Published in final edited form as:

Clin Gastroenterol Hepatol. 2015 August ; 13(8): 1437–1443. doi:10.1016/j.cgh.2015.03.022.

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

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Abstract

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

Methods—We performed a systematic search of MEDLINE database to identify publications through March 2014 on patients who were 40 years old and underwent duodenal biopsy analysis during EGD for GERD. Data collected were used to construct a decision tree to calculate cost effectiveness of EGD with and without celiac disease tests.

Results—Among 10,000 patients with refractory GERD who underwent 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

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Disclosures: all authors declare that they have no conflicts of interest and nothing to declare.

Details of ethics approval: This project did not require ethics approval.

Guarantor of the Article: Benjamin Lebwohl, MD, MS

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Acquisition of data: JJY, AT, BL

Analysis and interpretation of data: JJY, AT

Drafting of the manuscript: JJY

Critical revision of the manuscript for important intellectual content: JJY, PHRG, BL

Study supervision: BL, PHRG

All authors approve the final manuscript submitted and they approve the authorship list.

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\$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 <\$50,000/QALY when 1 of the following parameters were met: when the utility of living with GERD was <.88, when the prevalence of celiac disease in patients with refractory GERD was >1.8%, when biopsy analysis detected celiac disease with >98.1% specificity, when the cost of a gluten-free diet was <\$645.85/y, or if the cost of proton pump inhibitor therapy was >\$5874.01/y.

Conclusion—Based on base-case values, it is not cost effective to perform biopsy analysis to detect celiac disease in patients undergoing 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

celiac disease; gastroesophageal reflux; cost-effectiveness; duodenal biopsy; ICER; PPI; antibody; screening

INTRODUCTION

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 esophagogastroduodenoscopy (EGD) performed for 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 is often performed in undiagnosed CD patients presenting with refractory GERD, duodenal biopsy is not routinely obtained, 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 five years but no duodenal biopsy had been taken at the time.¹⁸ In another study of 17 patients with CD had previously undergone EGD, GERD was the second most common indication for the prior EGD (n=4, 24%), after dyspepsia.¹⁷ Since patients with refractory GERD often undergo 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, USA) to estimate the clinical and economic consequences of adding duodenal biopsy for diagnosing CD compared with no biopsy in patients undergoing EGD for the evaluation of refractory GERD. The target population is a cohort of 10,000 adults from the United States population at the age of 40 years. Because the screen-detected prevalence of CD has not been shown to vary by gender in the United States, we did not differentiate between men and women in this model.^{19–21} The time horizon of this analysis is the remaining estimated lifespan of 40-year-old adults²².

In our cost-effectiveness analysis comparing the routine duodenal biopsy strategy to 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 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 extracted. Costs were derived from published literature and other sources as noted below.

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 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 two strategies in patients with refractory GERD undergoing EGD: no duodenal biopsy, and duodenal biopsy (Figure 1). Whether biopsied 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 two 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 HLA-DQ locus would be performed. CD only develops in those who are genetically susceptible by carrying alleles that encode for HLA-DQ2 or HLA-DQ8 proteins²³. 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 CD—The prevalence of CD in patients with refractory GERD was not well established in literature. The study published by Ludvigsson et al¹¹ showed the highest prevalence at 2%, while the study published by Collin et al²⁵ showed the lowest prevalence at 0.6%. We conservatively decided to use 1% (0.3 – 2.5% for sensitivity analysis) which is the prevalence of CD in the general population (i.e. no increased prevalence of CD in this population of GERD patients) so as to favor the no-biopsy strategy.

Adherence to GFD—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 60% adherence rate to account for the fact that the time horizon of our study was 40 years, much longer than previously studied.

Recurrence of GERD 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 out 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 20% (7 – 80% for sensitivity analysis) recurrence rate to bias towards 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 serological tests. However, we were cautious at assigning 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 serological tests, we included tTG IgA and IgG, DGP IgG and IgA, EMA IgA, and quantitative IgA to exclude IgA deficiency. We assumed the serological 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 only be used if the tTG results were weakly positive.³¹ We chose to use 95.1% and 98.3% for the sensitivity and specificity of serological tests.²⁷

Quality of Life

There are limited data on the quality of life in GERD and treated CD, though two studies investigated the former^{32,33} and one investigated the latter.³⁴ For cost-effectiveness analysis, utility of these diseases are used, using a scale from 0 (total impairment) to 1 (full health). Gerson et al³² used time-tradeoff 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 a utility of 0.90 and 0.97 using time-tradeoff and standard-gamble respectively. For our sensitivity analysis, we used a wide range of 0.85 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 previously used in the cost-effectiveness study by Hershcovici 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 lab 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 leads to less resource utilization, or if refractory GERD patients need 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 (CPT code 43239) and that of without biopsy (CPT code 43235). We also added the cost of tissue exam 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 (e.g. hemorrhage) given the very low incremental morbidity of duodenal biopsy among patients (particularly adults) already undergoing EGD.³⁸

For the cost of PPIs, we used average wholesale pricing available on Lexi-Comp. 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 brand PPIs on the market.

The additional cost of the GFD compared to a regular diet was calculated based on data from the United States Department of Agriculture (USDA).¹⁶ We assumed that a CD patient consumes 10–20% gluten-free grains compared to the recommended 30% by the USDA.³⁹ The cost of gluten-free products was reported to be 1.3 to 4.2 times higher than their counter parts.^{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 the life-time, 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 one-way sensitivity analyses to evaluate the effects of varying costs and probabilities over ranges derived from available literature. All costs are reported as 2014 \$USD.

RESULTS

Base-case analysis

The results from the base-case analysis are shown in Table 2. We found that the biopsy strategy detected 70 out of 100 celiac patients in the cohort of 10,000 refractory GERD patients undergoing EGD if the prevalence of CD was 1% in this cohort; the number of patients needed to biopsy in order to identify one CD patient was therefore 143. Without biopsy, the average 40-year-old patient with refractory GERD would have a remaining quality-adjusted discounted life expectancy of 22.3800 QALYs. 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 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

One-way sensitivity analysis was performed on all variables in the model and demonstrated using the Tornado diagram (Figure 2). This analysis demonstrated 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 < \$50,000 per QALY for the biopsy arm when one of the following conditions was met: the utility of living with GERD was <0.88, the prevalence of CD in refractory GERD patients was >1.8%, the specificity of biopsy was >98.1%, the cost of GFD was <\$645.85 per year, or when the cost of PPI therapy was >\$5874.01 per year.

DISCUSSION

Because of its protean and subtle symptoms, the diagnosis of CD is challenging and often delayed. Since the majority of CD patients remain undiagnosed despite the availability of easy and accurate serological tests, and an effective treatment by diet modification,

additional approaches are warranted to identify more undiagnosed patients when they present in a healthcare 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 have also proposed routine duodenal biopsies in all patients undergoing diagnostic EGD. Despite the unclear mechanistic relationship between GERD and CD, patients with refractory GERD often undergo EGD, providing an opportunity for duodenal biopsy that can potentially lead to a CD diagnosis. To our knowledge, the diagnostic yield and the cost-effectiveness of this procedure have not been previously studied.

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 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 about 2.5 times the upper limit set at \$50,000. However, our model indicates that routine biopsy could be a cost-effective approach in this specific population of patients since 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%, i.e. 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 EGD for GERD was 1.8%, which has been reported in Sweden.¹¹ While 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 are several limitations to our study. Our model assumed that those patients with CD who did not get biopsies or who did get biopsied but not diagnosed with CD would never get diagnosed with CD for the remainder of their lives. We also assumed that all patients with GERD symptoms would require twice-daily PPI 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 (e.g. the prevalence of CD in 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 EGD for GERD, such as point-of-care serologic testing for CD,⁴⁴ or biopsy depending on endoscopic findings, e.g. water immersion.⁴⁵ Such an approach might move the ICER towards cost effectiveness, though 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 due to uncertainty of risk and so as to keep the model parsimonious. Our model likewise did not include the impact of repeat EGD (done 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 EGD in patients with GERD, and there is also uncertainty regarding the role of routine follow-up biopsy in patients with CD.²⁴

In conclusion, 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 above 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 versus CD maintaining a GFD.

Acknowledgments

Grant Support (Funding):

BL: The National Center for Advancing Translational Sciences, National Institutes of Health (UL1 TR000040)

Abbreviations used in this article

CD	celiac disease
DPG	deamidated gliadin peptide antibodies
EGD	esophagogastroduodenoscopy
EMA	endomysial antibodies
GERD	gastroesophageal reflux disease
ICER	incremental cost-effectiveness ratio
PPI	proton pump inhibitor
QALY	quality-adjusted life year
SF-36	Short-Form-36
tTG	tissue transglutaminase antibodies

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Figure 1.
Schema of the decision tree for biopsy versus no biopsy in patients with refractory GERD undergoing EGD

Figure 2.
Tornado diagram demonstrating results from one-way sensitivity analysis

Table 1

Inputs in decision analysis model

	Base-case value	Range	References
Clinical Variables			
Age (years)	40		
Remaining lifetime (years)	40	38 – 42	22
Prevalence of CD in patients with refractory GERD undergoing 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 serological tests	0.951	0.918 – 0.981	27
Specificity of celiac serological tests	0.983	0.971 – 0.996	27
Utilities			
Refractory GERD	0.94	0.85 – 0.99	32, 33
CD on GFD	0.98	0.95 – 0.985	34, 35
Costs (\$)			
Cost of biopsy and tissue exam by pathologist	130.00	36.47 – 224.39	36
Cost of celiac serological 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

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TABLE 2

Base-case analysis of performing a biopsy or not during 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