Positive Predictive Value of Tissue Transglutaminase IgA for Celiac Disease

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abstract

BACKGROUND AND OBJECTIVES: Recent changes in European diagnostic criteria allow for serologic diagnosis of celiac disease in children. Those guidelines have not been adopted in North America; hence, we aim to assess the positive predictive value (PPV) of tissue transglutaminase (tTG) immunoglobulin A (IgA) assays used in North America in identifying histologic findings of celiac disease.

METHODS: Multicenter retrospective cohort study of children (<18 years) with an elevated tTG IgA within 6 months of an esophagogastroduodenoscopy between January 2016 and December 2021. Biopsy-confirmed celiac disease was determined by the presence of intraepithelial lymphocytosis and villous atrophy. The primary outcomes were the PPV of an elevated tTG IgA and tTG IgA greater than or equal to 10 times the upper limit of normal (10× ULN).

RESULTS: Overall, 4019 children (63.3% female; 9% type 1 diabetes, 2% Down syndrome) were included. Histologic findings were consistent with celiac disease for 3321 children (PPV = 82.6% [95% CI, 81.4–83.8]). Among the 1739/4019 (43.2%) children with tTG IgA greater than or equal to 10× ULN, 1651 had biopsy-confirmed celiac disease ($PPV_{10\times}$ = 94.9% [95% CI, 93.8–95.9]). Five percent (88/1739) of children did not have histologic findings of celiac disease, including 41/1739 (2%) with normal histology. Diagnostic accuracy of tTG IgA varied widely among assays used in North America (PPV range: 71.5%–88.8%; $PPV_{10\times}$ range: 89.3%–97.3%). Assays performed worse in children with type 1 diabetes ($PPV_{10\times}$ 89% [95% CI, 83.5–92.8]).

CONCLUSIONS: Elevated tTG IgA in isolation is insufficient to confidently diagnose celiac disease. As tTG assay performance varied widely, diagnostic confirmation by a specialist prior to dietary changes is essential.

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WHAT'S KNOWN ON THIS SUBJECT: Although small intestinal biopsy remains the gold standard for diagnosing celiac disease, European pediatric guidelines include a nonbiopsy pathway when a very high anti–tissue transglutaminase immunoglobulin A (tTG IgA) is confirmed by a positive endomysial IgA antibody on a second blood sample.

WHAT THIS STUDY ADDS: Not all children with a highly positive tTG IgA have biopsy-confirmed celiac disease, with wide variability in diagnostic performance across assays common in North America. Confirmation by a gastroenterologist or specialist is necessary before making any dietary changes.

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INTRODUCTION

Celiac disease is an immune-mediated disorder triggered by gluten, a protein found in wheat, barley, and rye. The global prevalence of celiac disease is 1% with an increasing prevalence, particularly among children.[1,2] Initially, the diagnosis of celiac disease relied solely on the clinical response to gluten elimination,[3] followed by both the clinical and histologic response to gluten withdrawal (then rechallenge and withdrawal).[4] Subsequent recommendations eliminated repeat endoscopy for patients whose initial small intestinal biopsy is characteristic of celiac disease who respond clinically to gluten withdrawal.[5] More recently, highly sensitive serologic markers, such as anti–tissue transglutaminase immunoglobulin A (tTG IgA), have become available, which has shifted responsibility for disease screening from gastroenterology to primary care.

In 2012, the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommended that a biopsy is not required to diagnose celiac disease in symptomatic children with disease-permissive human leukocyte antigen (HLA) genotype (eg, DQ2/8), a tTG IgA greater than or equal to 10 times the upper limit of normal (10× ULN) and a positive antiendomysial antibody immunoglobulin A (EMA) on a separate blood sample.[6] These criteria were revised in 2020, to specify that only a highly positive tTG IgA greater than or equal to 10× ULN and a positive EMA on a second blood sample are sufficient to diagnose celiac disease, obviating the need for HLA testing or symptoms.[7] Critically, regardless of the diagnostic pathway, ESPGHAN recommends referral to a gastroenterologist or celiac disease expert for confirmation of diagnosis.

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition has yet to adopt similar serologic criteria for diagnosing celiac disease.[8] A clinical report in 2016 continued to recommend a confirmatory biopsy in all suspected cases of celiac disease.[9] This recommendation cited concerns of interassay variability and potentially missing coexisting diagnoses, such as eosinophilic esophagitis (EoE), if endoscopy is foregone. Interassay differences are critical, as assays are not standardized and those used to justify the 2012 ESPGHAN guidelines[6] differ from those currently used in North America. Most pediatric gastroenterologists in North America continue to recommend endoscopy for diagnostic confirmation,[10] although many use serologic criteria as well.[11]

Increased screening for celiac disease in primary care has raised concerns that patients may be told to adopt a gluten-free diet (GFD) prematurely without diagnostic confirmation or when they do not meet the specific thresholds. Although several studies in Europe and other countries have validated the serologic criteria endorsed by ESPGHAN,[12–15] only a few studies to date have evaluated the accuracy of a tTG IgA greater than or equal to 10× ULN in diagnosing celiac disease in North American children. Therefore, we assessed the positive predictive value (PPV) of both an elevated tTG IgA and when a single tTG IgA exceeds 10× ULN for biopsy-confirmed celiac disease for assays commonly used in North America.

METHODS

Cohort Identification

The study protocol was approved by the institutional or ethics review board at each participating center.

Children (aged <18 years) from 9 pediatric hospitals in the United States (Boston Children's Hospital; Mayo Clinic; Children's Hospital Colorado; Mass General Hospital for Children; Seattle Children's Hospital; Children's National Hospital; Children's Wisconsin; UCSF Benioff Children's Hospital; Children's Hospital of Philadelphia) and 3 in Canada (Alberta Children's Hospital; Stollery Children's Hospital; The Hospital for Sick Children) with a positive tTG IgA within 6 months of a diagnostic esophagogastroduodenoscopy performed between January 2016 and December 2021 were included. Cases with known celiac disease (eg, follow-up biopsy), GFD prior to endoscopy, or with incomplete assay or pathology data were excluded.

Medical records were reviewed in the few cases where endoscopy preceded the initial tTG IgA to verify that the tTG IgA preceded a GFD. For the primary analysis, if multiple positive tTG IgA levels were available, then the value prior to the date of endoscopy was used. For the secondary analysis, EMA at the time of tTG IgA was considered because this was the most common scenario. EMA positivity was based on laboratory reports of a positive result or when titers exceeded the normal reference range.

Calculating the Multiple of Upper Limit of Normal for tTG IgA

For each tTG IgA, multiples of the upper limit of normal (MULN) were calculated by dividing the tTG IgA value by the manufacturer-recommended cutoff (eg, for the EliA CeliKey IgA Immunoassay, we used an ULN of 7 as values <7 were normal).

Classification of Histologic Findings

Histologic findings were extracted from pathology reports. For duodenal specimens, the following data were collected: location if known (duodenal bulb or distal duodenum), quantity of biopsies taken, presence or absence of histologic findings compatible with celiac disease based on Marsh classification[16] (eg, intraepithelial lymphocytosis [IELs], crypt hyperplasia [CH], or villous atrophy/blunting [VA]). If IELs and VA were present, but the mention of crypt length was not reported, this was recorded as "CH not reported."

Duodenal findings were assigned a Marsh score, unless previously assigned by the reviewing pathologist, based on the microscopic findings defined by Marsh.[16] If VA was present in the absence of IELs, this was defined as "non-specific enteropathy." Similarly, if there were inflammatory changes consistent with other causes of duodenitis (eg, peptic duodenitis), this was classified as "non-specific duodenitis." In cases where duodenal biopsies were separated and reported based on location (ie, duodenal bulb and distal duodenum), the most severe Marsh score was used for primary analysis.

In cases with discrepant reporting of histopathologic findings in the original pathology report (eg, mention of "no diagnostic pathology" in conjunction with increased intraepithelial lymphocytes), a pathologist at the respective site was consulted to provide a final assessment of the histologic features, which was used for data analysis. Cases with Marsh 2, Marsh 3, or IELs and VA with no mention of CH were defined as biopsy-confirmed celiac disease. All other findings, including Marsh 1 lesions, were considered not celiac disease histopathology.

When biopsies were obtained from multiple locations in either the esophagus or stomach, the most severe histopathologic finding (eg, the highest number of eosinophils per high-power field [eos/hpf], presence of *Helicobacter pylori* infection [*H pylori*]) was reported and used for analysis.

Statistical Analysis

Continuous variables were reported as means (±SD) and categorical variables were reported as proportions. A Clopper-Pearson interval was used to calculate 95% CI for proportions. A 2-tailed unpaired *t* test and χ^2 test were used to compare continuous and categorical variables, respectively.

RESULTS

Patient Characteristics

Overall, 4019 children (63.3% female, 9% with type 1 diabetes [T1D] and 2% with Down syndrome) met the study inclusion criteria (Table 1). The EliA Celikey assay (33.4%, 1344/4019) was the most common assay, followed by the Bioplex 2200 (22.4%, 901/4019), QUANTA Lite R h-tTG IgA (20.3%, 815/4019), QUANTA Flash h-tTG IgA (11.4%, 458/4019), and the QUANTA Lite h-tTG IgA (7.9%, 319/4019) assays. The specific assay used was unable to be determined in 182/4019 (5%) cases. A summary of the most common tTG IgA assays including the ULN used for calculating MULN is listed in Table 2.

tTG IgA Positivity and Biopsy-Confirmed Celiac Disease

Overall, 3321/4019 children with a positive tTG IgA had biopsy-confirmed celiac disease based on the histologic findings, resulting in a positive predictive value (PPV_{ANY}) of 82.6% (95% CI, 81.4–83.8) (Table 1). Of the remaining 698 patients, 141 (4%) had Marsh 1 lesions, 68 (2%) had nonspecific enteropathy, and 32 (1%) had nonspecific duodenitis. One case was unable to be interpreted due to poor tissue quality. The remaining 443 (11%) had normal (ie, Marsh 0) histology.

There were 1739/4019 patients (43.3%) with a tTG IgA greater than or equal to 10× ULN, of whom 1651/1739 had biopsy-confirmed celiac disease, resulting in a $PPV_{10\times}$ of 94.9% (95% CI, 93.8–95.9) (Table 1). Eighty-eight of 1739 patients (5.1%) had non–celiac disease duodenal histology including 41/1739 (2% of the total) with normal biopsies. The distribution of the duodenal histology stratified by MULN for a positive tTG IgA is shown in Figure 1 and Supplemental Figure 1.

As prior studies found the $PPV_{10\times}$ to be lower in children with T1D,[17] we compared the $PPV_{10\times}$ of children with and without T1D in our cohort. One hundred ninety-six of 364 children (52.8%) with T1D had a tTG IgA greater than or equal to 10× ULN (Table 1). The $PPV_{10\times}$ in children with T1D was lower (89%; 95% CI, 83.5–92.8) than that in those without T1D (95.7%; 95% CI, 94.6–96.7) (Supplemental Table 1).

PPV Based on Different tTG IgA Assays

Subgroup analysis based on tTG IgA assay was performed to calculate assay-specific PPV_{ANY} and $PPV_{10\times}$ (Table 3; Supplemental Figure 2). For the QUANTA Lite h-tTG IgA assay, $PPV_{5\times}$ was calculated as the upper limit of normal is 20 and in some laboratories, the upper limit of detection is 100 U/mL. There was a notable increase in PPV across all assays when the tTG IgA was greater than or equal to 10× ULN (PPV_{ANY} range: 71.5%–88.8%; $PPV_{10\times}$ range: 89.3%–97.3%). The EliA Celikey IgA assay had both the highest PPV_{ANY} (88.8%) and the highest $PPV_{10\times}$ (97.3%). The QUANTA Lite h-tTG IgA assay had the lowest PPV_{ANY} (71.5%), whereas the QUANTA Flash h-tTG IgA assay had the lowest $PPV_{10\times}$ (89.3%).

Among the 1646 children with EMA at the time of initial tTG IgA, 1209 (73.5%) were EMA positive (Table 1). Of those with a tTG IgA greater than or equal to 10× ULN, 46/718 (6.4%) with celiac disease had a negative EMA, whereas 28/37 (75.6%) without celiac disease had a positive EMA, including 14 children with Marsh 1 histopathology (Supplementary Table 2). Thus, the $PPV_{10\times+EMA}$ was 96% (674/702).

Extraintestinal Histopathology

Esophageal biopsies were available for 2980/4019 (74.1%) children, of which 2415/2980 (81%) were normal (Table 4). Most of the remaining children (14.3%, 425/2980) had esophageal eosinophilia, with 175/2980 (6%) having at least 15 eos/hpf in at least 1 esophageal biopsy. Fifty-eight of 2980 (2%) children had either lymphocytic or neutrophilic esophagitis, and 2/2980 (0.1%) children

TABLE 1. Clinical Characteristics and Duodenal Histology in Children With an Elevated tTG IgA and a tTG IgA Greater Than or Equal to 10× ULN

	tTG IgA ≥1× ULN (n = 4019)	tTG IgA ≥10× ULN (n = 1739)
Clinical Characteristics		
Age at endoscopy, y		
Mean (SD)	10 (4.4)	9.6 (4.5)
Female, n (%)	2543 (63.3)	1096 (63.0)
Type 1 diabetes, n (%)	364 (9)	196 (11)
Down syndrome, n (%)	68 (2)	30 (2)
tTG assay, n (%)		
Bioplex 2200 Celiac IgA (Bio-Rad)	901 (22.4)	432 (24.8)
EliA Celikey IgA (Thermo Fisher)	1344 (33.4)	547 (31.5)
QUANTA Lite R h-tTG IgA (INOVA/Werfen)	815 (20.3)	410 (23.6)
QUANTA Lite h-tTG IgA (INOVA/Werfen)	319 (7.9)	14 (1)
QUANTA FLASH h-tTG IgA (INOVA/Werfen)	458 (11.4)	261 (15.0)
Other/unknown	182 (5)	75 (4)
EMA contemporaneous with tTG, n	1646	755
EMA positive, n (%)	1209 (73.5)	702 (93.0)
EMA negative, n (%)	437 (26.5)	53 (7)
Duodenal Histology		
Biopsy-confirmed celiac disease, n (%) [95% CI]	3321 (82.6) [81.4–83.8]	1651 (94.9) [93.8–95.9]
Marsh 2	26 (1) [0.4–1.0]	8 (1) [0.2–0.9]
Marsh 3	2422 (60.3) [58.7–61.8]	1222 (70.3) [68.1–72.4]
IELs and VA, CH not reported	873 (21.7) [20.5–23.0]	421 (24.2) [22.2–26.3]
Not celiac disease, n (%) [95% CI]	698 (17.4) [16.2–18.6]	88 (5.1) [4.6–6.8]
Marsh 0/Normal	443 (11.0) [10.1–12.0]	41 (2) [1.7–3.2]
Marsh 1	141 (4) [3.0–4.1]	29 (2) [1.1–2.4]
Nonspecific enteropathy[a]	68 (2) [1.3–2.1]	13 (1) [0.4–1.3]
IELs, CH and VA not reported	9 (0) [0.1–0.4]	—
Nonspecific duodenitis[b]	32 (1) [0.6–1.1]	5 (0) [0.1–0.7]
Crypt hyperplasia without IELs	4 (0) [0–0.3]	—
Unable to be determined due to quality of sample	1 (0) [0–0.1]	—

Abbreviations: CH, crypt hyperplasia; EMA, antiendomysial IgA; IELs, intraepithelial lymphocytosis; IgA, immunoglobulin A; tTG, tissue transglutaminase; ULN, upper limit of normal; VA, villous atrophy.

[a] Villous atrophy without intraepithelial lymphocytosis.

[b] Peptic or nonspecific (acute, chronic) inflammation.

had candida esophagitis. A highly positive tTG IgA was not associated with esophageal abnormalities ($P = .48$), histologic esophagitis ($P = .48$), or eosinophilia greater than or equal to 15 eos/hpf ($P = .80$).

Gastric biopsies were available for 3534/4019 (87.9%) children, 912/3534 (25.8%) of whom had histologic gastritis, including 1.4% (51/3534) with evidence of *Helicobacter* infection (49 cases of *H pylori* and 2 cases of *H heilmannii*) (Table 4). Lymphocytic gastritis was present in 41/3534 (1%) children. Eosinophilic gastritis (n = 4) and intestinal metaplasia (n = 2) were relatively rare. There was no difference in the frequency of *H pylori* in children with a positive tTG IgA compared with those with a tTG IgA greater than or equal to 10× ULN ($P = .82$).

DISCUSSION

It is increasingly common for practitioners to diagnose celiac disease based on serologic tests without a confirmatory biopsy.[11,18] In this international multicenter cohort of more than 4000 children, a very high tTG IgA greater than or equal to 10× ULN had a PPV of 94.9% for histologic findings of celiac disease with considerable variations in PPV (89.3% to 97.3%) based on the assay used. PPV was even lower (89%) in children with T1D, underscoring the importance of biopsy confirmation in this high-risk population. Although this lends credence to the notion that a highly positive tTG IgA correlates with enteropathy in most children, 1 in 20 children with a tTG IgA greater than or equal to 10×

TABLE 2. tTG IgA Assays

Assay	Type	Reference Range[a]	Upper Limit of Normal
BioPlex 2200 Celiac IgA (Bio-Rad) (Hercules, CA)	Semiquantitative multiplexed flow, bead-based immunoassay	Negative < 15 U/mL, positive ≥ 15 U/mL	15
EliA CeliKey IgA Immunoassay (Thermo Fisher Scientific) (Waltham, MA)	Semiquantitative fluoroenzyme immunoassay	Negative < 7 U/mL, equivocal 7–10 U/mL, positive > 10 U/mL	7
QUANTA Lite R h-tTG IgA (INOVA Diagnostics/Werfen) (Bedford, MA)	Enzyme-linked immunosorbent assay	Negative < 4 U/mL, weakly positive 4–10 U/mL, positive > 10 U/mL	4
QUANTA Lite h-tTG IgA (INOVA Diagnostics/Werfen) (Bedford, MA)	Enzyme-linked immunosorbent assay	Negative < 20 U/mL, positive ≥ 20 U/mL	20
QUANTA Flash h-tTG IgA (INOVA Diagnostics/Werfen) (Bedford, MA)	Semiquantitative chemiluminescent immunoassay	Negative < 20 CU, weakly positive 20–30 CU, positive > 30 CU	20

Abbreviations: CU, chemiluminescent units; IgA, immunoglobulin A; tTG, tissue transglutaminase; U, units.

[a] Provided by manufacturer.

ULN did not have histologic findings diagnostic of celiac disease. This included 2% who had normal small intestinal biopsies on a gluten-containing (unrestricted) diet, highlighting the limitations of making a celiac disease diagnosis based solely on a single, highly positive tTG IgA level. Notably, EMA only marginally improved specificity as 76% of children without celiac disease and tTG IgA greater than or equal to 10× ULN had a positive EMA, albeit on the same sample.

Another concern regarding serologic diagnosis of celiac disease relates to variations in performance across different tTG IgA assays because they are not standardized.[19,20] For some assays, a threshold of greater than or equal to 10× ULN may be highly predictive of celiac disease,[12,13,21–25] but it may be suboptimal for others.[26,27] In our study, both the PPV_{ANY} and $PPV_{10\times}$ were similar for 3 of the 4 assays analyzed whereas the $PPV_{10\times}$ for the other assay (QUANTA Flash h-tTG IgA) was notably lower. The QUANTA Lite h-tTG IgA had the lowest PPV_{ANY}; however, the $PPV_{10\times}$ could not be calculated as the value required to meet that threshold (200 U/mL) exceeded the upper limit of detection (100 U/mL) in some cases. These factors must be accounted for when considering a diagnosis of celiac disease, and any future practice guideline should emphasize the importance of clinician familiarity with each assay's performance and awareness of which assay was used.

Current ESPGHAN guidelines cite the high specificity of EMA as justification for the recommendation that a positive EMA from a second, separate blood sample can be used as a confirmatory test in lieu of biopsy for children with very high tTG IgA greater than or equal to 10× ULN.[7] A second sample also serves to ensure that there have not been any errors in sample labeling or processing that produced a spurious initial result or due to other causes of transient elevations, such as an intercurrent illness,[28] when the initial test was performed. We found variations across providers, practices, and countries, which resulted in EMA not being performed in all cases or tested on the same blood sample as the tTG IgA. In our study, 76% of children without biopsy-confirmed celiac disease with tTG IgA greater than or equal to 10× ULN also had positive EMA on the same sample, which is expected as tTG IgA and EMA both recognize transglutaminase-2.[29] Thus, a second, independent confirmatory test, such as a biopsy, remains valuable.

Aside from confirming a celiac disease diagnosis, an endoscopy may provide additional information that can affect clinical care and aid in identifying comorbid conditions such as EoE. Pacheco et al reported the frequency of abnormal esophageal and gastric biopsies in children who underwent an endoscopy for a positive tTG IgA to be 14% and 33%, respectively, although the proportion of cases where clinical intervention was employed was much lower.[30] In our cohort, 6% of children with esophageal biopsies had eosinophilia compatible with EoE

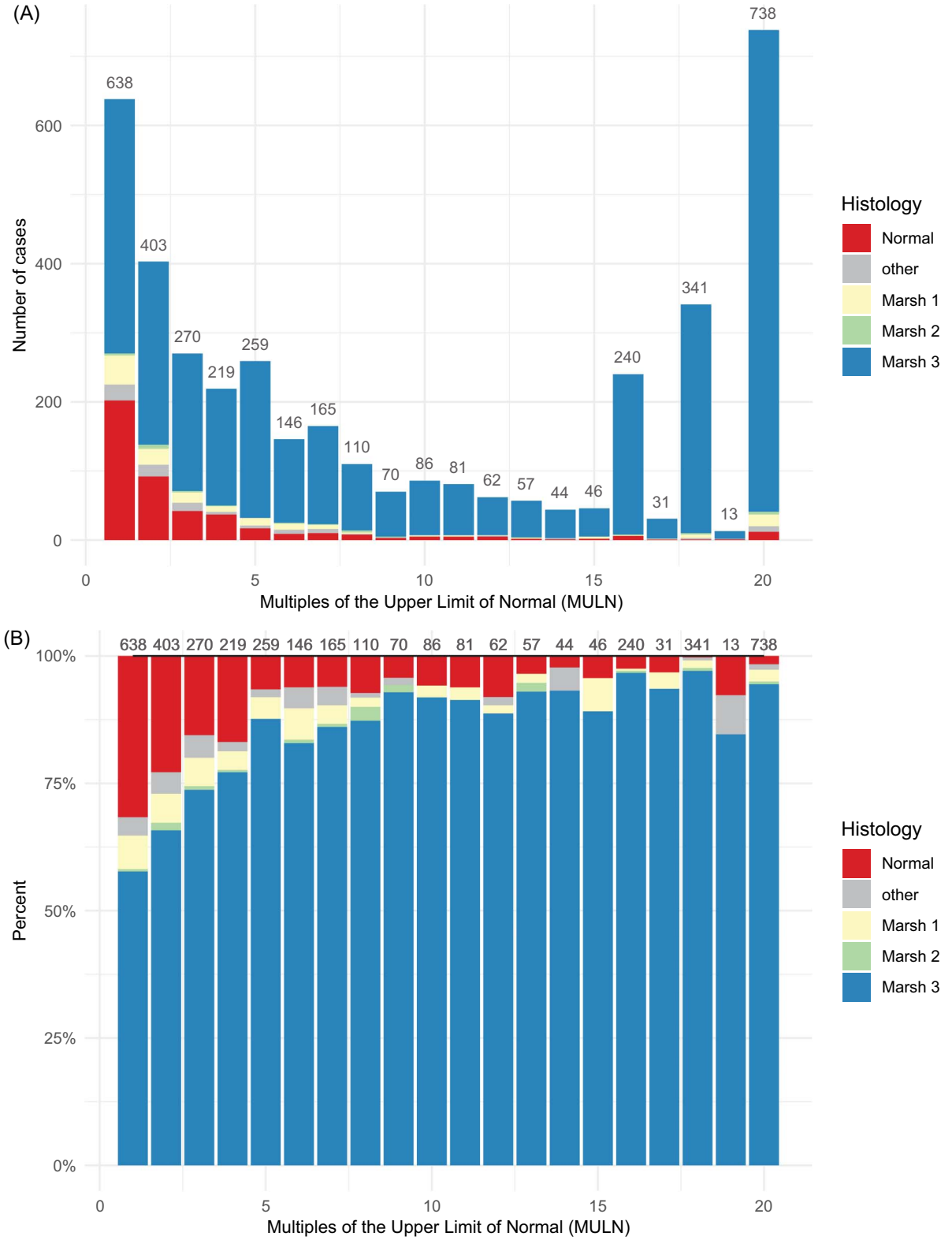

FIGURE 1.

(A) Distribution and (B) frequency of duodenal histologic findings and tTG elevation for a given increment of multiples of the upper limit of normal (ie, 1 to <2× ULN, 2 to <3× ULN…). "Marsh 3" includes all cases with villous atrophy and intraepithelial lymphocytosis irrespective of crypt length reporting. tTG, tissue transglutaminase; ULN, upper limit of normal.

TABLE 3. Duodenal Histology in Children With an Elevated tTG IgA Based on tTG Assay

	BioPlex 2200 Celiac IgA				EliA Celikey IgA				QUANTA Flash h-tTG IgA			
tTG IgA	**≥1× ULN (n = 901)**		**≥10× ULN (n = 432)**		**≥1× ULN (n = 1344)**		**≥10× ULN (n = 547)**		**≥1× ULN (n = 458)**		**≥10× ULN (n = 261)**	
	n (%)	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**
Biopsy-confirmed celiac disease	732 (81.2)	78.5–83.7	408 (94.4)	91.9–96.4	1194 (88.8)	87.0–90.5	532 (97.3)	95.5–98.5	344 (75.1)	70.9–79.0	233 (89.3)	84.9–92.8
Marsh 2	9 (1)	—	2 (0)	—	3 (0)	—	2 (0)	—	5 (1)	—	3 (1)	—
Marsh 3	549 (60.9)	—	312 (72.2)	—	982 (73.1)	—	425 (77.7)	—	231 (50.4)	—	172 (66)	—
IELs and VA, CH not reported	174 (19)	—	94 (22)	—	209 (15.6)	—	105 (19)	—	108 (24)	—	58 (22)	—
Not celiac disease	169 (19)	16.3–21.5	24 (6)	3.6–8.1	150 (11)	9.5–13.0	15 (3)	1.5–4.5	114 (25)	21.0–29.1	28 (11)	7.3–15.1
Marsh 0/Normal	121 (13)	—	15 (4)	—	83 (6)	—	4 (1)	—	65 (14)	—	14 (5)	—
Marsh 1	42 (5)	—	8 (2)	—	25 (2)	—	7 (1)	—	25 (6)	—	8 (3)	—
Nonspecific enteropathy[a]	4 (0)	—	0 (0)	—	15 (1)	—	2 (0)	—	22 (5)	—	6 (2)	—
IELs, CH, and VA not reported	0 (0)	—	0 (0)	—	5 (0)	—	0 (0)	—	0 (0)	—	0 (0)	—
Crypt hyperplasia without IELs	0 (0)	—	0 (0)	—	2 (0)	—	0 (0)	—	1 (0)	—	0 (0)	—
Nonspecific duodenitis[b]	2 (0)	—	1 (0)	—	20 (2)	—	2 (0)	—	0 (0)	—	0 (0)	—

	QUANTA Lite R h-tTG IgA				QUANTA Lite h-tTG IgA			
tTG IgA	**≥1× ULN (n = 815)**		**≥10× ULN (n = 410)**		**≥1× ULN (n = 319)**		**≥5× ULN (n = 157)[c]**	
	n (%)	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**
Biopsy-confirmed celiac disease	673 (82.6)	79.8–85.1	391 (95.4)	92.9–97.2	228 (71.5)	66.2–76.4	147 (94)	88.6–96.9
Marsh 2	4 (0)	—	0 (0)	—	2 (0)	—	0 (0)	—
Marsh 3	427 (52.4)	—	263 (64.1)	—	150 (47)	—	100 (64)	—
IELs and VA, CH not reported	242 (29.7)	—	128 (31)	—	76 (24)	—	47 (30)	—
Not celiac disease	142 (17)	14.9–20.2	19 (5)	2.8–7.1	91 (29)	23.6–33.8	10 (6)	3.1–11.4
Marsh 0/Normal	84 (10)	—	6 (2)	—	72 (23)	—	5 (3)	—
Marsh 1	34 (4)	—	6 (2)	—	10 (3)	—	1 (1)	—
Nonspecific enteropathy[a]	14 (2)	—	5 (1)	—	9 (3)	—	4 (3)	—
IELs, CH and VA not reported	2 (0)	—	0 (0)	—	0 (0)	—	0 (0)	—
Crypt hyperplasia without IELs	0 (0)	—	0 (0)	—	0 (0)	—	0 (0)	—
Nonspecific duodenitis[b]	8 (1)	—	2 (1)	—	0 (0)	—	0 (0)	—

Abbreviations: CH, crypt hyperplasia; IELs, intraepithelial lymphocytosis; IgA, immunoglobulin A; PPV, positive predictive value. tTG, tissue transglutaminase; ULN, upper limit of normal; VA, villous atrophy.

[a] Villous atrophy without intraepithelial lymphocytosis.

[b] Peptic or nonspecific (acute, chronic) findings without mention of IEL, CH, or VA.

[c] $PPV_{5\times}$.

TABLE 4. Extraintestinal Histopathologic Findings Identified During Diagnostic Endoscopy in Children With an Elevated tTG IgA

	tTG IgA ≥1× ULN	tTG IgA ≥10× ULN	*P* Value
Esophagus			
Esophageal biopsies collected, n (% of total)	2980 (74.1)	1287 (74.0)	—
Histology, n (%)			
Normal	2415 (81.0)	1031 (80.1)	.48
Esophagitis	506 (17.0)	230 (17.9)	.48
Eosinophils	425 (14.3)	195 (15)	.44
≥15 eos/hpf	175 (6)	73 (6)	.80
Lymphocytic	43 (1)	15 (1)	.47
Neutrophilic	15 (1)	7 (1)	.87
Candida	2 (0)	1 (0)	.90
No esophageal biopsy taken, n (% of total)	1039 (25.9)	452 (26.0)	—
Stomach			
Gastric biopsies collected, n (% of total)	3534 (87.9)	1565 (90.0)	—
Histology, n (%)			
Normal	2434 (68.9)	978 (62.5)	<.0001
Gastritis	912 (25.8)	512 (32.7)	<.0001
H pylori	49 (1)	23 (2)	.82
H heilmannii	2 (0)	1 (0)	.92
Lymphocytic	41 (1)	23 (2)	.36
Eosinophilic	4 (0)	0 (0)	.18
Chronic gastritis without *Helicobacter*	816 (23.1)	465 (29.7)	<.0001
Not specified	186 (5)	75 (5)	.48
Intestinal metaplasia	2 (0)	0 (0)	.35
No gastric biopsy taken, n (% of total)	485 (12.1)	174 (10)	—

Abbreviations: eos/hpf, eosinophils per high-power field; IgA, immunoglobulin A; tTG, tissue transglutaminase; ULN, upper limit of normal.

(ie, ≥15 eos/hpf) although both symptoms of esophageal dysfunction and the exclusion of other causes for eosinophilia, such as gastroesophageal reflux, are required to make a diagnosis.[31] Although the association between EoE and celiac disease has been reported, albeit weak,[32] most cases of esophageal eosinophilia identified during endoscopy in children with newly diagnosed celiac disease were clinically insignificant and uncommonly due to EoE.[33,34] Additionally, 1.4% of children had *H pylori* identified on gastric biopsies, which may have been an incidental finding given the frequency of routine biopsies that are taken in children undergoing endoscopy.[35,36] In contrast to EoE, *H pylori* is not always treated because shared decision-making with both the patient and family is recommended.[37]

Despite the high predictive value of a tTG IgA greater than or equal to 10× ULN, histopathologic confirmation remains valuable as not all children with a very elevated tTG IgA have enteropathy. Of the 1739 children in our cohort with a tTG IgA greater than or equal to 10× ULN, 70 (4%) had either IELs without VA (ie, Marsh 1) or normal duodenal histology, fulfilling criteria for potential celiac disease, which is a distinct condition from celiac disease.[38] Potential celiac disease was more common in children with T1D and a tTG IgA greater than or equal to 10× ULN (11%) compared with those without T1D (3%), validating the lower specificity of a positive tTG in this high-risk group and the potential need for population-specific cutoffs.[17,39] A prospective study of children with potential celiac disease found the cumulative incidence of the progression to VA was 43% at 12 years of follow-up, with 32% of children having normalization of their serology despite remaining on a gluten-containing diet.[40] The management of potential celiac disease is neither straightforward nor standardized.[41] Given the importance of making an accurate diagnosis, as well as the socioeconomic and psychologic impact associated with the diagnosis and its treatment,[42,43] the possibility of mislabeling some children with celiac disease based on a single highly positive tTG IgA should not be overlooked.

Our study has several limitations that are important to acknowledge. The prevalence of celiac disease across all participating centers is unknown, although we postulate it is higher than the global prevalence of celiac disease (approximately 1%)[44] because all sites are referral centers

for pediatric celiac disease. Therefore, the PPV may be lower in regions with lower disease prevalence. In addition, the negative predictive value of a normal tTG IgA could not be calculated as all children in our study had an elevated tTG IgA. According to guidelines, however, celiac disease can be often ruled out when a tTG IgA is normal given its high negative predictive value.[45] Furthermore, this retrospective study relied on clinician documentation in medical records for key information such as diet status at the time of endoscopy. Although we excluded children who were on a GFD, the amount of gluten that was being consumed leading up to endoscopy is unknown. Consequently, the potential for gluten reduction (but not elimination) and the possibility that some children with intraepithelial lymphocytosis without VA (ie, Marsh 1) histopathology may eventually progress to gluten-induced enteropathy cannot be excluded.

Additionally, we used pathology reports and the original pathologist's interpretation of biopsy specimens for classifying histologic findings. Although there are guidelines on how to properly assess duodenal biopsies when celiac disease is suspected,[46] there is no standardized method for reporting.[47] Whereas a Marsh score was able to be assigned in most cases based on the pathologist's description in the original pathology report, there were a few cases where consultation with a second local pathologist was necessary due to unclear reporting of findings. Interobserver agreement in classifying celiac disease lesions may also vary depending on the grading scale used,[48] pathology practice setting,[49] or knowledge of positive serology,[50] resulting in a different diagnosis in some cases. In their studies assessing the performance of tTG IgA in diagnosing celiac disease in children, both Wolf et al[13] and Werkstetter et al[12] found discrepancies in histologic reporting when a central pathologist was used in 3.2% and 7.1% of cases, respectively. Although the inclusion of a central pathologist may have addressed this issue, our methodology mirrors the practice of most clinicians (ie, referring to the original pathology report) when confirming a celiac disease diagnosis.

CONCLUSION

This study is the largest multicenter pediatric study assessing the performance of common tTG IgA assays in North America. We also highlight the fact that although our findings corroborate reports of smaller cohorts from North America,[21–25,39,51] not all children with a tTG IgA greater than or equal to 10× ULN have enteropathy when endoscopy is performed to confirm a celiac disease diagnosis. At scale, strict application of serologic criteria may lead to overdiagnosis of celiac disease and prescription of a strict lifelong restrictive diet to many children who may not benefit. Additionally, in the absence of standardization, a universal cutoff is inappropriate as the $PPV_{10\times}$ varies meaningfully among assays commonly used in North America. For now, all data support the recommendation that all children with an elevated tTG IgA should be referred to a gastroenterologist or celiac disease specialist and continue to eat gluten until they have confirmatory testing.

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ABBREVIATIONS

10× ULN: 10 times the upper limit of normal
CH: crypt hyperplasia
EMA: antiendomysial antibody immunoglobulin A
EoE: eosinophilic esophagitis
eos/hpf: eosinophils per high-power field
ESPGHAN: European Society of Paediatric Gastroenterology, Hepatology and Nutrition
GFD: gluten-free diet
HLA: human leukocyte antigen
IELs: intraepithelial lymphocytosis
MULN: multiples of the upper limit of normal
PPV: positive predictive value
tTG IgA: anti–tissue transglutaminase immunoglobulin A
T1D: type 1 diabetes
ULN: upper limit of normal
VA: villous atrophy

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Drs Chang, Silvester, and Absah conceptualized and designed the study, carried out the initial analyses, drafted the initial manuscript, and critically reviewed and revised the manuscript. Ms Wong and Ms Baek designed the data collection instruments, collected data, and critically reviewed and revised the manuscript. Ms Cardenas collected data, drafted the initial manuscript, and critically reviewed and revised the manuscript. Drs Stahl, Liu, Gidrewicz, Turner,

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