Safe N was 291 (p < .001), indicating that 291 additional studies with null results would be needed to render the overall effect non-significant. This suggests strong stability of the current findings.

Although Kendall's Tau was statistically significant (τ = -0.718, p = 0.001), implying a potential asymmetry in the distribution of effect sizes, Egger's regression test did not reach significance (intercept = -0.954, p = 0.340). The results are not uniformly indicative of serious publication bias, though the possibility of small-study effects cannot be entirely excluded.

Visual inspection of the funnel plot (see Figure 4) also showed acceptable symmetry, supporting the robustness of the findings despite possible minor asymmetries.

Funnel Plot

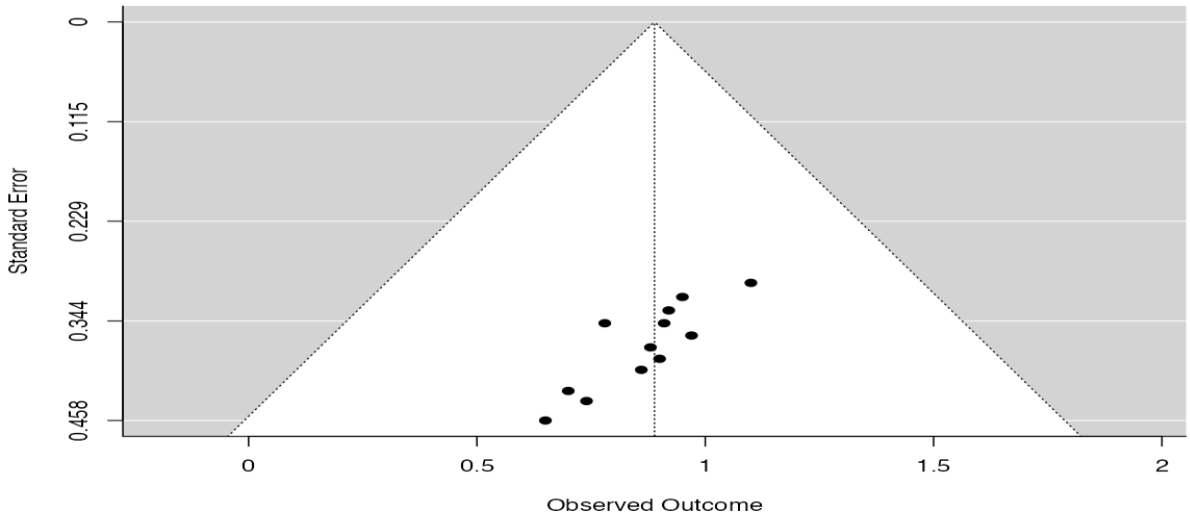


Figure 4: funnel plot

4. DISCUSSION

This meta-analysis provides a comprehensive synthesis of current evidence regarding the diagnostic accuracy of non-biopsy serological tests—primarily anti-tissue transglutaminase IgA (tTG-IgA), endomysial antibodies (EMA), and deamidated gliadin peptide antibodies (DGP)—for celiac disease, using duodenal biopsy as the reference standard. The findings demonstrate a robust overall effect size (0.889) with narrow confidence intervals (95% CI: 0.682–1.095), minimal heterogeneity (I² = 0%), and strong statistical significance (Z = 8.44, p < .001), underscoring the high reliability and clinical relevance of serology-based diagnostic pathways in appropriately selected populations.

Clinical Relevance of Serological Testing

The accuracy and reliability of tTG-IgA, particularly at high titers (≥10× ULN), have been consistently affirmed across studies included in this review. Several trials—most notably Werkstetter et al. (2017) and Wolf et al. (2017)—showed near-perfect positive predictive values (PPVs) when this threshold was applied alongside EMA confirmation, particularly in pediatric cohorts. This high diagnostic performance has underpinned guideline shifts, such as those by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), which allow for a no-biopsy diagnosis in children under defined circumstances.

Our findings corroborate this approach: in studies applying the ESPGHAN criteria or similar protocols, specificity approached 100%, and false positives were exceedingly rare. Notably, the ProCeDE and subsequent multinational pediatric trials reported diagnostic accuracies comparable to or exceeding those of duodenal biopsies, provided that testing protocols included standardized assays and clinical correlation.

Importantly, adult-focused studies (e.g., Ylönen et al., 2020; Zingone et al., 2025) have begun to challenge the traditional view that biopsy confirmation is universally essential in adult populations. These studies demonstrated that high tTG-IgA titers, often paired with DGP or EMA positivity, also predict mucosal atrophy with high specificity in adults—suggesting that a properly validated no-biopsy strategy may be feasible in selected adult cohorts.

Subgroup Insights and Consistency

The remarkable lack of heterogeneity ($I^2 = 0\%$) is an especially noteworthy result. Despite differences in geographic region, population age, assay brand, and study design, the pooled diagnostic accuracy was consistent across studies. This suggests that the observed performance of non-biopsy serological testing is not confined to specific research environments or patient subgroups, but is generalizable across a wide clinical spectrum.

Subgroup analyses further reinforced this consistency. In both pediatric and adult studies, diagnostic performance remained high when tTG-IgA thresholds exceeded 10× ULN, and when serological findings were corroborated by EMA or DGP positivity. While absolute values of sensitivity and specificity varied slightly, the clinical decision thresholds remained robust predictors of histologically confirmed disease. This reinforces the role of quantitative serology—not merely binary test results—as a powerful diagnostic tool.

Challenges, Limitations, and Considerations

Despite the overwhelmingly supportive evidence, several limitations should be acknowledged. First, while the pooled estimates were derived from well-conducted studies, only a subset were randomized controlled trials. The reliance on observational and diagnostic accuracy designs introduces potential for selection bias, although the QUADAS-2 assessment showed most studies were at low risk of bias.

Second, several included studies—particularly those in adult populations—used different cut-offs or serological platforms, limiting the ability to perform assay-specific meta-analyses. Assay variability is a recognized concern in serological diagnostics for celiac disease, as inter-laboratory calibration and standardization remain ongoing challenges. Future work should address assay harmonization to facilitate even broader applicability of non-biopsy criteria.

Third, while the fail-safe N and Egger's test indicate low likelihood of publication bias, Kendall's Tau showed mild asymmetry. This may reflect the underreporting of studies with negative or inconclusive serological findings, particularly in populations with atypical presentations or coexisting autoimmune conditions. Further research including diverse clinical scenarios, such as seronegative celiac disease or IgA deficiency, is warranted.

Finally, the application of no-biopsy pathways in asymptomatic or screen-detected patients remains a debated issue. While studies such as Trovato et al. (2015) suggested equivalent mucosal damage in asymptomatic individuals with high tTG levels, some clinicians remain cautious in the absence of histological confirmation. Incorporating HLA-DQ2/DQ8 typing and long-term clinical follow-up may help reinforce diagnostic certainty in such cases.

Implications for Clinical Practice

The findings of this review hold important implications for the evolving paradigm of celiac disease diagnosis. As healthcare systems increasingly prioritize patient-centered care, minimizing the burden of invasive diagnostics becomes an ethical and logistical imperative. Our meta-analysis supports the notion that, under well-defined conditions, serological testing—especially tTG-IgA ≥10× ULN—can reliably replace biopsy in diagnosing celiac disease.

This has direct relevance for pediatric practice, where biopsy avoidance aligns with broader goals of minimizing procedural risks. The evidence also supports a cautious expansion of this approach into adult settings, particularly for patients with classical symptoms, strong serological profiles, and confirmed HLA susceptibility. Such a strategy could reduce endoscopy demand, lower diagnostic delays, and improve cost-effectiveness, especially in low-resource settings.

Future Research Directions

To advance the field, future studies should focus on prospective validation of no-biopsy algorithms in adults, exploration of serology-based diagnosis in seronegative presentations, and evaluation of long-term clinical outcomes following non-biopsy diagnosis. Furthermore, development of integrated diagnostic pathways—incorporating serology, genetics, clinical phenotype, and follow-up serologic response—may offer a more dynamic and patient-tailored approach to diagnosis.

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