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REVIEW ARTICLE

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Next-generation immunoassays for autoantibody detection in celiac disease: emerging technologies and diagnostic advances

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ABSTRACT

The appearance of disease-specific autoantibodies (Aab) is a hallmark of celiac disease (CeD). The recent adaption of a no-biopsy approach places greater reliance on Aab testing. Despite their widespread use, conventional assay formats such as enzyme-linked immunosorbent assays (ELISA) continue to exhibit inherent methodological deficiencies that cannot be readily mitigated. Radio-binding assays (RBA) have historically defined the benchmark for assay performance, but the requirement for radiolabeled reagents and dedicated facilities renders this strategy an untenable solution beyond a limited number of specialized laboratories. This review aims to outline the future role of Aab in the diagnostic algorithm of CeD and to highlight the next-generation techniques that could replace the conventional testing methods. We discuss the diagnostic utility of ELISA, RBA, Electrochemiluminescence assay (ECL), luciferase immunoprecipitation systems (LIPS), antibody detection by agglutination polymerase chain reaction (ADAP) and dissociation enhanced lanthanide fluorescence immunoassay (DELFIA) techniques with emphasis on measuring anti-Transglutaminase 2 (TG2) Aab in the diagnosis of CeD. With the advantages of automation and multiplexing, the new generation of Aab testing modalities like ECL and ADAP may demonstrate sufficient sensitivity and accuracy to warrant inclusion in future CeD diagnostic guidelines. While multiplexing allows the inclusion of multiple Aabs testing from small volumes of blood in an automated manner, this generation of immunoassays are well suited for large-scale screenings and may replace the conventional ELISA and RBA techniques in the near future.

KEY MESSAGES

- Conventional Aab testing with different ELISA kits or RBAs used in specialized laboratories handling radioactivity are still widely being used as clinical diagnostics or in research settings. The analytical performance is still affected by accessibility of limited automation, inter-assay and platform variability, and lack of assay harmonization, emphasizing the need for further technological improvement.
- With the advantage of automation, multiplexing, and low-volume serum requirements, the new generation of Aab assays such as ECL, DELFIA and ADAP may hold potential for CeD diagnostics and monitoring.
- The recommendation is to use automated and multiplex platforms for the initial screening of large populations, followed by confirmatory testing in individuals who are Aab positive on screening, using a different modality to confirm results and accurately determine Aab levels.

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Antibody detection using agglutination PCR; Autoantibody testing; Celiac disease; Electrochemiluminescence assay; Radio-binding assay

Introduction

Celiac disease (CeD) is a multifactorial disorder affecting about 1% of the population worldwide, with a rising prevalence [1]. It is a chronic immune-mediated enteropathy triggered by dietary gluten in

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individuals genetically predisposed through HLA-DQ2 or DQ8 haplotypes [2,3]. HLA-DQ2/DQ8 testing is therefore a useful tool to rule out CeD due to its high negative predictive value, albeit their presence doesn't confirm the disease [4].

Central in CeD pathogenesis are long-lived, HLA-restricted CD4+ gluten-specific T cells, detectable in the small intestine and blood, which are the primary drivers of the pro-inflammatory response to gluten [5]. As these T cells are difficult to measure in clinical settings due to their low abundance, the field has focused on circulating antibodies as screening and diagnostic markers. Autoantibodies (Aab) in CeD are believed to arise *via* a hapten-carrier mechanism in which tissue TG2 enzymes modify gluten through deamidation and, in the process, form stable enzyme-substrate complexes [6,7]. These complexes are internalized by TG2-specific B cells, which then present deamidated gluten peptides to pathogenic CD4+ T cells. This interaction amplifies the pathogenic T cell response in CeD and triggers the differentiation of B cells into plasma cells that secrete Aab against TG2, gliadin and deamidated gliadin peptides (DGP). In this context, CeD-specific autoimmunity, assessed through serological testing, plays a pivotal role in screening, diagnosis and monitoring of disease activity [5,8].

The first CeD-associated Aab to be reported as serological screening markers, in 1964, were anti-gliadin antibodies (AGA) of the IgA and IgG isotypes that target dietary gliadin [9]. However, the determination of AGA showed a limited diagnostic accuracy due to the antigenic expression of many epitopes as non-specific targets for CeD and leads to false positivity [10]. In 1970, a highly specific anti-reticulin antibody (ARA) was discovered, and the detection of CeD-specific R1-ARA subtype was performed using an immunofluorescence-based assay [11]. Multifaceted procedures and poor sensitivity were the major drawbacks for the low diagnostic accuracy of ARA [12]. The subsequent discovery of the anti-endomysial antibodies (EMA) assay in 1983 [13] replaced the ARA antibody detection and remained a mainstay for the diagnosis of CeD due to its excellent predictive value. It also has been reported that the principal autoantigen target for the EMA is TG2 [14].

In 1997, the limitations of time-consuming methodology and expensiveness of immunofluorescence-based EMA testing were overcome by the discovery of IgA and IgG Aabs against TG2 (TG2-IgA and TG2-IgG) [14]. This discovery established TG2-IgA to be the most suitable diagnostic marker for CeD [14,15]. However, the limitation of false negative result in cases with total IgA deficiency (2-2.5% in patients with CeD) was ruled out using IgG class Aabs, including TG2-IgG, EMA-IgG and DGP-IgG [16,17]. It is reported that DGP displays CeD B-cell epitopes with more specificity than a non-deamidated peptide [18,19]. Despite the expanding repertoire of serological biomarkers, TG2-based immunoassays have consistently demonstrated superior clinical utility and are considered a cornerstone for the diagnosis of CeD. However, there are some pitfalls using TG2-IgA as a biomarker, such as IgA deficiency, diagnosis of CeD on very young children and the presence of non-atrophic or mild enteropathy can lead to misleading results. While the conventional serological assays are bound to depict methodological deficiencies, emerging next-generation testing platforms could be the answer to these shortcomings.

Selection of serological assays thus depends on screening goals and setting. In population screening, the aim is to benefit apparently asymptomatic individuals, so the assay should be as sensitive and minimally invasive as possible. In symptomatic patients, diagnostic testing should strive to use a serology assay with positive predictive value as close to 100% as possible [12]. The new generation of assays utilizes advanced multiplex platforms with automation, and the usage of minimal sample volumes substantially improves the efficiency of large-scale screening.

This review aims to address open questions about whether next-generation antibody testing can overcome limitations of conventional assays in CeD. It also evaluates which emerging techniques and methodologies improve diagnostic accuracy while remaining cost-effective. In addition, it evaluates the pros and cons of these methodologies for their relevance and applicability in clinical practice.

Key autoantibodies used for the diagnosis of CeD

TG2-IgA is widely recognized as the first-line serological test for CeD, demonstrating excellent diagnostic performance with sensitivity of approximately 90-98% and specificity of 95-97% [20]. Moreover, TG2-IgA

levels correlate strongly with severity of duodenal lesion [21]. According to the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) 2020 guidelines, a non-biopsy approach for CeD can be considered when TG2-IgA levels are ≥10 times the upper limit of normal (ULN), provided that both TG2-IgA and EMA are positive [22]. This is because high levels of TG2-IgA carry exceptionally high positive predictive value (PPV) for CeD in children and adults [23]. The guidelines recommend that only TG2-IgA and EMA-IgA be used for a non-biopsy diagnosis, and that only assays with calibrator curve-based quantification and a measurement range that includes values ≥10x the ULN value be used. If the TG2-IgA levels are moderately elevated, a diagnostic biopsy is needed to confirm CeD diagnosis. However, the recent guidelines from the European Society for the Study of Coeliac Disease (ESSCD) published in 2025 recommended only TG2-IgA as a single test in the initial CeD testing strategy and EMA is not required. To ensure diagnostic accuracy in ambiguous cases, a provision for EMA testing is also reserved [24].

EMA testing is regarded as one of the most specific assays for CeD diagnosis with a sensitivity and specificity of 95–100% and 99–100%, respectively [25]. EMA is highly specific; its routine use is constrained by several technical, operational, and economic reasons. Although EMA targets TG2 too, instead of solid-phase, the analytical platform utilize the liquid phase to preserve the natural form of TG2 and the detection is performed using Indirect Immunofluorescence (IF) on monkey esophagus or human umbilical cord [26]. Therefore, it is generally regarded as the second-line confirmatory test after TG2-IgA [22,27–29]. Some studies suggest that EMA could be useful in patients with a high suspicion of CeD and inconclusive histopathology, given its excellent specificity for CeD [30–32]. In contrast to EMA, which relies on indirect detection of Aabs through immunofluorescence, DGP assays utilize an ELISA-based approach targeting deamidated gliadin peptides. Although it has been suggested that DGP-IgG may offer some advantages for detecting CeD in early life [16], its overall diagnostic accuracy and clinical utility are not exceptionally promising over TG2-IgA [33]. Nevertheless, it remains useful in the diagnostic work-up of cases with total IgA deficiency [34].

Limitations of current serological testing

Despite their widespread use, conventional serological assays for CeD have several limitations.

In the primary diagnostic setting, TG2-IgA exhibits high sensitivity (approximately 90–98%), and false-negative results are uncommon. Reported false-negative rates are mainly associated with specific clinical contexts, including IgA deficiency, early-stage enteropathy, or patients adhering to a gluten-free diet. Importantly, reduced sensitivity of serological markers is primarily observed in follow-up settings, particularly in patients adhering to a gluten-free diet and does not reflect their high diagnostic accuracy in untreated individuals. Some retrospective studies with a large sample size reported the prevalence of sero-negative CeD (SNCeD) from 1.8% to 2.7% in the adult CeD population. The major proportion of the patients were presented with flat villi; however, some cases with milder enteropathy were reported [35–37]. Emerging tools like intestinal TG2 deposits, microRNA, proteome analysis and flow cytometry assessment could be useful in the detection of these cases [38].

Additionally, patients with total IgA deficiency may experience false negative results when relying solely on IgA class serological tests. In cases of strong clinical suspicion, total IgA measurement should be performed, followed by TG2-IgG and/or DGP-IgG as an alternative when IgA deficiency is present. However, clinicians should be aware of higher rates of false positivity in individuals with normal IgA levels. Therefore, with the potential exception to TG2-IgG and/or DGP-IgG testing using ELISA is recommended only in cases of confirmed IgA deficiency [39]. An exception is TG2-IgG measured in RBA, for which diagnostic accuracy appears comparable to that of TG2-IgA [40]. Inter- and intra-laboratory variability remains substantial, contributing to both false-negative and false-positive results [41–43]. Despite a pooled TG2 assay sensitivity of 98%, an Indo-Canadian study using four commercial assays reported sensitivity ranging from 76 to 98% and a false-negative rate of up to 24%. Notably, TG2-IgA levels could reach ≥10x ULN in one assay while up to 4% of the same samples were seronegative in another, underscoring marked inter-assay variability [44].

Regarding EMA, the assay is relatively expensive, operationally demanding, highly user-dependent, and it is often unavailable, particularly in primary care settings. As a result of these limitations with EMA, some countries use DGP-IgG as a second line test, and some repeat the initial TG2-IgA assay [45–47]. In addition, EMA may exhibit reduced sensitivity compared to TG2-IgA in patients with early stages enteropathy and in children younger than three years of age [16].

International standards for these assays do not currently exists and comparison of Aab levels is not feasible when tests are performed in different laboratories or using kits from different manufacturers [41,47]. Moreover, the calibrators and controls provided with commercial kits often have arbitrary assigned units, they use variable TG2 antigen, and the cut offs are calculated using poorly defined populations. Consequently, quantitative values from different kits are not directly comparable and cut offs may therefore vary substantially [44,48,49]. For monitoring CeD regression, clinicians often repeat Aab testing at multiple time points, sometimes across different laboratories. Different diagnostic kits and assay specific cut offs are often used, which complicates interpretation and contributes to variation in diagnostic performance [44,50]. High TG2-IgA levels have a strong predictive value for villous atrophy. However, cut-offs guiding biopsy avoidance require local validation, with emphasis on harmonization of serological assays [51].

Comparative performances of different methodologies

ELISA is a widely used solid phase immunoassay technique for detecting and quantifying specific antibodies. When assessing TG2-IgA, it works on the principal of indirect immune linked enzyme reaction where wells of microplate are coated with human recombinant TG2 antigen following by the binding of specific antibodies from the sera to the antigen upon incubation. Washing removes unbound antigen, antibodies and other protein complexes. A substrate is then added to produce a color change that is stopped with acid. This resulting color intensity measured by a spectrophotometer reflects the levels of antibody-antigen complexes in the sample [52] (Figure 1A).

A meta-analysis investigated the diagnostic accuracy of ELISA using different TG2 antigens. The sensitivity and specificity for recombinant human TG2 was 94% and 97%, purified human TG2 was 90% and

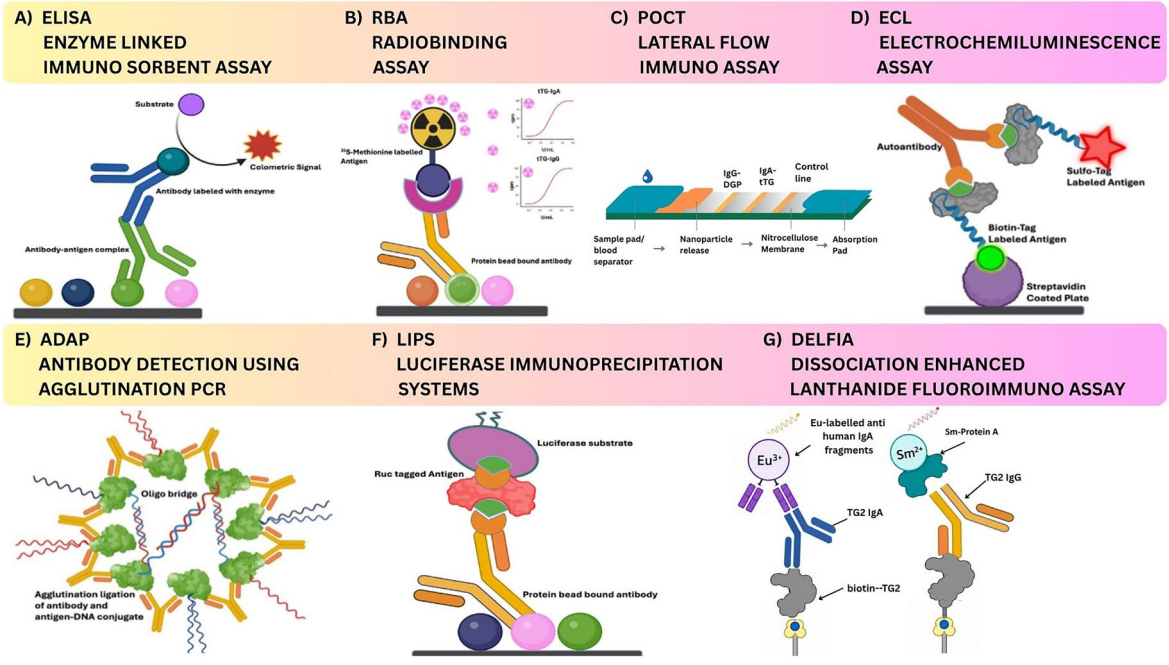

Figure 1. Signature illustrations of A) Enzyme linked immunosorbent assay (ELISA), B) Radiobinding assay (RBA), C) Point-of-care testing: lateral-flow immunoassay (POCT), D) Electrochemiluminescence assay (ECL), E) Antibody detection using agglutination polymerase chain reaction (ADAP-PCR), F) Luciferase Immunoprecipitation systems (LIPS), and G) Dissociation enhanced lanthanide fluoroimmunoassay (DELFIA). (Made in Biorendr).

92%, and guinea pig TG2 was 92% and 89% respectively [52]. Although, ELISA is cost-effective and reliable across age group but still have many clinical and technical limitations [42].

RBAs have historically been considered as the gold standard testing methods for assaying Aab [53]. A radiolabeled recombinant human TG2 antigen is incubated with patient's serum to form of antigen-antibody complexes and bound radioactivity is proportional to the corresponding TG2-IgA concentration (Figure 1B) [54]. Since it detects Aab by forming immune complexes with radiolabeled antigen in solution, the increased epitope exposure enhances antibody binding, and the bound radioactivity is then quantified [52].

Although RBA is highly sensitive for detecting TG2-IgA in CeD, particularly at low levels missed by ELISA [55,56], it has limitations that prevent its use as the preferred screening assay. Firstly, the RBA requires radiolabeled isotopes, necessitating specialized facilities, licensing for radioactive materials, strict waste disposal, and additional logistical and safety measures. Secondly, RBA relies on manual procedures and lacks standardized protocols, leading to interobserver variability. For large-scale screening, it is also labor-intensive and cost-inefficient [56]. In contrast to RBA, point-of-care tests (POCT) are readily available and user-friendly, which makes them suitable for local settings where rapid and straightforward results are required, particularly when TG2-IgA results are needed (Figure 1C). However, POC testing for the diagnosis of CeD needs further validation in primary care settings [57].

Emerging autoantibody technologies

The electrochemiluminescence (ECL) method is an ultrasensitive analytical technique that relies on the conversion of electrical energy into light [58]. It operates on the principle of antigen-antibody interaction, utilizing a capture autoantibody, immobilized on a solid support, such as microplate or a magnetic bead, to bind the target antigen. Detection is achieved through a labeled antibody conjugated with a luminescent marker and an electrochemically active molecule, enabling precise antigen quantification (Figure 1D) [59].

Antibody detection by agglutination polymerase chain reaction (ADAP) overcomes the limitations of conventional serological assays by enabling multiplex detection of antigen-specific antibodies with ultra-high sensitivity, while preserving the native conformation of the antigen [60]. The conceptual framework was derived from the principle underlying latex agglutination assay and the proximity ligation assay methodologies [61]. ADAP relies on antibody-driven aggregation of antigen–DNA conjugates, followed by oligonucleotide ligation and subsequent PCR amplification (Figure 1E). A unique advantage of this assay is that it preserves the native conformation of the antigen and does not require washing to remove unbound secondary antibodies [61–65]. Conversion of antibody-antigen binding interaction takes place into an amplifiable DNA barcode, which undergoes agglutination upon the presence of the antibodies in the reaction. The two halves of the DNA are joined *via* bridging oligonucleotides facilitated by ligases, and the resulting DNA barcode is quantified by qPCR. The method consists of sequential steps, including conjugation followed by agglutination, ligation, pre-amplification and quantification [60].

Luciferase immunoprecipitation system (LIPS) offers a nonradioactive, fluid-phase alternative to RBA for Aab detection. It is based on the formation of immune complexes between recombinant antigens and antibodies, with the antigen genetically fused to a luciferase reporter. Specifically, the DNA encoding the antigen of interest is fused to Renilla luciferase (Ruc), a light-emitting enzyme derived from sea pansy, enabling quantification of antibodies through luminescence [66]. The crude Ruc-antigen is incubated with the serum sample, and the mixture is transferred to a filter plate containing protein A/G–conjugated beads. After washing away unbound antigen, the luciferase substrate coelenterazine is added, and antibody levels are quantified by measuring emitted light (Figure 1F) [67].

Another is automated DELFIA (Dissociation enhanced lanthanide fluorescent immunoassay) assay using dual-label time resolved fluorometry (TRF) for the detection of TG2 isoforms IgA and IgG simultaneously. The assay utilized recombinant TG2 in solid phase to capture anti-TG2 Aabs. Assay is performed in streptavidin coated microplate, and the solid phase is prepared by the addition of biotinylated rhTG2 in the wells. After washing, calibrators, diluted samples, and controls are incubated, followed by addition of a tracer mixture containing europium-labelled anti-human IgA and samarium-labelled protein A.

Subsequent signal detection is performed using time-resolved fluorometry, with results expressed as counts per second for each label (Figure 1G) [68].

Both ECL and ADAP require less sample volume and scales readily to automated platforms, which can enhance sensitivity and specificity and reduce background interference and have been already used in general population-based screenings of children for CeD and other related autoimmune diseases [53,69,70]. However, the challenge with both assays is their complexity, which complicates standardization and leads to inter-laboratory variability [43]. LIPS assay has also been successfully used to detect Aab in type 1 diabetes, Sjogren's syndrome and Systemic lupus erythematosus with high sensitivity and specificity comparable to radioimmunoprecipitation [71–75]. However, its clinical utility for CeD Aab has not yet been established. TG2 measurement using high capacity, fully automated DELFIA method has recently been described and suitable for CeD screening in the general population [68]. A comparative depiction between the immunoassays for the clinical/translational applicability parameters, diagnostic parameters and technological advances are provided in the Figure 2 and summary Table 1.

Discussion

The first international guidelines for CeD were issued by ESPGHAN in 1969 and for a long time upper gastrointestinal endoscopy with duodenal biopsy remained the cornerstone of the diagnosis. Since 1990s, diagnostic accuracy for CeD Aab testing has progressively improved, and these assays now play a crucial role in the diagnostic work-up since Aabs were introduced as diagnostic markers for CeD. Additionally, for the first time, the ESPGHAN 2012 guidelines introduced a non-biopsy approach for CeD, which was further updated and simplified in the 2020 guidelines by removing the requirements for clinical symptoms and HLA testing [22,77].

The expansion of large-scale CeD screening necessitates simplified, standardized, and cost-efficient diagnostic workflows compatible with small sample volumes and decentralized settings. Lateral flow immunoassay-based POCT offers a practical alternative, demonstrating high sensitivity (94–99.5%) and specificity (93.1-99.5%) in symptomatic populations. However, limitations include false positivity in IgA-deficient individuals and lack of multiplexing capacity [57]. In contrast, automated multiplex platforms such as ECL and ADAP enable simultaneous detection of multiple Aab, supporting integrated

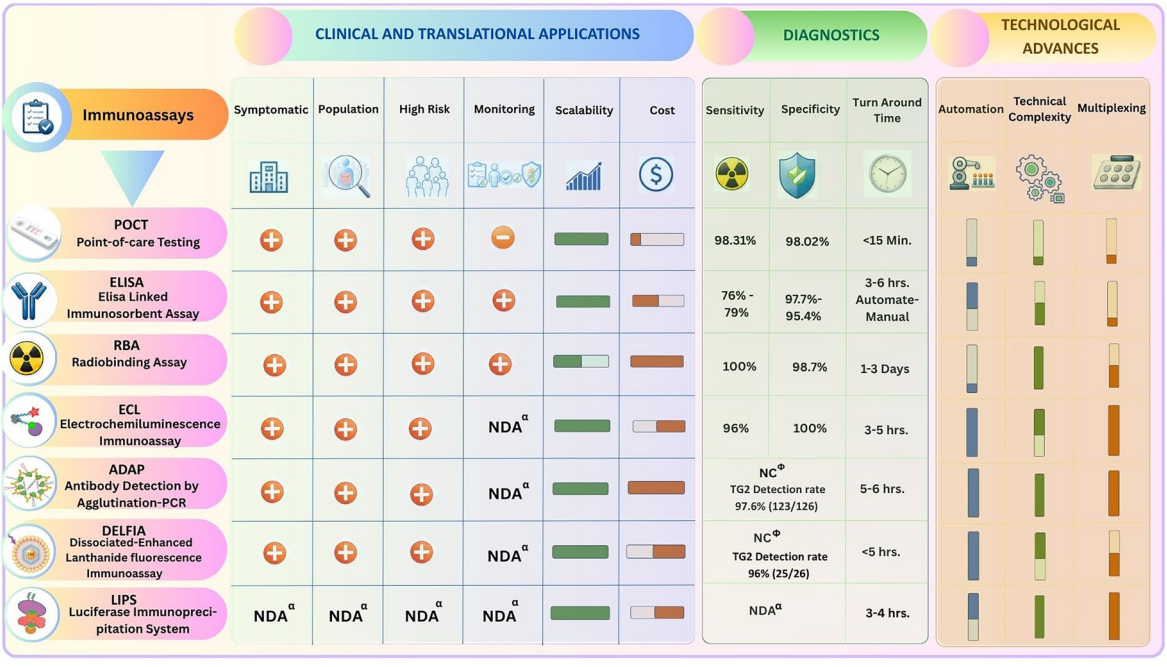

Figure 2. Comparative depiction between the immunoassays for the clinical and translational applicability parameters, diagnostic parameters and technological advances. (Made in Canva).
NDA$^{\alpha}$: No Data Available; NC$^{\Phi}$: 27 Not Calculated

Table 1. Summary table depicting the head-to-head comparison between the assays.

Analytical Assays	Sensitivity/ Specificity (TG2)	Scalability	Turnaround Time	Cost	Automation	Technical Complexity	Clinical Applications/ Translational applicability	
							Setting	Applications
POCT*	98.31%/ 98.02% Parrinello G et al. 2024 [57]	High; Portable Single use cartridge; Field deployable	<15 min; Immediate results	Low; No Capital Equipment Required	Minimal	Very low	1. Primary care, Community clinics 2. Rural /Remote health clinic 3. School screening program	1. Case-finding screening in symptomatic individuals 2. Population screening 3. First-Degree Relative screening
ELISA*	76%-97.9%/ 97.7%-95.4% Singh P et al. 2020 [44]	Very High; 96–384 well plates, manual to fully automated	3–6 Hrs; Manual 2–3 Hrs; Automated	Low to moderate; Routine Lab Testing Equipment Required	Moderate to high	Low to moderate	1. District general hospital 2. Tertiary care hospital 3. Reference laboratory 4. National screening program	1. Global first line standard serology assay 2. Gluten Free Diet compliance monitoring 3. Population & High-Risk Group screening
RBA*	100%- 98.7% Candon S et al. 2012 [55]	Low to Moderate; 96–384 welled plate use, Restricted to licensed radioactive facilities,	1-3 days; Batch Processing	High; Equipment Cost, Radioisotope cost, Disposal cost	Low	High	1. Reference research centers 2. Academic medical research Center	1. Declining clinical adoption 2. Reference research center for validation of new analytical platform
ECL*	96%-100% He L et al. 2022 [76]	Very high; 96–384 welled plate use, Automated, Multiplexed use	3–5 Hrs; Batch Processing	Moderate to high; Equipment cost and reagent cost	High	Moderate to high	1. Academic medical research center 2. Reference research centers 3. Tertiary care hospitals	1. Case-finding program 2. Large scale longitudinal studies 3. Multiplexed autoantibodies profiling 4. Population & High-Risk Group screening
ADAP*	NC$^{\Phi}$ TG2 Detection rate 97.6% (123/126) Lind A et al. 2023 [40]	Very high; 96–384 well plate use, Automated, Multiplexed, Low blood sample requirement	5–6 Hrs; Batch Processing	High	Very High	High	1. Academic medical research center 2. Reference research centers 3. Tertiary care hospitals	4. Large scale longitudinal studies 5. Multiplexed autoantibodies profiling 6. Population & High-Risk Group screening
Delfia Assay*	NC$^{\Phi}$ TG2 Detection rete 96% (25/26) Klaasen R A et al. 2022 [68]	High; 96–84 well plate use, Automated, Dual–Plexed DBS Compatible	<5 Hrs	Moderate to high; Equipment and reagent cost	High	Moderate to high	1. District general hospital 2. Tertiary care hospital 3. Reference laboratory 4. Private labs 5. National screening program	1. Case-finding screening in symptomatic individual 2. General population screening 3. First-Degree Relative screening 4. Population & High-Risk Group screening
LIPS*	NA^{a}	High; 96 well plate use, Automated and Multiplexed	3–4 Hrs	Moderate to High; Equipment and Reagent cost	Moderate to high	High	Experimental phase	Experimental stage

Abbreviations: *POCT: Point-Of-Care-Testing; Lateral Flow Immuno Assay; ELISA: Enzyme Linked Immuno Sorbent Assay; RBA: Radio Binding Assay; ECL: Electrochemiluminescence Assay; ADAP: Antibody Detection Using Agglutination PCR Assay; LIPS: Luciferase Immunoprecipitation System Assay; DELFIA: Dissociated Enhanced Fluorescence Immunoassay. NC$^{\Phi}$: Not Calculated; NA^{a}: Not Available.

screening for CeD and related autoimmune diseases, such as type 1 diabetes and autoimmune thyroid disease. While analytically advantageous, these technologies require centralized infrastructure and higher operational costs, which may limit their applicability in population-wide screening programs. If POCT is to be considered, a second confirmatory assessment at a separate time point, using either an alternative assay or the same platform, can improve result reliability and provide additional quantitative information on autoantibody levels [78].

Although ELISA is the well-established and cost-effective method from primary to tertiary care centers for the diagnosis and monitoring of CeD [20], it has certain limitations. However, despite of the pitfalls, this method is still the most utilized across the globe [79,80]. Likewise, RBA has long been considered the gold standard for antibody analysis. Its unparalleled sensitivity and specificity made it a reference method in research and tertiary care settings, serving as a benchmark against which newer assays are often compared. Despite the emergence of alternative methods, RBA's historical reliability and precision continue to underscore its significance in immunodiagnostics. However, its use of radioactive materials, high cost, labor-intensive and time-consuming protocol, limited scalability, inter-laboratory variability, and requirement for specialized training restrict its broader application.

With the new generation of assays now under evaluation, promising alternatives are emerging for the detection of TG2-IgA, potentially improving the shortcomings of conventional methods like ELISA and RBA. In this context, the ECL method offers several advantages, including high efficiency with low sample volume, excellent sensitivity, and the absence of need for radioactive labeled isotope. Modern luminophores used in the ECL assays are highly stable, self-emitting without an external light source, and can label a wide range of molecules with minimal noise or background interference. For example, multiplex ECL testing required only 30% of the labor and supply costs, and just 25% of the sample volume [70]. In a comparative analysis between ECL and RIA (radioimmunoassay), ECL demonstrated a higher TG2 (73%) positivity than RIA (62%) among type 1 diabetes patients. Moreover, in longitudinal analyses of children in the DAISY cohort, ECL identified seroconversion to TG2 Aab positivity at a mean of 2.5 years earlier than RIA, thereby enabling an earlier definition of the onset of CeD autoimmunity [81].

LIPS is another promising assay, providing high diagnostic accuracy with a faster workflow. LIPS has been validated for IA2, IA2 beta, GADA and IAA, but has not yet been applied or documented for the assessment of CeD related Aabs. Further studies are therefore warranted to validate its performance for TG2-IgA testing. In contrast, Delfia-based testing is an automated, multiplex (two-plexed), and highly sensitive method that correctly identify 96% of biopsy-positive CeD, 88% of newly diagnosed CeD patients and 99.4% those not with CeD in a Norwegian cohort [68]. This performance, derived from a centralized laboratory setting, obviates the need of additional testing to account for IgA deficiency. Nevertheless, it offers limited added value within an integrated multi-disease screening framework for CeD.

ADAP is an ultra-sensitive, high-throughput multiplexing capable of simultaneously testing autoimmune conditions, including CeD [82]. Its sensitivity and specificity are comparable to RBA [40]. Lind A et al. reported that high TG2-IgA levels (≥10x ULN) measured by ADAP may obviate the need for intestinal biopsy by enabling assessment across an extended dynamic range through serial dilutions. To date, ADAP-based TG2 assays (including both isotypes) have been evaluated in a single Swedish center. Comparative data indicates a lower detection limit versus RBA in untreated CeD sera, supporting earlier detection of TG2 Aab. However, evidence for its use in monitoring gluten-free diet adherence remains limited [40]. The authors recommended that ADAP technology could also be applied as the first-line screening method of concurrent large-scale population screening for CeD with the added advantage that both IgA and IgG antibodies can be detected in a single reaction, eliminating the need for separate total IgA measurement.

The new generation of assays also has limitations and must be carefully evaluated before being implemented in large-scale population screenings for CeD. For ECL, these include relatively high costs, susceptibility to light leakage, and high background luminescence of the reagents [83,84], which can lead to an underestimation of the actual signal [85,86]. For ADAP, limitations include inhibition of PCR

amplification by heparinized blood and challenges in measuring very high TG2-IgA levels, which require serial sample dilution for accurate quantification [40,82].

Conclusion

While ELISA remains the mainstay in routine laboratories and RBA in some specialized centers, newer approaches such as ECL and PCR-based ADAP show promise with higher sensitivity and specificity for TG2 Aab. These offer multiplexing, high-throughput capability, and independence from total IgA measurement, potentially supporting large-scale screening. In the future, non-serological approaches that detect the causative gluten-specific T cell, such as whole blood interleukin-2 secretion, may offer an alternate biologically appealing, blood-based, biopsy-sparing diagnostic approach for CeD [87]. However, large-scale multicenter studies are needed to confirm to clinical reliability and cost-efficacy, and to assess how these approaches might pair with conventional TG2 Aab for screening. Moreover, despite improved analytical sensitivity, there is currently limited evidence demonstrating that these newer immunoassays correlate more accurately with mucosal healing or disease activity compared to conventional serology. Future assay development should focus on further validation of Aab tests to create minimally invasive, scalable, and cost-effective diagnostic platforms for CeD.

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Data availability statement

Data sharing is not applicable, as no new data is generated or analyzed in this study

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