

# Prevalence of Celiac Disease in At-Risk and Not-At-Risk Groups in the United States

## A Large Multicenter Study

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**Background:** Celiac disease (CD) is an immune-mediated enteropathic condition triggered in genetically susceptible individuals by the ingestion of gluten. Although common in Europe, CD is thought to be rare in the United States, where there are no large epidemiologic studies of its prevalence. The aim of this study was to determine the prevalence of CD in at-risk and not-at-risk groups in the United States.

**Methods:** Serum antigliadin antibodies and anti-endomysial antibodies (EMA) were measured. In EMA-positive subjects, human tissue transglutaminase IgA antibodies and CD-associated human leukocyte antigen DQ2/DQ8 haplotypes were determined. Intestinal biopsy was recommended and performed whenever possible for all EMA-positive subjects. A total of 13 145 subjects were screened: 4508 first-degree and 1275 second-degree relatives of patients with biopsy-proven CD, 3236 symptomatic patients (with either gastrointestinal symptoms or a disorder associated with CD), and 4126 not-at-risk individuals.

**Results:** In at-risk groups, the prevalence of CD was 1:22 in first-degree relatives, 1:39 in second-degree relatives, and 1:56 in symptomatic patients. The overall prevalence of CD in not-at-risk groups was 1:133. All the EMA-positive subjects who underwent intestinal biopsy had lesions consistent with CD.

**Conclusions:** Our results suggest that CD occurs frequently not only in patients with gastrointestinal symptoms, but also in first- and second-degree relatives and patients with numerous common disorders even in the absence of gastrointestinal symptoms. The prevalence of CD in symptomatic patients and not-at-risk subjects was similar to that reported in Europe. Celiac disease appears to be a more common but neglected disorder than has generally been recognized in the United States.

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**C**ELIAC DISEASE (CD) is an immune-mediated enteropathy triggered in genetically susceptible individuals by the ingestion of gluten-containing grains (wheat, barley, and rye). The disease is associated with human leukocyte antigen (HLA) DQ2 and DQ8 haplotypes. In the continued presence of gluten, CD is self-perpetuating.<sup>1</sup> Given the undisputed role of gluten in causing inflammation and autoimmunity, CD represents a unique example of an immune-mediated disease for which early serologic diagnosis and dietary treatment can prevent severe, sometimes life-threatening complications.

The advent of new serologic tests, including for antigliadin antibodies (AGA) and anti-endomysial antibodies (EMA), enabled large-scale screening studies in Eu-

rope that revealed that CD is one of the most common genetic diseases of humankind, occurring in from 1 of 130 to 1 of 300 individuals in the European general population.<sup>2-5</sup> Recently, several authors have reported data on the prevalence of CD in parts of Africa,<sup>6</sup> South America,<sup>7</sup> and Asia,<sup>8-11</sup> showing that CD is more common than previously thought in these areas as well.

Serologic studies have demonstrated that the clinical manifestations of CD are more protean than previously reported.<sup>12</sup> Numerous clinical manifestations, including typical gastrointestinal symptoms as well as atypical and asymptomatic forms, have been described.<sup>13</sup> Within the US scientific community it is generally held that CD is a rare disorder in the United States.<sup>14,15</sup> However, this perception is unsubstantiated by any large epidemiologic study, and it remains a controversial issue.<sup>16,17</sup>

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Given the common European ancestry of a large proportion of the US population, it is likely that CD in the United States is more common than currently recognized. Moreover, our previous observations among US blood donors<sup>18</sup> and symptomatic children<sup>19</sup> showed a prevalence of EMA-positive subjects similar to that described in Europe.

The main aim of the present study was to perform a large multicenter screening study to determine the prevalence of CD in the United States in at-risk groups (first- and second-degree relatives of patients with biopsy-proven CD and children and adults with symptoms frequently associated with CD) and in not-at-risk groups (blood donors, schoolchildren, and subjects seen in outpatient clinics for routine checkups).

## METHODS

### STUDY POPULATIONS

Subjects whose blood was tested by the University of Maryland Center for Celiac Research, Baltimore, between February 1996 and May 2001 were included in the present study. We enrolled 13 145 subjects residing in 32 states of the United States who were either at risk (n=9019) or not at risk (n=4126) for CD.<sup>3,16</sup> Of all subjects, 57% were female. The age distribution of the subjects screened was as follows: 0 to 19 years, 27.3%; 20 to 44 years, 38.0%; 45 to 59 years, 20.1%; 60 years or older, 14.6%. This distribution corresponds closely to the age distribution of the population in the 2000 census.<sup>20</sup> Of screened subjects, 94% were white, 3% black, 1.5% Hispanic, 1% Asian, and 0.5% other races.

At-risk subjects were either relatives of patients with CD or were patients who presented with CD-associated symptoms (diarrhea, abdominal pain, and constipation) or with CD-associated disorders (type 1 diabetes mellitus, Down syndrome, anemia, arthritis, osteoporosis, infertility, and short stature). A total of 4508 first-degree and 1275 second-degree relatives of patients with biopsy-proven CD (as established by either medical records or verbal reports) were recruited during CD support group meetings. A total of 1209 households with 1 or more individuals with CD were included in our survey. In addition, 1326 children and 1910 adults with either CD-associated symptoms or CD-associated disorders were enrolled.

Not-at-risk groups were recruited using the 3 main strategies described in the literature: blood donors, schoolchildren, and patients seen in outpatient clinics for routine checkups.<sup>16,21,22</sup> Serum samples from 2000 subjects (mean age, 39 years; age range, 19-65 years) were obtained from the Red Cross blood bank from blood donors.<sup>18</sup> We obtained 1119 samples from schoolchildren (mean age, 12.3 years; age range, 6-18 years) in 4 West Virginia counties. Finally, we screened 1007 adults (mean age, 39 years; age range, 19-71 years) and children (mean age, 13.7 years; age range, 2-18 years) who were enrolled either during routine visits to health care providers or during CD support group meetings.

The institutional review board of the University of Maryland School of Medicine approved this study. Before being tested, subjects completed a questionnaire and signed a consent form. Children between the ages of 13 and 18 years signed a separate assent form.

### ANTIBODY MEASUREMENTS

About 7 mL of blood was drawn from each subject. Presence of IgA and IgG AGA was measured by enzyme-linked immunosorbent assay (Eurospital, Trieste, Italy) using cutoffs as rec-

ommended by the manufacturer. Presence of IgA EMA was measured by an immunofluorescence method using human umbilical cord vein or monkey esophagus as substrate<sup>18</sup>; a positive fluorescence at dilutions equal to or greater than 1:10 was considered positive. Serum samples testing positive for IgG AGA but not IgA AGA were tested for total IgA concentration to detect IgA deficiency. All EMA-positive samples were also screened with the newly developed human tissue transglutaminase (hTTG) IgA enzyme-linked immunosorbent assay.<sup>22</sup> The hTTG results were expressed as a percentage of the positive control serum. Serum samples were considered positive when the value was higher than 13%, a cutoff representing more than 2 SDs above the mean of 100 healthy subjects (60 male and 40 female, aged 1-56 years) for hTTG.<sup>22</sup>

### HLA HAPLOTYPES

The blood of EMA-positive subjects and race-matched EMA-negative individuals were tested for HLA DQ2 and DQ8 haplotypes. Genomic DNA was extracted from whole blood samples using the QIAamp DNA Mini Kit (Qiagen Inc, Valencia, Calif). The HLA typing was performed as previously described<sup>23</sup> using the Eu-DQ Kit (Eurospital). This HLA kit contained multiplex polymerase chain reactions for DQ $\alpha$ 1\*0501-DQ $\beta$ 1\*0302 and DQ $\beta$ 1\*02 primers, with beta globin primer as the internal control. The amplicons obtained were resolved on 2% agarose gel and stained using ethidium bromide.

### DIAGNOSTIC CRITERIA

The criteria for the diagnosis of CD were either EMA-positive serologic findings with an intestinal biopsy consistent with CD or EMA-positive serologic findings with HLA haplotypes compatible with CD when a biopsy was not performed. Endoscopic biopsy of the intestine was recommended and performed if possible for all individuals who were either EMA positive or were AGA IgG positive and IgA deficient. Two independent investigators at the University of Maryland Center for Celiac Research blindly evaluated the biopsy specimens. If discrepancies were detected, the chief pathologist at the University of Maryland was the third evaluator. We used the modified Marsh classification<sup>24</sup> to score the severity of small bowel lesions.

### STATISTICAL ANALYSIS

The relationship of several risk factors to diagnosis of CD was evaluated using logistic regression. Separate models were used to analyze the effect of genetic relatedness to CD patient (first- vs second-degree relatives), adult status, female sex, and presence of symptoms or diseases. To examine geographic patterns of CD prevalence, state of residence was collapsed into 5 geographic regions: West, Midwest, South, Mid-Atlantic, and Northeast. The CD prevalence among the 5 regions was compared using the Fisher exact test. A multivariate analysis also was performed, which included all 4 independent variables and the geographic regions (except for the South, which was the reference region). Race was not included because of the modest number of nonwhites in our sample.

The relationship between presence of symptoms and diagnosis of CD was analyzed within the subgroups of CD relatives and CD nonrelatives by logistic regression. The method of Hosmer and Lemeshow<sup>25</sup> was used to validate the logistic regression. Collinearity and overfitting were assessed by examination of standard errors of regression parameters, per Hosmer and Lemeshow.<sup>25</sup> Two-sided hypotheses were evaluated throughout; 95% confidence intervals (CIs) were used. The HLA frequencies in the clinical groups were compared using 2-sided

**Table 1. Prevalence of Celiac Disease in At-Risk and Not-At-Risk Subjects**

Subjects	No. of Subjects Screened	Endomysial Antibody Positive		95% Confidence Interval
		No.	Prevalence, %	
<b>At-Risk Subjects</b>				
First-degree relatives	4508	205	4.55	3.90-5.20
Male	1853	89	4.80	3.86-5.90
Female	2655	116	4.37	3.60-5.20
Children	1294	54	4.17	3.10-5.40
Adults	3214	151	4.70	3.98-5.50
Second-degree relatives	1275	33	2.59	1.80-3.60
Male	524	12	2.29	1.20-4.00
Female	751	21	2.80	1.70-4.30
Children	613	19	3.10	1.90-4.80
Adults	662	14	2.11	1.20-3.50
Symptomatic adults	1910	28	1.47	0.97-2.10
Male	418	5	1.20	0.40-2.80
Female	1492	23	1.54	0.98-2.30
Symptomatic children	1326	53	4.00	2.99-5.20
Male	757	27	3.57	2.40-5.20
Female	569	26	4.57	3.00-6.70
<b>Not-At-Risk Subjects</b>				
	4126	31	0.75	0.50-1.10
Male	2057	16	0.78	0.40-1.30
Female	2069	15	0.72	0.40-1.20
Adults	2845	27	0.95	0.60-1.40
Children	1281	4	0.31	0.09-0.80
<b>All Subjects</b>				
Male	5609	149	2.66	2.20-3.10
Female	7536	201	2.67	2.30-3.10
Children	4514	130	2.88	2.40-3.40
Adults	8631	220	2.55	2.20-2.90

**Table 2. HLA Haplotypes in Patients With Newly Diagnosed Celiac Disease Identified by This Study\***

HLA Haplotypes	No. (%) of Subjects		
	EMA Positive With Biopsy	EMA Positive Without Biopsy	EMA Negative†
HLA-DQ2	76 (78)	82 (72)	36 (39)
HLA-DQ8	16 (16)	23 (20)	16 (17)
HLA-DQ2/DQ8	6 (6)	9 (8)	3 (3)
HLA other than DQ2/DQ8	0 (0)	0 (0)	37 (41)

\*Comparison of a random sample from endomysial antibody (EMA)-positive subjects who had an intestinal biopsy, EMA-positive subjects without an intestinal biopsy, and EMA-negative subjects.

†HLA distribution in the US general population: DQ2 and/or DQ8, 37%.<sup>26</sup>

Fisher exact tests. The HLA frequencies (HLA DQ2 alone, DQ8 alone, DQ2/DQ8 heterozygote, and other HLA genotypes) were compared among the 3 clinical groups (EMA-positive/biopsy performed, EMA-positive/biopsy not performed, and EMA-negative) and evaluated at  $\alpha = .05$ . The 3 pairwise comparisons of the clinical groups were each evaluated at a Bonferroni-corrected  $\alpha = .0167$ .

## RESULTS

The general demographic characteristics of the subjects screened and the number of new patients with CD identified in this study are summarized in **Table 1**. Of the 13 145 subjects screened, 350 (2.7%) were EMA positive. All EMA-positive individuals were also hTTG positive and, when tested, had an HLA haplotype compatible with CD<sup>26</sup> (**Table 2**). IgG and/or IgA AGA were positive in 89.2% of EMA-positive cases. When the pediatric population was

subdivided into several age groups (1-5, 6-10, 11-15, and 16-18 years), the prevalence of CD was relatively similar across all groups, with overlapping confidence limits (data not shown). These results suggest that CD is as frequent among adolescents as among younger children.

Of 350 EMA-positive cases, 143 (41%) were asymptomatic. Intestinal biopsies were performed in 116 (33%) of the 350 EMA-positive cases, and in all cases a lesion compatible with the diagnosis of CD was found (**Table 3**). Only 40 subjects (34%) showed classic subtotal (Marsh stage 3b) or total (Marsh stage 3c) villous atrophy.<sup>24</sup> Of the remaining 234 EMA-positive patients, 56 chose to initiate a gluten-free diet without confirming the diagnosis by biopsy, 55 remained on an unrestricted diet, 71 had requests for a biopsy denied by either their physician or health care insurance company, and 52 were undecided.

**Table 3. Summary of Serological Testing and Histopathological Findings**

Group	No.	Endomysial Antibody Positive, No.	Prevalence, Ratio (%)	Intestinal Biopsies, No.					Not Done
				Marsh Classification*					
				1	2	3a	3b	3c	
<b>At-Risk Population</b>									
First-degree relatives	4508	205	1:22 (4.55)	0	14	20	16	10	145
Second-degree relatives	1275	33	1:39 (2.59)	0	4	5	1	1	22
Symptomatic adults	1910	28	1:68 (1.47)	0	4	7	2	2	13
Symptomatic children	1326	53	1:25 (4.00)	0	6	11	4	2	30
<b>Total</b>	<b>9019</b>	<b>319</b>	<b>1:28 (3.54)</b>	<b>0</b>	<b>28</b>	<b>43</b>	<b>23</b>	<b>15</b>	<b>210</b>
<b>Not-At-Risk Population</b>									
Adults	2845	27	1:105 (0.95)	0	2	2	1	0	22
Children	1281	4	1:320 (0.31)	0	0	1	0	1	2
<b>Total</b>	<b>4126</b>	<b>31</b>	<b>1:133 (0.75)</b>	<b>0</b>	<b>2</b>	<b>3</b>	<b>1</b>	<b>1</b>	<b>16</b>

\*Modified Marsh classification<sup>24</sup>: 1, infiltrative changes; 2, hyperplastic changes; 3a, mild villous flattening; 3b, marked villous atrophy; and 3c, flat mucosa.

**Table 4. Presence of Clinical Symptoms and Celiac Disease Among First- and Second-Degree Relatives**

Group	No.	Symptomatic Cases			Asymptomatic Cases		
		Screened, No.	Positive, No.	Prevalence, Ratio (%)	Screened, No.	Positive, No.	Prevalence, Ratio (%)
First-degree adults	3214	1679	89	1:20 (5.3)	1535	62	1:24 (4.04)
First-degree children	1294	592	20	1:30 (3.38)	702	34	1:21 (4.84)
Second-degree adults	662	386	8	1:48 (2.07)	276	6	1:46 (2.17)
Second-degree children	613	259	9	1:29 (3.47)	354	10	1:35 (2.82)
<b>Total</b>	<b>5783</b>	<b>2916</b>	<b>126</b>	<b>1:23 (4.32)</b>	<b>2867</b>	<b>112</b>	<b>1:25 (3.91)</b>

**Table 5. Prevalence of Celiac Disease (CD) in Specific Clinical Conditions and Prevalence of Specific Symptoms or Disorders in Newly Diagnosed Cases of CD**

Clinical Conditions	Subjects Screened, No.	Prevalence of CD, Ratio (%)	Prevalence of Symptoms or Diseases Among New CD Cases, * %
<b>Gastrointestinal</b>			
Chronic diarrhea	1848	1:26 (3.85)	35.3
Abdominal pain	1695	1:31 (3.23)	27.8
Constipation	1530	1:38 (2.63)	20.2
<b>Extraintestinal</b>			
Down syndrome	66	1:11 (9.09)	3.0
Infertility (idiopathic)	48	1:16 (6.25)	1.5
Type 1 diabetes mellitus	295	1:23 (4.35)	6.5
Anemia	73	1:24 (4.17)	1.5
Short stature	140	1:25 (4.00)	1.0
Joint pain	1779	1:31 (3.23)	29.3
Arthritis	99	1:33 (3.00)	1.5
Fatigue	1787	1:34 (2.94)	26.3
Asthma	487	1:35 (2.63)	7.1
Osteoporosis	435	1:39 (2.56)	5.5
Sjögren syndrome	98	1:49 (2.00)	1.0

\*Note that patients had more than 1 symptom or disease.

When the findings from EMA-positive subjects who underwent an intestinal biopsy were compared with those of EMA-positive subjects who did not have a biopsy, there were no differences in the presence of symptoms or the HLA pattern ( $P=.70$ ). In contrast, results from EMA-negative subjects were significantly different from those of EMA-positive subjects in presence of symptoms and HLA pattern ( $P<.001$ ).

## AT-RISK SUBJECTS

### Relatives of Patients With CD

Among relatives of patients with CD, 205 first-degree relatives (1:22) and 33 second-degree relatives (1:39) tested positive (Tables 1 and 3). Of the 238 relatives with positive serologic findings, 71 (37 asymptomatic, 34 symp-

**Table 6. Logistic Regression Analysis of Endomysial Antibody Positivity\***

Independent Variables	Odds Ratio (95% Confidence Interval)	
	Unadjusted	Adjusted (Multivariate)
Genetic relatedness†	1.8 (1.2-2.6)	1.7 (1.2-2.5)
Adult (vs child aged ≤18 y)	1.2 (0.9-1.5)	1.2 (0.8-1.6)
Female sex	1.1 (0.9-1.4)	1.0 (0.7-1.3)
Presence of symptoms/diseases	2.1 (1.6-2.7)	1.2 (0.9-1.6)

\*Unadjusted models included only the independent variable listed in the first column. The adjusted model included all 4 independent variables.

†First-degree (vs second-degree) relatives of patients biopsy positive for celiac disease.

tomatic) had the diagnosis confirmed by biopsy (Table 3). The symptoms and demographic characteristics of the newly detected cases of CD among relatives are listed in **Table 4**. The prevalence of CD among relatives of patients with CD was statistically homogeneous in symptomatic and asymptomatic cases (odds ratio [OR], 1.2; CI, 0.9-1.7). Of the newly diagnosed pediatric cases, only 40% were symptomatic, while 59% of newly diagnosed adult cases were symptomatic.

#### Symptomatic Patients

Twenty-eight of 1910 symptomatic adults (1:68) and 53 of 1326 symptomatic children (1:25) were EMA positive (Table 3). Abdominal pain, diarrhea, and constipation were among the most frequently reported symptoms (**Table 5**). However, only 35% of newly diagnosed patients with CD had chronic diarrhea, while a large percentage had extraintestinal symptoms. When minority populations were considered separately, the prevalence of CD was similar (1:48 among blacks, 1:44 among Asians, and 1:66 among Hispanics).

#### NOT-AT-RISK SUBJECTS

The serologic criteria for the diagnosis of CD were met in 27 of 2845 not-at-risk adults (1:105) and 4 of 1281 children (1:320) (Fisher exact test  $P=.03$ ; Table 3). Of these 31 EMA-positive subjects, 7 (30%) underwent small bowel biopsy. All biopsy specimens revealed a lesion consistent with CD (Table 3). The overall prevalence of CD among minority groups was 1:236.

#### LOGISTIC REGRESSION ANALYSIS

Results of univariate and multivariate logistic regressions are summarized in **Table 6**. In the unadjusted models, first-degree relatives of patients with CD (OR, 1.8; CI, 1.2-2.6) and subjects with symptoms of disease (OR, 2.1; CI, 1.6-2.7) carried a higher risk of CD. In the overall adjusted model (which included degree of relatedness, sex, and adults vs children), first-degree relatives carried a higher risk of CD than second-degree relatives (OR, 1.7; CI, 1.2-2.5). By contrast, female sex (OR, 1.0; CI, 0.7-1.3;  $P=.75$ ), presence of symptoms (OR, 1.2; CI,

0.9-1.6;  $P=.25$ ), and adult status (OR, 1.2; CI, 0.8-1.6;  $P=.34$ ) did not reach statistical significance. Removal of the latter 3 factors did not significantly affect the model (likelihood ratio statistic,  $P=.50$ ). A subanalysis including only nonrelatives of patients with CD revealed that the presence of symptoms significantly predicted CD positivity (OR, 2.1; CI, 1.6-2.7;  $P<.001$ ); neither sex (OR, 1.0) nor age (OR, 1.0) attained significance. Compared with the South, 2 geographic regions had higher CD prevalence: the West (OR, 1.7; CI, 1.03-2.7) and the Northeast (OR, 1.6; CI, 1.1-2.4).

#### COMMENT

The present report describes the largest multicenter epidemiologic study ever performed to establish the prevalence of CD in the United States in at-risk and not-at-risk groups. Our findings represent the best approximation of the prevalence of CD in the United States. The 2 epidemiologic studies previously performed in the United States showed an extremely low prevalence of CD.<sup>14,15</sup> However, both studies failed to consider the protean clinical manifestations of the disease, including atypical and silent forms that were frequently detected in our study. Furthermore, the previous 2 reports were local surveys, while our epidemiologic screening included 32 states.

Our findings suggest that CD is a much greater problem in the United States than has previously been appreciated. We found the prevalence of the disease to be similar to that reported in Europe,<sup>3,5,27,28</sup> ranging from 4.54% among first-degree relatives of patients with CD to 0.75% in the not-at-risk subjects. The prevalence of CD was as high in first- and second-degree relatives without symptoms as in relatives with symptoms, highlighting the importance of genetic predisposition as a risk factor for CD. In nonrelatives, the presence of symptoms significantly increased the risk of CD. Of particular interest is the high prevalence of CD found among individuals affected by numerous common disorders, including type 1 diabetes mellitus, anemia, arthritis, osteoporosis, infertility, and Down syndrome, even in the absence of gastrointestinal symptoms. Among not-at-risk subjects, the prevalence of CD in adults was significantly higher (1:105) than in children (1:320), suggesting a correlation between the duration of gluten exposure and the development of an immune response to gluten in genetically susceptible individuals. When considered as overall groups, children had a slightly higher CD prevalence than adults (Table 1). This increased prevalence in children may reflect sampling disparities in that fewer than one third of subjects were in the not-at-risk group, where sampling error in the modest number of positives might have affected the OR.

One limitation of the present study is the lack of random sampling of the population. Inclusion of relatives attending CD support group meetings could have introduced a bias toward enrichment for the disease by attracting symptomatic subjects. However, the number of symptomatic and asymptomatic relatives screened was similar, and the prevalence of CD in relatives was independent of the presence of symptoms (Table 4).

The lack of confirmation of the diagnosis by means of an intestinal biopsy in all EMA-positive subjects rep-

resents another potential limitation of the study. We estimated the prevalence of CD by assuming that all EMA-positive subjects who also were hTTG positive and HLA compatible had CD. This assumption is supported by previous studies<sup>29,30</sup> and by our observation that all EMA-positive subjects who underwent intestinal biopsy had a lesion consistent with CD. We also found no significant difference in symptoms and HLA haplotypes between the EMA-positive subjects who had the diagnosis confirmed by intestinal biopsy and those who did not.

The study may have underestimated the prevalence of CD owing to the less than 100% sensitivity of the IgA EMA test. Another potential limitation of our study is the low proportion of subjects belonging to ethnic or racial minorities. However, our data suggest the prevalence of CD in these groups may be similar to that of whites. Additional large-scale studies that use random sampling and include proportional representation of minority groups in the United States are warranted to confirm our findings.

If CD is as common in the United States as our study suggests, one must question why it is not diagnosed more frequently. Foremost among the possible explanations is that if physicians believe that CD is rare, they are less likely to test for it. A failure by physicians to appreciate that many individuals with the disease initially present without gastrointestinal symptoms is another reason why CD testing may not be performed. Use of only the more widely known but less sensitive and less specific AGA serologic test instead of EMA and hTTG tests<sup>16,21</sup> could also result in missed diagnoses. Even when gastrointestinal symptoms are present and a gastrointestinal endoscopy is performed, endoscopists do not always obtain intestinal biopsy specimens that could demonstrate the presence of CD. Finally, failure by pathologists to recognize early features of CD (Marsh stages 1, 2, and 3a<sup>24</sup>) could be a significant problem in the United States. Our study suggests that a minority of patients (34%) will have the classic flat mucosa, while most have various degrees of partial villous atrophy that could be misinterpreted by those unfamiliar with the architectural changes found in the early stages of the disease.

In the present study, physicians or insurance companies denied payment for an intestinal biopsy in 21% of EMA-positive patients, claiming that the costs of this procedure were not justified by the symptoms. This attitude probably reflects the lack of appreciation of the magnitude of the problem in the United States and the potential consequences of a delayed diagnosis.<sup>31,32</sup> Furthermore, a recently published survey of 1612 patients with CD in the United States revealed that the average gap between the onset of symptoms and the time CD diagnosis was confirmed was 11 years.<sup>33</sup>

In conclusion, we have undertaken the first large multicenter CD epidemiologic screening study in the United States. Our results suggest that CD occurs frequently not only in patients with gastrointestinal symptoms, but also in first- and second-degree relatives and patients with numerous common disorders even in the absence of gastrointestinal symptoms. The prevalence of CD in symptomatic patients and not-at-risk subjects was similar to that reported in Europe. Given the high mor-

bidity and mortality related to untreated CD<sup>31,34-36</sup> and the prolonged delay in diagnosis in the United States,<sup>33</sup> serologic testing of at-risk patients (ie, case finding) is important to alleviate unnecessary suffering, prevent complications, and improve the quality of life of a multitude of individuals with CD.

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