Ethnic Variations in Duodenal Villous Atrophy Consistent With Celiac Disease in the United States

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BACKGROUND & AIMS: **Celiac disease is a common disorder with a worldwide distribution, although the prevalence among different ethnicities varies. We aimed to measure the prevalence of duodenal villous atrophy among patients of different ethnicities throughout the United States.**

METHODS: **We performed a cross-sectional study of all patients who had duodenal biopsies submitted to a national pathology laboratory between January 2, 2008 and April 30, 2015. The prevalence of villous atrophy was calculated for the following ethnicities by using a previously published algorithm based on patient names: North Indian, South Indian, East Asian, Hispanic, Middle Eastern, Jewish, and other Americans.**

RESULTS: **Among all patients (n = 454,885), the median age was 53 years, and 66% were female. The overall prevalence of celiac disease was 1.74%. Compared with other Americans (n = 380,163; celiac disease prevalence, 1.83%), celiac disease prevalence was lower in patients of South Indian (n = 177, 0%; $P = .08$), East Asian (n = 4700, 0.15%; $P \leq .0001$), and Hispanic (n = 31,491, 1.06%; $P \leq .0001$) ethnicities. Celiac disease was more common in patients from the Punjab region (n = 617, 3.08%) than in patients from North India (n = 1195, 1.51%; $P = .02$). The prevalence of celiac disease among patients of Jewish (n = 17,806, 1.80%; $P = .78$) and Middle Eastern (n = 1903, 1.52%; $P = .33$) ethnicities was similar to that of other Americans. Among Jewish individuals (n = 17,806), the prevalence of celiac disease was 1.83% in Ashkenazi persons (n = 16,440) and 1.39% in Sephardic persons (n = 1366; $P = .24$).**

CONCLUSIONS: **Among patients undergoing duodenal biopsy, individuals from the Punjab region of India constitute the ethnic group in the United States with the highest prevalence of villous atrophy consistent with celiac disease. Compared with other Americans, villous atrophy prevalence on duodenal biopsy is significantly lower among U.S. residents of South Indian, East Asian, and Hispanic ancestry.**

Keywords: Celiac Disease; Population; Epidemiology; Ethnic Groups.

Celiac disease (CD) is an immune-based disorder triggered by the consumption of gluten in genetically susceptible people who are subject to as yet unidentified environmental triggers.[1] A recent study found that the overall prevalence of CD in the general population of the United States (U.S.) is 0.7%, which is equal to approximately 1.8 million Americans.[1] When initially characterized, CD was thought to be a disease of white Europeans, although it is now recognized as one of the most common genetic disorders with a worldwide distribution. However, the prevalence in different ethnicities varies.[2] The prevalence of CD among Europeans is thought to be about 1%–1.5%,[2] with a similar estimated prevalence of about 1.1% in the adult Israeli population[3] and 1.2% in the United Arab Emirates,[4] whereas the disease appears to be less common in Indonesia,[2] South Korea,[2] and the Philippines,[2] which may be related to the lower consumption of wheat in those populations. A retrospective study from the northern part of India reported a significant increase in the prevalence of CD during the past decade.[5] In 1 study of ethnic minorities with

Abbreviations used in this paper: CD, celiac disease; CI, confidence interval; EGD, esophagogastroduodenoscopy; OR, odds ratio; U.S., United States.

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biopsy-proven CD at a pediatric clinic in Canada (n = 54), South Asians were found to comprise a significant majority (81%) of the ethnic minorities with CD.[6] CD in the Asia-Pacific region is considered to be underdiagnosed, although there are expectations for this to change.[7]

Few studies have investigated racial and ethnic variation of CD prevalence in the U.S. Blacks and Hispanics undergoing upper endoscopy are less likely to be biopsied than whites; therefore, CD may be underdiagnosed in these populations.[8] One serologic screening study that estimated the prevalence of CD in the U.S. population found the disease to be predominantly present in non-Hispanic whites and less common among Hispanics and non-Hispanic blacks.[1] There is also uncertainty regarding whether the female predominance observed in European studies of CD[9–11] applies to different ethnicities in the U.S.

In this study, we aimed to measure the prevalence of duodenal villous atrophy (the histologic hallmark of CD) among different ethnicities throughout the U.S. By using a large pathology database of duodenal samples from endoscopic procedures performed by U.S. physicians and diagnosed by a central group of pathologists, we sought to quantify the prevalence of CD among individuals of different ethnic backgrounds, all of whom underwent duodenal biopsy. We also aimed to determine whether the gender distribution in CD differed between these ethnic groups.

Methods

Data Source

We used a large national pathology database of subjects who underwent esophagogastroduodenoscopy (EGD) with duodenal biopsy between January 2, 2008 and April 30, 2015 in endoscopy centers distributed throughout the U.S. The mucosal biopsy specimens were evaluated and reported by a single group of gastrointestinal pathology fellowship–trained histopathologists at 3 different laboratories of Miraca Life Sciences. Pathologists participate in daily consensus conferences, and each reviews specimens from multiple different states. All data were derived from preexisting records. No direct contact with either patients or health care providers was made, and no individual patient information was revealed. All patient records were de-identified before being analyzed.

Ethnicity Categories

A series of computer algorithms based on first and last name analysis were used to categorize patients by ethnicity. This method of ethnic classification, modified from similar existing models[12,13] and described in detail in a recent publication,[14] was first validated by a progressive process, which consisted of adjusting the algorithms against lists of persons of known ethnicity until the specificity was greater than 95%. This level of specificity compares favorably with that of self-reported ethnic classification[15,16] and is substantially more accurate than the assignment of ethnicity by visual inspection as determined by the IC codes used in the United Kingdom.[17] The last validation step, which was specific for this cohort of patients, included prearranged visits to medical practices where substantial numbers of patients of different ethnicities were recruited and had telephone interviews with practice managers. These visits and interviews, which were aimed at determining the level of coincidence between the ethnic categories assigned by our algorithm and the ethnicities recorded by the practices, revealed an essentially perfect concurrence. By using this approach, patients were stratified into the following ethnicities: North Indian (with further subdivision into Punjabis or Other North Indian), South Indian, East Asian, Hispanic, Middle Eastern, Jewish (with further subdivision into Ashkenazi or Sephardic), and Other Americans. The latter group served as a reference and included individuals (mostly whites and blacks) not specifically associated with any of the other ethnic groups. Patients with a combination of names that suggested more than 1 ethnicity (3.7%) were classified as undetermined and excluded from further analysis.

Celiac Disease

We calculated the prevalence of CD among each of the ethnic groups described above. Patients were considered to have CD if duodenal biopsies showed villous atrophy. We then calculated the prevalence of various degrees of villous atrophy: partial villous atrophy (corresponding to Marsh 3a) and subtotal or total villous atrophy (Marsh 3b and Marsh 3c).[18]

Statistical Analysis

The distributions by age, gender, and ethnicity were calculated and expressed as a percentage of the total study population. The prevalence of CD among different ethnicities was compared by using the χ^2 test, with the group "Other Americans" serving as a reference for all comparisons. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated by using logistic regression. We then recalculated ORs and 95% CIs, adjusting for age and gender. Because gastric colonization with *Helicobacter pylori* varies by ethnicity[19] and the presence of *H pylori* correlates inversely with CD,[20] we then also adjusted for *H pylori* status by using a multivariate model restricted to those individuals who had a concurrent gastric biopsy.

The prevalence of CD between the genders was compared overall and then stratified by ethnicity. We used logistic regression to measure the association between female gender and CD by using ORs and 95% CIs; we then adjusted for age and *H pylori* status.

We used SAS (Cary, NC) version 9.4 for all analyses. All reported *P* values are 2-sided. The Institutional Review Board of Columbia University Medical Center deemed this "non-human subjects research" because the data were stripped of all identifiers before being provided to the investigators.

Results

During the study period, there were 458,256 unique individuals with duodenal biopsies. We excluded 11 for likely erroneous age (recorded as older than 99 years). In addition, we excluded 2931 patients whose biopsies showed duodenal neoplasia and 429 patients whose biopsies showed *Giardia lamblia*. The remaining 454,885 patients served as our study population. Demographic information and histologic findings are summarized in Table 1. The median age was 53 years, and the majority of patients (75%) were older than 40 years; 66% were female. The most common indications for duodenal biopsy were gastroesophageal reflux disease, dyspepsia/epigastric pain, anemia, and diarrhea (Table 1). CD was diagnosed in 7928 patients, which was equivalent to 1.74% of those who underwent duodenal biopsy. The prevalence of villous atrophy consistent with CD varied by indication for biopsy; it was lowest (1.25%) among those with gastroesophageal reflux disease and highest (2.04%) among those with diarrhea.

Table 1. Demographics and Histologic Findings of Patients Undergoing Duodenal Biopsy (n = 454,885)

	N (%)
Age (*y*)	
0–19	17,353 (3.81)
20–39	95,610 (21.02)
40–59	173,267 (38.09)
60+	168,655 (37.08)
Gender	
Male	153,145 (33.69)
Female	301,404 (66.31)
Ethnicity	
Undetermined	16,833 (3.70)
Other Americans	380,163 (83.57)
North Indian	1812 (0.40)
Punjabis	617 (34.05)
Other North Indians	1195 (65.95)
South Indians	177 (0.04)
East Asians	4700 (1.03)
Hispanics	31,491 (6.92)
Middle Eastern	1903 (0.42)
Jewish	17,806 (3.91)
Ashkenazi	16,440 (92.33)
Sephardic	1366 (7.67)
Indications for biopsy[a]	
Dyspepsia/epigastric pain	71,815 (16)
Anemia	68,663 (15)
Diarrhea	79,393 (17)
Weight loss	35,227 (8)
Gastroesophageal reflux disease	178,073 (39)
Other	108,014 (24)
Not listed	81,633 (18)
CD	7928 (1.74)
Concurrent gastric biopsy	375,448 (82.54)
H pylori	36,405 (9.70)

[a]Total is greater than 100% because of patients having multiple indications listed.

Table 2 shows the prevalence of villous atrophy consistent with CD by ethnicity. Compared with the prevalence of CD among Other Americans (1.83%), the lowest prevalence of CD was found among patients identified as South Indians (0 of 177, OR and CI not calculable), East Asians (0.15%; OR, 0.08; 95% CI, 0.04–0.17; $P < .0001$), and Hispanics (1.06%; OR, 0.58; 95% CI, 0.52–0.64; $P < .0001$). These comparisons were essentially unchanged when CD was subdivided into partial villous atrophy and subtotal/total villous atrophy and when ORs were adjusted for age, gender, and *H pylori* status (Table 2). Among North Indians, there was a trend toward higher prevalence (2.04%) when compared with Other Americans (1.83%) that did not reach statistical significance (OR, 1.41; 95% CI, 0.99–2.00; $P = .06$).

Of the 1812 patients with North Indian origin, 617 were Punjabis; 19 of Punjabi patients (3.08%) had villous atrophy consistent with CD. The prevalence of CD was significantly higher in Punjabis (3.08%) than that in Other North Indian patients (3.08% vs 1.51% [18/1195]; $P = .02$) Among Jewish individuals (n = 17,806), the prevalence of CD was 1.83% (301/16,440) in Ashkenazi subjects and 1.39% in Sephardic subjects (19/1366; $P = .24$).

The distribution of villous atrophy consistent with CD by gender and ethnicity is shown in Table 3. Although 5338 of the patients with CD (67%) were female, this apparent majority was due to the fact that women comprised 66% of all individuals undergoing duodenal biopsy, and the prevalence of CD was nearly identical in men and women (1.7% and 1.8%, respectively). The similar prevalence of CD between genders was present across all ethnicities, although there was a non-significant trend toward female predominance in North Indian, Hispanic, Middle Eastern, and Jewish patients (Table 3).

Figure 1 shows the prevalence of villous atrophy consistent with CD by age, stratified by ethnicity. The distributions were fairly even among the groups where CD was more prevalent. There was an increase in CD among Jewish and North Indian patients in the youngest age group (0–19 years), although comparisons of the ethnic groups in this age stratum did not yield statistically significant differences because of the low number of children with CD in these groups.

Discussion

In our analysis of more than 400,000 duodenal biopsies from a nationwide pathology database, we found that the prevalence of CD in those undergoing duodenal

Table 2. Prevalence of Villous Atrophy Consistent With CD by Ethnicity and Stratified by Degree of Villous Atrophy

Ethnicity	CD (%)	OR	95% CI	*P* value	OR[a]	95% CI	*P* value	OR[b]	95% CI	*P* value
CD										
Other Americans	6943 (1.83)	1.00	Reference	Reference	1.00	Reference	Reference	1.00	Reference	Reference
North Indians	37 (2.04)	1.12	0.81–1.55	.49	1.09	0.79–1.51	.60	1.41	0.99–2.00	.057
South Indians	0 (0.00)	NC	NC	NC	NC	NC	NC	NC	NC	NC
East Asians	7 (0.15)	0.08	0.04–0.17	<.0001	0.08	0.04–0.17	<.0001	0.12	0.06–0.25	<.0001
Hispanics	334 (1.06)	0.58	0.52–0.64	<.0001	0.57	0.51–0.64	<.0001	0.71	0.63–0.80	<.0001
Middle Eastern	29 (1.52)	0.83	0.58–1.20	.33	0.81	0.56–1.16	.25	1.01	0.67–1.53	.96
Jewish	320 (1.80)	0.98	0.88–1.10	.78	0.99	0.89–1.11	.90	1.04	0.91–1.19	.61
Partial villous atrophy										
Other Americans	3410 (0.90)	1.00	Reference	Reference	1.00	Reference	Reference	1.00	Reference	Reference
North Indians	15 (0.83)	0.92	0.55–1.54	.76	0.91	0.55–1.51	.72	1.30	0.78–2.16	.32
South Indians	0 (0.00)	NC	NC	NC	NC	NC	NC	NC	NC	NC
East Asians	5 (0.11)	0.12	0.05–0.28	<.0001	0.12	0.05–0.29	<.0001	0.17	0.07–0.40	<.0001
Hispanics	220 (0.70)	0.78	0.68–0.89	.0003	0.78	0.68–0.89	.0003	0.96	0.82–1.11	.60
Middle Eastern	19 (1.00)	1.11	0.71–1.75	.64	1.10	0.70–1.73	.68	1.40	0.85–2.30	.18
Jewish	159 (0.89)	1.00	0.85–1.17	.99	1.01	0.86–1.18	.94	1.06	0.88–1.28	.52
Subtotal/total villous atrophy										
Other Americans	3533 (0.93)	1.00	Reference	Reference	1.00	Reference	Reference	1.00	Reference	Reference
North Indians	22 (1.21)	1.31	0.86–2.00	.21	1.26	0.83–1.92	.28	1.51	0.94–2.45	.09
South Indians	0 (0.00)	NC	NC	NC	NC	NC	NC	NC	NC	NC
East Asians	2 (0.04)	0.05	0.01–0.18	<.0001	0.05	0.01–0.19	<.0001	0.07	0.02–0.28	.0002
Hispanics	114 (0.36)	0.39	0.32–0.47	<.0001	0.38	0.32–0.46	<.0001	0.45	0.36–0.56	<.0001
Middle Eastern	10 (0.53)	0.56	0.30–1.05	.07	0.54	0.29–1.00	.05	0.62	0.29–1.30	.21
Jewish	161 (0.90)	0.97	0.83–1.14	.73	0.99	0.84–1.16	.86	1.01	0.83–1.23	.94

NC, not calculated because of insufficient number of patients with CD.
[a]Adjusted for age and gender.
[b]Adjusted for age, gender, and *H pylori* status.

biopsy was lower in patients identified as South Indian, East Asian, and Hispanic when compared with Other Americans. North Indian patients identified with ancestry in the Punjab region had a significantly higher prevalence of CD on duodenal biopsy compared with all Other North Indian patients. There were no significant differences in prevalence of CD between Middle Eastern and Jewish patients when compared with Other Americans.

Table 3. Distribution of Villous Atrophy Consistent With CD by Gender and Ethnicity

Ethnicity	No. with CD (%)	OR	95% CI	*P* value	OR[a]	95% CI	*P* value	OR[b]	95% CI	*P* value
Other										
Overall	6936 (1.83)									
Men	2290 (1.79)	1.00	Reference	Reference	1.00	Reference	Reference	1.00	Reference	Reference
Women	4646 (1.84)	1.03	0.98–1.08	.25	1.02	0.97–1.08	.36	0.99	0.93–1.05	.71
North Indian										
Overall	37 (2.04)									
Men	15 (1.62)	1.00	Reference	Reference	1.00	Reference	Reference	1.00	Reference	Reference
Women	22 (2.49)	1.55	0.80–3.01	.19	1.54	0.79–2.98	.21	1.49	0.73–3.04	.27
Hispanic										
Overall	333 (1.06)									
Men	82 (0.90)	1.00	Reference	Reference	1.00	Reference	Reference	1.00	Reference	Reference
Women	251 (1.12)	1.26	0.98–1.61	.07	1.27	0.99–1.63	.07	1.22	0.92–1.61	.16
Middle Eastern										
Overall	29 (1.53)									
Men	14 (1.31)	1.00	Reference	Reference	1.00	Reference	Reference	1.00	Reference	Reference
Women	15 (1.81)	1.39	0.67–2.89	.38	1.40	0.67–2.91	.3744	1.30	0.57–2.97	.54
Jewish										
Overall	319 (1.79)									
Men	99 (1.55)	1.00	Reference	Reference	1.00	Reference	Reference	1.00	Reference	Reference
Women	220 (1.93)	1.26	0.99–1.59	.063	1.26	0.99–1.60	.063	1.33	0.997–1.77	.053

[a]Adjusted for age and gender.
[b]Adjusted for age and *H pylori* status.

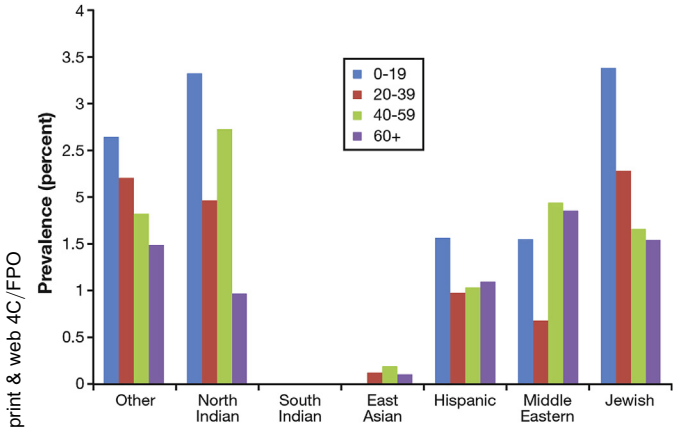

Figure 1. Prevalence of villous atrophy consistent with CD by age, stratified by ethnicity.

In this population, the prevalence of CD was 1.74%, slightly more than double the prevalence reported in the screening studies.[1,21] Our study population consisted of patients undergoing duodenal biopsy for various indications, including symptoms clinically suggestive of CD. Significantly fewer Hispanic and East Asian patients were found to have CD, which is consistent with prior reports.[2,21,22] Susceptibility to CD is predominantly associated with the HLA-DQ2, which varies geographically and is found in higher frequency in Western Europe and in portions of Africa and India.[23] In studies of CD in India, the prevalence of compatible HLA haplotypes is similar to those in Western countries and does not vary substantially between regions.[24] Large regional variation in the wheat consumption in India[24] is possibly a more significant reason to explain why cases of CD in India are primarily reported from Northern regions, with only isolated case reports from the rest of the country[25] and virtually no cases reported in Southern India,[24] which is in keeping with the findings of our study. Our finding of a higher prevalence of CD in patients with Punjabi ancestry is also consistent with previous reports.[26]

Our study population of patients undergoing duodenal biopsy was majority female, which is consistent with prior reports in this setting and elsewhere that women undergoing EGD are more likely to have duodenal biopsies than men.[8,27] However, we found that CD was equally prevalent among men and women undergoing duodenal biopsy, which was true in all ethnic groups studied. Several screening studies of CD in the U.S. have shown that CD is equally prevalent among men and women,[28–30] but screening studies of children in the U.S.[31] and elsewhere[10,11] have shown a female predominance. Regardless of whether gender affects the true prevalence of CD, women are more likely to be diagnosed with CD than are men.[32] Our findings support the notion that CD should be considered as a diagnosis in men as often as it is considered in women.

We found no significant difference in the prevalence of CD on duodenal biopsy between patients of Ashkenazi and Sephardic origin. Although the high prevalence of inflammatory bowel disease in Ashkenazi Jews is well-documented, we are not aware of any studies investigating the prevalence of CD in Sephardic versus Ashkenazi Jews. One study of the prevalence of CD among the adult Jewish population in Israel included only 850 subjects and did not differentiate between Ashkenazi and Sephardic ancestry.[3] Our comparison may have been limited by the small number of patients of Sephardic ancestry in the study population.

This study has several strengths, including its large sample size and uniform reporting of histologic findings, because all biopsies were read and reported by a central group of pathologists with subspecialty training in gastrointestinal pathology who practice in the same environment, use uniform diagnostic criteria and standardized diagnostic codes, and participate in daily consensus conferences where cases and diagnostic criteria are discussed. On review of the reporting of villous atrophy by different pathologists on the same specimen, there was good to excellent agreement for variable villous atrophy (Marsh 3a) and villous atrophy (Marsh 3b and 3c). As such, diagnosis of duodenal biopsies consistent with CD was very consistent across all pathologists. Pathology specimens came from multiple centers around the country; thus, patients in our study population were representative of the U.S. general population and allowed us to generate true prevalence data among patients undergoing duodenal biopsy. Although some geographic regions have a higher proportion of certain ethnicities and it is indeed possible that certain pathologists see more patients of a certain group, this is unlikely to have biased our results. We found no distinct geographic predominance with regard to patients of Indian, Jewish, or Middle Eastern descent. As such, there were essentially equal chances that any pathologist interpreted biopsies from these ethnicities. The largest proportions of East Asian patients in our patient population are in New York, New Jersey, California, Alaska, and Hawaii. These 5 states have more than 20 pathologists who share the diagnostic work. Similarly, Hispanic patients are distributed almost equally in California, the Southwest (including Texas), and the Northeast. Therefore, it is extremely unlikely that all of the pathologists interpreting biopsies from these different states have a bias for a low rate of CD diagnosis.

Our study has several limitations. We were able to measure villous atrophy but not the clinical entity of CD. Because we had no serologic data on patients with duodenal biopsies that showed villous atrophy, it is possible that some patients may have been misclassified as having CD, although even the most common cause of seronegative villous atrophy is still CD.[33] Nevertheless, some patients with alternative causes of villous atrophy (such as tropical sprue[33] or sprue-like enteropathy due to olmesartan[34]) would have been classified as having CD in this analysis. In particular, multiple studies have shown that tropical sprue is still the most common cause of malabsorption syndrome in India,[35,36] whereas CD is

emerging as a more important cause of malabsorption than previously thought.[35–37] However, such cases of tropical sprue and sprue-like enteropathy due to olmesartan are far less common than CD in the U.S.[38,39] Our study population only included those undergoing duodenal biopsy; thus our prevalence calculations do not include those patients who may be diagnosed with CD on the basis of serology and symptoms alone, and they do not take into account undiagnosed CD. Because ethnicity was derived on the basis of a name-based algorithm, misclassification of ethnicity is possible. For example, the proportion of patients in our sample classified as Hispanic was 6.9%, far lower than the prevalence of 16.3% that was based on self-report in the 2010 U.S. Census.[40] However, such misclassification would bias our results toward the null, because it is unlikely that misclassification is differential by CD status. Therefore, it is possible that the prevalence of CD differs by ethnicity to a greater extent than reported in this study. Misclassification was mitigated in part by our excluding patients whose names were deemed ambiguous or dual-classified by our algorithm. Another limitation to the name-based algorithm is the lack of data on year of immigration to the U.S., which would help inform if and when dietary and other environmental exposures affect the risk of CD. Although the national setting enhances the generalizability of our findings, the pathology specimens were submitted from private offices and ambulatory surgical centers and not from hospital-based endoscopy suites, raising the possibility that these data are not entirely representative of the U.S. population.

In conclusion, we found that in the U.S., the prevalence of CD in those undergoing duodenal biopsy is significantly lower among patients of South Indian, East Asian, and Hispanic descent. Among patients of North Indian descent undergoing duodenal biopsy, CD is significantly more common in those from the Punjab region than in all other patients from North India. Patients of Jewish and Middle Eastern ethnicity had CD prevalence similar to that of other Americans. Men and women had a similar prevalence of villous atrophy on duodenal biopsy, regardless of ethnicity. These findings may have clinical relevance to gastroenterologists across the U.S. and may aid in their diagnostic practices.

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Conflicts of interest
The authors disclose no conflicts. Q2

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