

Cost Effectiveness of Routine Duodenal Biopsy Analysis for Celiac Disease During Endoscopy for Gastroesophageal Reflux

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BACKGROUND & AIMS: Some patients with refractory gastroesophageal reflux disease (GERD) actually have undiagnosed celiac disease. These patients often undergo an esophagogastroduodenoscopy (EGD) to determine the etiology and severity of GERD. Performing routine duodenal biopsy analysis during an EGD could identify patients with celiac disease. We evaluated the cost effectiveness of this approach.

METHODS: We performed a systematic search of the MEDLINE database to identify publications through March 2014 on patients who underwent a duodenal biopsy analysis during an EGD for GERD. Data collected were used to construct a decision tree to calculate the cost effectiveness of an EGD with and without celiac disease tests.

RESULTS: Among 10,000 patients with refractory GERD who underwent an EGD, we predicted a biopsy strategy would detect 70% of patients with celiac disease if the prevalence of celiac disease was 1% in this cohort. Biopsy analysis at the start of the EGD procedure would increase the remaining quality-adjusted life years (QALYs) by 0.0032, and increase the lifetime cost by \$389/patient. Compared with no biopsy, the biopsy strategy cost \$55,692.86/case of celiac disease detected, and \$121,875/QALY gained. The incremental cost-effectiveness ratio for the biopsy strategy met the threshold of less than \$50,000/QALY when 1 of the following parameters was met: when the utility of living with GERD was less than 0.88, when the prevalence of celiac disease in patients with refractory GERD was greater than 1.8%, when biopsy analysis detected celiac disease with more than 98.1% specificity, when the cost of a gluten-free diet was less than \$645.85/y, or if the cost of proton pump inhibitor therapy was more than \$5874.01/y.

CONCLUSIONS: Based on base-case values, it is not cost effective to perform a biopsy analysis to detect celiac disease in patients undergoing an EGD for refractory GERD. However, the approach becomes cost effective when the prevalence of celiac disease in this population is 1.8% or greater.

Keywords: ICER; PPI; Antibody; Screening.

Celiac disease (CD) is an autoimmune disorder precipitated by dietary gluten in genetically susceptible individuals,¹ and occurs in approximately 1% of the general population worldwide.² Although the prevalence of CD has been increasing over time,³⁻⁵ the majority of patients remain undiagnosed.^{6,7} In the United States, only 17% of patients with CD are diagnosed.⁸ Among those with known CD, symptoms were present for a mean of 11 years before diagnosis.⁹ A gluten-free diet (GFD) usually results in marked improvement of symptoms. In 77% of celiac patients surveyed, quality of life improved after diagnosis.⁹

Unsuspected CD is sometimes detected when villous atrophy is recognized on duodenal biopsy during an esophagogastroduodenoscopy (EGD) performed for a variety of indications.¹⁰ In adults, EGD is performed for refractory gastroesophageal reflux disease (GERD) to

determine its etiology when proton pump inhibitors (PPIs) do not relieve symptoms. CD patients often report GERD symptoms, but the frequency of these symptoms is unclear.¹¹⁻¹³ Nevertheless, a GFD can be an effective treatment in these patients and reduces the relapse rate of GERD symptoms.¹⁴⁻¹⁶

Even though EGD often is performed in undiagnosed CD patients presenting with refractory GERD, a duodenal

Abbreviations used in this paper: CD, celiac disease; CPT, Current Procedural Terminology; DGP, deamidated gliadin peptide antibodies; EGD, esophagogastroduodenoscopy; EMA, endomysial antibodies; GERD, gastroesophageal reflux disease; GFD, gluten-free diet; ICER, incremental cost-effectiveness ratio; PPI, proton pump inhibitor; QALY, quality-adjusted life-year; tTG, tissue transglutaminase antibodies.

biopsy specimen is not obtained routinely, resulting in a potential missed opportunity for diagnosing CD.¹⁷ In one study, 13.6% of patients later diagnosed with CD had an EGD performed within the previous 5 years but no duodenal biopsy specimen had been taken at the time.¹⁸ In another study of 17 patients with CD who previously had undergone an EGD, GERD was the second most common indication for the prior EGD ($n = 4$; 24%), after dyspepsia.¹⁷ Because patients with refractory GERD often undergo an EGD, this procedure provides an opportunity to obtain duodenal biopsy specimens to establish the diagnosis of CD.

We aimed to estimate the potential clinical and economic consequences of routine duodenal biopsy for diagnosing CD in patients with refractory GERD undergoing EGD. We developed a decision-analysis model to study the number of CD cases that might be uncovered by this strategy, the associated gains in quality-adjusted life-years (QALYs), and the cost per case detected and QALY gained.

Methods

We constructed a decision-analysis model (using TreeAge Pro Version 2014, TreeAge Software, Inc, Williamstown, MA) to estimate the clinical and economic consequences of adding a duodenal biopsy for diagnosing CD compared with no biopsy in patients undergoing EGD for the evaluation of refractory GERD. The target population was a cohort of 10,000 adults from the US population, with an age of 40 years. Because the screen-detected prevalence of CD has not been shown to vary by sex in the United States, we did not differentiate between men and women in this model.^{19–21} The time horizon of this analysis was the remaining estimated lifespan of 40-year-old adults.²²

In our cost-effectiveness analysis comparing the routine duodenal biopsy strategy with the no-biopsy strategy, the outcomes of interest were the number of CD cases detected, QALYs gained, and the incremental cost-effectiveness ratio (ICER). We calculated the ICER from the additional expected cost and QALYs. All future costs and life years were discounted at a rate of 3% per year.

Data Source

We performed a systematic search of MEDLINE database to identify English language publications through March 2014 using the following terms: celiac disease, gastroesophageal reflux disease (GERD), prevalence, sensitivity, specificity, serological tests, deamidated gliadin antibodies (DGP IgA and IgG), endomysial antibodies (EMA IgA), tissue transglutaminase antibodies (tTG IgA and IgG), CD genotyping (HLA-DQ), esophagogastroduodenoscopy (EGD), duodenal biopsy, GFD, PPI medication, quality of life, utility, quality-adjusted

life-years (QALYs), cost, cost-effectiveness analysis. All relevant publications were retrieved and pertinent data were extracted. Costs were derived from published literature and other sources as noted later.

Base-Case Patient

The base-case patient was a 40-year-old with a history of typical GERD symptoms including substernal burning and/or regurgitation unresponsive (refractory) to twice-daily PPIs. No prior testing with an EGD, ambulatory esophageal pH testing, or esophageal manometry were performed. The patient consumed a regular diet. The base-case values and ranges used in the sensitivity analysis are presented in Table 1. Variable estimates were based on published data, and we systematically biased our analysis in favor of the no-biopsy strategy.

Decision-Analysis Model

A decision-analysis model was constructed to focus on 2 strategies in patients with refractory GERD undergoing an EGD: no duodenal biopsy or duodenal biopsy (Figure 1). Whether undergoing a biopsy or not, the patient may or may not have underlying CD. If the biopsy results were positive for CD, a panel of antibodies (tTG IgA, DGP IgA, EMA IgA, and, if IgA deficient, IgG antibodies of tTG and DGP) would be collected to confirm the diagnosis and to establish a baseline for future comparisons. If CD were confirmed by these 2 methods, the patient would be placed on a GFD, but the patient may or may not adhere to the diet. Even with adherence to the diet, the patient's GERD symptoms may or may not improve or recur. We assumed that PPIs would be discontinued if symptoms resolved on a GFD, and that PPIs would be continued if symptoms did not improve, recurred, or if the patient did not adhere to the GFD. If the biopsy results were positive for CD, but the panel of antibodies did not indicate CD or were indeterminate, genotyping of the HLA-DQ locus would be performed. CD only develops in patients who are genetically susceptible by carrying alleles that encode for HLA-DQ2 or HLA-DQ8 proteins.²³ HLA genotyping in biopsy-positive but antibody-negative individuals would be particularly useful for excluding CD. The practice of performing HLA testing in the event of discordance between histology and serology is in accordance with clinical guidelines.²⁴

Clinical Variables and Assumptions

Prevalence of celiac disease. The prevalence of CD in patients with refractory GERD was not well established in the literature. The study published by Ludvigsson et al¹¹ showed the highest prevalence at 2%, whereas the study published by Collin et al²⁵ showed the lowest prevalence at 0.6%. We conservatively decided to use

Table 1. Inputs in Decision Analysis Model

	Base-case value	Range	References
Clinical variables			
Age, y	40		
Remaining lifetime, y	40	38–42	22
Prevalence of CD in patients with refractory GERD undergoing an EGD	0.01	0.003–0.025	11, 25, 46
Probability of GERD recurrence on GFD (no improvement)	0.2	0.07–0.80	15, 16
Probability of adhering to GFD for 40 years	0.6	0.42–0.91	15, 26
Prevalence of HLA DQ2/DQ8	0.37		47
Testing parameters			
Sensitivity of biopsy	0.700	0.558–1.000	28, 29
Specificity of biopsy	0.950	0.817–0.991	28
Sensitivity of celiac serologic tests	0.951	0.918–0.981	27
Specificity of celiac serologic tests	0.983	0.971–0.996	27
Utilities			
Refractory GERD	0.94	0.85–0.99	32, 33
CD on a GFD	0.98	0.95–0.985	34, 35
Costs, \$			
Cost of biopsy and tissue examination by pathologist	130.00	36.47–224.39	36
Cost of celiac serologic tests	75.00	47.37–101.00	31, 37
Cost of HLA typing	555.80		31, 37
Cost of PPIs per year	3000.00	2945.76–8043.84	48
Cost of GFD per year	1269.00	56.00–2480.00	16, 39–41

1% (0.3%–2.5% for sensitivity analysis), which is the prevalence of CD in the general population (ie, no increased prevalence of CD in this population of GERD patients) to favor the no-biopsy strategy.

Adherence to a gluten-free diet. The definition of adherence varies widely from different studies, and the method used to collect this information also varies. Based on a literature review by Hall et al,²⁶ the rate of strict adherence ranges from 42% to 91%. In the study by Usai et al,¹⁵ 80% of CD patients adhered strictly to the GFD after 2 years. We used a 60% adherence rate to account for the long time horizon of 40 years in our study.

Recurrence of gastroesophageal reflux disease symptoms. GERD symptoms may recur even in patients with a strict GFD, and the literature on the topic of response of GERD symptoms to a GFD is sparse. In the study by Nachman et al,¹⁶ 2 of 28 CD patients (7%) with strict dietary compliance reported GERD symptoms 4 years after diagnosis. At the other end, Usai et al¹⁵ reported a 20% recurrence rate after 6 months of strict dietary control in CD patients. We used a 20% (7%–80% for sensitivity analysis) recurrence rate to bias toward the no-biopsy strategy.

Diagnostic Testing Parameters

Small intestinal mucosal biopsy is still the gold standard for diagnosing CD despite the availability and convenience of serologic tests. However, we were cautious to assign a high sensitivity for our base case because the accuracy of the biopsy relies on multiple factors, including the number of biopsy samples obtained, the

location of the biopsies, and the quality of the samples.^{27,28} The disease does not affect the small intestine uniformly, and endoscopic markers also have poor sensitivity at locating the diseased tissues, especially in patients with patchy villous atrophy.^{29,30} The specificity of biopsy is reported to be higher (95%).²⁸

For our panel of serologic tests, we included tTG IgA and IgG, DGP IgG and IgA, EMA IgA, and quantitative IgA to exclude IgA deficiency. We assumed the serologic tests would be conducted in a step-wise fashion to minimize cost, starting with quantitative IgA followed by tTG IgA or IgG, depending on the result of the previous test. DGP IgG or IgA and EMA IgA will be used only if the tTG results were weakly positive.³¹ We chose to use 95.1% and 98.3% for the sensitivity and specificity, respectively, of serologic tests.²⁷

Quality of Life

There are limited data on the quality of life in GERD and treated CD, although 2 studies investigated the former^{32,33} and 1 study investigated the latter.³⁴ For cost-effectiveness analysis, the utility of these diseases are used, using a scale from 0 (total impairment) to 1 (full health). Gerson et al³² used time trade-off and standard gamble techniques to measure utility in chronic GERD patients on medications (85% on PPIs, 48% on twice-daily PPIs). The utility was found to be 0.94 with either technique, and this value was used in our base-case analysis. Ethiopia et al³³ conducted a similar study that resulted in a utility of 0.90 and 0.97 using time trade-off and standard gamble techniques, respectively. For our sensitivity analysis, we used a wide range of 0.85

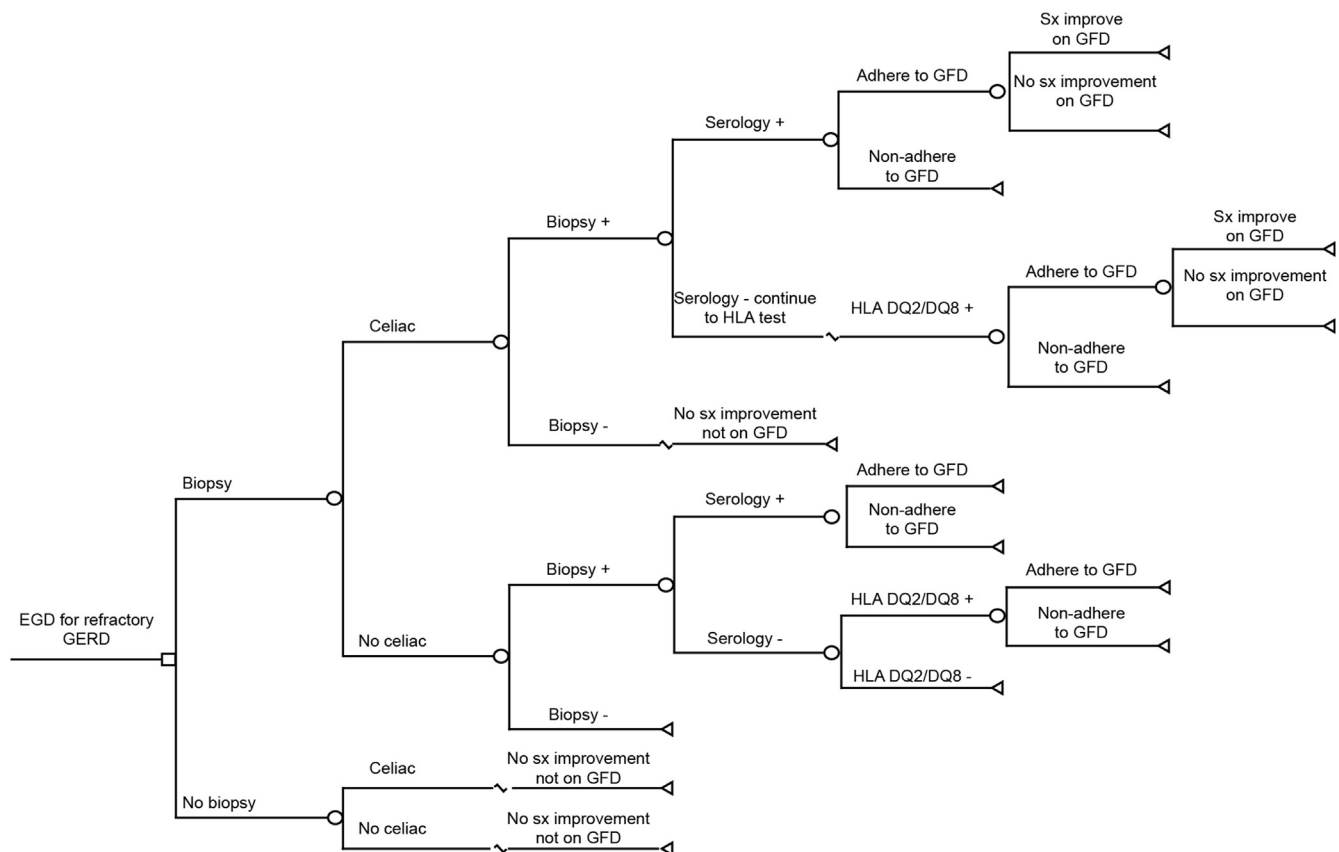


Figure 1. Schema of the decision tree for biopsy vs no biopsy in patients with refractory GERD undergoing EGD. Sx, symptom.

to 0.99. For the utility of CD on GFD, we used 0.98 with a range of 0.95 to 0.985 for sensitivity analysis, the same numbers that were used previously in the cost-effectiveness study by Herscovici et al,³⁵ which were derived from quality-of-life scores obtained from a questionnaire of treated CD patients.³⁴

Costs

Costs were derived from published literature and 2014 Medicare data. We used the average payments for each coded procedure based on the 2014 Medicare Physician Fee Schedule,³⁶ and laboratory tests were based on the 2014 Clinical Diagnostic Laboratory Fee Schedule.³⁷ There are no available data comparing the costs of GERD and CD care. We assumed that the medical costs for treated CD were the same as the costs for GERD care. If symptomatic improvement on a GFD lead to less resource utilization, or if refractory GERD patients needed more diagnostic tests, then our assumption about the cost of chronic care would bias toward the no-biopsy strategy.

For the cost of biopsy, we used the difference between the reported average payment of endoscopy with biopsy (Current Procedural Terminology [CPT] code 43239) and that of endoscopy without biopsy (CPT code 43235). We also added the cost of tissue examination by a pathologist (CPT code 88305). We did not include the

cost associated with increased procedure time to perform the duodenal biopsy, or increased risk (eg, hemorrhage) given the very low incremental morbidity of duodenal biopsy among patients (particularly adults) already undergoing an EGD.³⁸

For the cost of PPIs, we used average wholesale pricing available on Lexi-Comp (Hudson, OH). For our base case, we used the cost of twice-daily dosing of generic pantoprazole (lowest cost of all PPIs available) for chronic use (40 years). In our sensitivity analysis, we included the cost of name brand PPIs on the market.

The additional cost of the GFD compared with a regular diet was calculated based on data from the US Department of Agriculture.¹⁶ We assumed that a CD patient would consume 10% to 20% gluten-free grains compared with the recommended 30% by the US Department of Agriculture.³⁹ The cost of gluten-free products was reported to be 1.3 to 4.2 times higher than their counterparts.^{40,41} We calculated that a patient with CD would spend, on average, \$1268 more for a GFD per year. We extrapolated that for 40 years.

Outcomes, Cost Effectiveness, and Sensitivity

The main outcomes evaluated in the model were the number of CD patients diagnosed in the biopsy arm, costs accrued over their lifetime, and QALYs. We

calculated the ICER by dividing the additional cost of the biopsy arm by the difference in effectiveness (measured by QALYs). We performed 1-way sensitivity analyses to evaluate the effects of varying costs and probabilities over ranges derived from the available literature. All costs are reported as 2014 US dollars.

Results

Base-Case Analysis

The results from the base-case analysis are shown in [Table 2](#). We found that the biopsy strategy detected 70 of 100 celiac patients in the cohort of 10,000 refractory GERD patients undergoing an EGD if the prevalence of CD was 1% in this cohort; the number of patients needed to biopsy to identify 1 CD patient therefore was 143. Without a biopsy, the average 40-year-old patient with refractory GERD would have a remaining quality-adjusted discounted life expectancy of 22.3800 QALYs. An up-front biopsy would increase the QALYs to 22.3832. The discounted lifetime cost of caring for refractory GERD without biopsy was \$71,425 per patient. Testing for CD starting with a biopsy would increase the lifetime cost to \$71,816 per patient, a 0.55% increase. Compared with no biopsy, the biopsy strategy cost \$55,692.86 per celiac case detected, and \$121,875 per QALY gained.

One-Way Sensitivity Analyses

A 1-way sensitivity analysis was performed on all variables in the model and shown using the Tornado diagram ([Figure 2](#)). This analysis showed that the model results were sensitive to the following variables: utility of GERD, prevalence of CD in refractory GERD patients, specificity of biopsy, cost of GFD, and cost of PPI therapy. The ICER met the threshold of less than \$50,000 per QALY for the biopsy arm when one of the following conditions was met: the utility of living with GERD was less than 0.88, the prevalence of CD in refractory GERD patients was greater than 1.8%, the specificity of biopsy was greater than 98.1%, the cost of a GFD was less than \$645.85 per year, or when the cost of PPI therapy was greater than \$5874.01 per year.

Discussion

Because of its protean and subtle symptoms, the diagnosis of CD is challenging and often delayed. Because the majority of CD patients remain undiagnosed despite the availability of easy and accurate serologic tests and an effective treatment by diet modification, additional approaches are warranted to identify more undiagnosed patients when they present in a health care setting.

The relationship between GERD and CD has led to calls for CD screening in patients with GERD symptoms.^{14,25,42} Green and Murray⁴³ also have proposed routine duodenal biopsies in all patients undergoing a diagnostic EGD. Despite the unclear mechanistic relationship between GERD and CD, patients with refractory GERD often undergo an EGD, providing an opportunity for duodenal biopsy that potentially can lead to a CD diagnosis.

We developed a decision-analysis model to evaluate the potential clinical benefits and the associated costs of routine duodenal biopsy in refractory GERD patients undergoing EGD in the common scenario in which CD serology has not yet been performed at the time of the EGD. Our results suggest that routine biopsy during EGD can uncover the majority of cases of CD in a population of patients with refractory GERD at a cost of \$55,692 per case. The resultant improvement in quality of life could be achieved at a cost that was approximately 2.5 times the upper limit set at \$50,000. However, our model indicated that routine biopsy could be a cost-effective approach in this specific population of patients because the ICER was sensitive to a number of factors in the model. For example, we conservatively estimated a prevalence of CD in this group of symptomatic individuals with GERD to be 1% (ie, not greater than that of the general population). On sensitivity analysis the ICER met criteria for cost effectiveness when the prevalence of CD among patients undergoing an EGD for GERD was 1.8%, which has been reported in Sweden.¹¹ Although less is known regarding the response of GERD symptoms to the GFD, our sensitivity analysis showed that this variable did not impact cost effectiveness across a wide range of estimates.

There were several limitations to our study. Our model assumed that those patients with CD who did not undergo a biopsy or who did undergo a biopsy but were not diagnosed with CD would never get diagnosed with CD for the remainder of their lives. We also assumed that

Table 2. Base-Case Analysis of Performing a Biopsy or Not During an EGD of Refractory GERD Patients

Strategy	Cost	Incremental cost	Effectiveness	Incremental effectiveness	Cost/effectiveness	Incremental cost/effectiveness
No biopsy	\$71,425.00		22.3800		\$3197.47	
Biopsy	\$71,814.85	\$389.85	22.3832	0.0032	\$4208.43	\$121,875.34

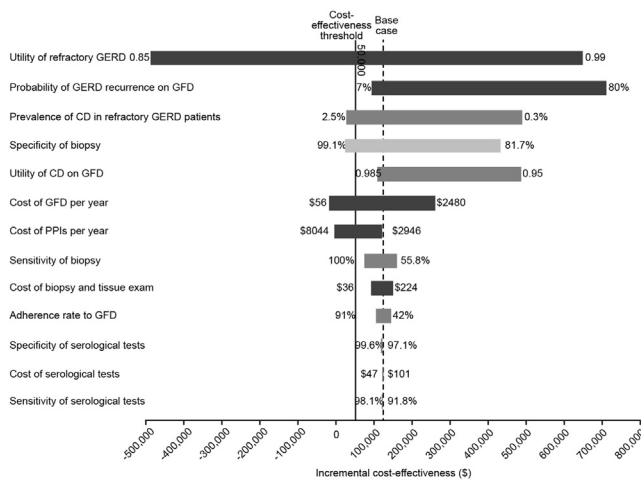


Figure 2. Tornado diagram showing results from 1-way sensitivity analysis.

all patients with GERD symptoms would require twice-daily PPI therapy for the remainder of their lives. Both of these limitations can be addressed in future studies using a state transition Markov model. Inherent to any decision-analysis model, uncertainties on the precise values of some inputs required us to make some assumptions. However, our study used conservative estimates throughout the decision analysis by biasing toward the no-biopsy strategy. Through sensitivity analysis using wide ranges, we identified critical variables that would impact the final outcome and others that would not. Thus, these critical variables (eg, the prevalence of CD in the refractory GERD patient population, and the quality of life of living with refractory GERD) point out areas for future clinical investigation. Our model did not consider alternatives to universal duodenal biopsy during an EGD for GERD, such as point-of-care serologic testing for CD,⁴⁴ or biopsy depending on endoscopic findings (eg, water immersion).⁴⁵ Such an approach might move the ICER toward cost effectiveness, although the imperfect sensitivities of these techniques may lead to undiagnosed individuals. We did not include proposed deleterious consequences of long-term PPI use such as osteoporosis or pneumonia owing to uncertainty of risk and to keep the model parsimonious. Our model likewise did not include the impact of a repeat EGD (performed to document villous healing in CD patients or to investigate persistent GERD symptoms regardless of CD status) because there is great uncertainty (and therefore variability among practitioners) regarding whether and when to repeat an EGD in patients with GERD, and there also is uncertainty regarding the role of routine follow-up biopsy in patients with CD.²⁴

In conclusion, a routine duodenal biopsy can detect the majority of CD cases present in a population of patients with refractory GERD undergoing EGD. This strategy approaches cost-effectiveness thresholds when the prevalence of CD in this population is slightly greater than that of the general population, even with a modest

improvement in quality of life on GFD. Further research should focus on determining the true prevalence of CD in patients with refractory GERD, and the quality of life of living with refractory GERD vs CD maintaining a GFD.

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Reprint requests

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Conflicts of interest

The authors disclose no conflicts.

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