Testing for Celiac Sprue in Irritable Bowel Syndrome With Predominant Diarrhea: A Cost-Effectiveness Analysis

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Background & Aims: **Some patients with diarrhea-predominant irritable bowel syndrome (IBS-D) may have undiagnosed celiac sprue (CS). Because the symptoms of CS respond to a gluten-free diet, testing for CS in IBS may prevent years of morbidity and attendant expense. We sought to determine whether this might be a cost-effective diagnostic strategy in IBS-D.** ***Methods:*** **We used decision analysis to calculate the cost-effectiveness of 2 competing strategies in IBS-D: (1) start empirical IBS treatment and (2) perform serologic test for CS followed by endoscopic biopsy for positive tests. The base-case cohort had a CS prevalence of 3.4%, which was varied between 0% and 100% in sensitivity analysis. The outcome measure was cost per symptomatic improvement.** ***Results:*** **Under base-case conditions, testing for CS instead of starting empiric IBS therapy cost an incremental $11,000 to achieve one additional symptomatic improvement. Testing for CS became the dominant strategy when the prevalence of CS exceeded 8%, the specificity of CS testing exceeded 98%, or the cost of IBS therapy exceeded $130/month. The incremental cost-effectiveness of testing for CS exceeded $50,000 when the prevalence fell below 1%.** ***Conclusions:*** **Testing for CS in patients with IBS-D has an acceptable cost when the prevalence of CS is above 1% and is the dominant strategy when the prevalence exceeds 8%. The decision to test should be based on a consideration of the population prevalence of underlying CS, the operating characteristics of the screening test employed, and the cost of proposed therapy for IBS.**

Most patients with irritable bowel syndrome (IBS) have no detectable organic disease to account for their symptoms.[1,2] The symptom-based Rome criteria[3] for the diagnosis of IBS reliably exclude organic disease and have a positive predictive value of 98%.[4] Nonetheless, many clinicians remain unsettled by the prospect of overlooking alternative treatable diagnoses and instead perform a series of diagnostic tests that rarely alters the clinical impression.[1,2,5] This practice is supported by current professional society guidelines that recommend performing a limited battery of tests to exclude common organic diseases masquerading as IBS.[6,7] For example, the American Gastroenterological Association (AGA) suggests performing a serum chemistry panel, complete blood count, stool examination for ova and parasites, fecal occult blood test, erythrocyte sedimentation rate, and albumin level in patients with suspected IBS.[7] In contrast, a recent systematic review of the literature concluded that there is insufficient evidence to support any of these diagnostic tests in the diagnosis of IBS.[8] Because the pursuit of intermingled conditions is usually fruitless and expensive, the practice has been questioned.[5]

Testing for underlying celiac sprue (CS) may be an exception. Data indicate that up to 75% of patients with CS present with symptoms suggestive of IBS, including recurrent abdominal discomfort, bloating, or diarrhea in the absence of alarming symptoms and signs.[9] Because the symptoms of CS often respond to a gluten-free diet—a relatively inexpensive albeit burdensome treatment—testing for CS early in the management of diarrhea-predominant irritable bowel syndrome (IBS-D) may be cost-effective on the basis of preventing years of morbidity and attendant expense. Noninvasive serologic tests are available for diagnosing CS with a high degree of sensitivity and specificity. For example, the IgA anti-endomysial antibody (anti-EMA) and IgA antitissue transglutaminase antibody (anti-TTG) are reported to be up to 98% sensitive and 100% specific for CS.[10] Recent epidemiologic data indicate that CS is more prevalent in the United States than previously reported.[11] A series of

Abbreviations used in this paper: CS, celiac sprue; IBS-C, constipation-predominant irritable bowel syndrome; IBS-D, diarrhea-predominant irritable bowel sydrome.

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over 4000 asymptomatic subjects screened for CS found a prevalence of 1:133.[11] Moreover, data indicate that CS may be even more prevalent in patients with suspected IBS-D, as evidenced by a case-control study revealing that patients fulfilling the Rome II criteria are 7 times more likely to have histologically confirmed CS than matched controls.[12] Taken together, these data suggest that a "test and treat" strategy for CS in patients with IBS-D may be worthwhile.

The potential cost-effectiveness of testing for CS will likely depend on several epidemiologic variables, including the prevalence of underlying sprue in the target population of IBS-D (which will vary with patient demographic characteristics) and the sensitivity and specificity of CS diagnostic tests in IBS-D. The optimal diagnostic strategy will also vary in lockstep with provider behavior characteristics, including the proportion of clinicians that remember to test for CS in patients with persistently symptomatic IBS-D, the diagnostic delay time that elapses before testing ultimately occurs, and the cost and effectiveness of treatments selected for IBS. In light of the uncertainty surrounding the role of CS testing in IBS-D, we sought to determine whether and under what circumstances this might be a cost-effective diagnostic strategy in IBS-D. We therefore performed an economic analysis to estimate the cost-effectiveness of CS testing vs. empiric IBS therapy in the management of patients with Rome II-positive IBS-D symptoms. We performed the analysis from a third party payer perspective over a 10-year time horizon and based the analysis on a study hypothesis that empiric IBS therapy is more cost-effective than CS testing. We therefore systematically biased our model in favor of empiric IBS therapy and placed the burden of proof for cost-effectiveness on CS testing.

Materials and Methods

Decision Model Framework

Decision analysis is a quantitative method for estimating the financial costs and clinical outcomes of alternative strategies under conditions of uncertainty.[13] Using decision analysis software (DATA 4.0, TreeAge Software, Inc., Williamstown MA), we evaluated 2 strategies for the management of a hypothetical cohort of patients fulfilling the Rome II criteria for IBS-D. Patients with a history of gastrointestinal alarm symptoms (i.e., gastrointestinal bleeding, dysphagia, weight loss) or alarm signs (i.e., iron-deficiency anemia, occult blood positive stools) were not included in the analysis. We assumed that all patients entered the hypothetic model after demonstrating a normal serum chemistry panel, complete blood count, stool examination for ova and parasites, thyroid stimulating hormone level, erythrocyte sedimentation rate, and structural evaluation of the colon. We therefore limited our analysis to IBS patients without evidence of alternative organic diagnoses. On entering the model, patients either received empirical IBS therapy or underwent initial diagnostic testing for CS, as described below.

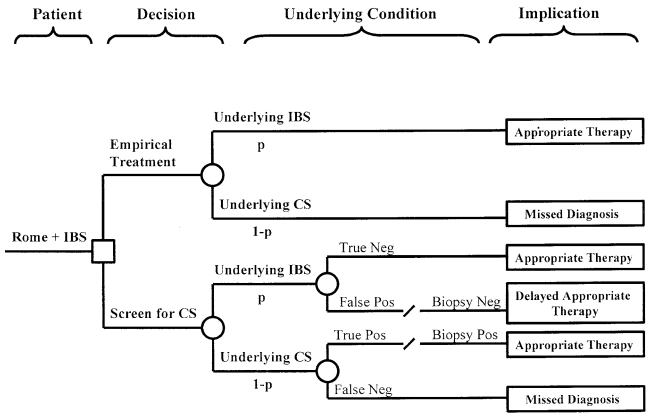

Figure 1. Truncated decision model. The base-case patient fulfills the Rome II criteria for irritable bowel syndrome (IBS) and has no alarming gastrointestinal symptoms or signs. The *square node* denotes a decision point at which the clinician may either treat with empirical therapy for presumed IBS or test for celiac sprue (CS). *Circular nodes* denote chance points that are governed by probabilities. The Bayesian tree accounts for the prevalence of underlying IBS (*p*) and CS (*1-p*), along with the sensitivity and specificity of diagnostic tests for CS. See text for details about individual strategies and for assumptions about downstream costs and effects (not represented in the Figure).

Figure 1 depicts a truncated version of the decision tree, which is designed to reflect the imperfections of diagnostic testing and the prevalence of underlying disease states in the hypothetical cohort. This Bayesian approach incorporates both the prevalence of underlying CS and the characteristics of the diagnostic tests (i.e., sensitivity and specificity). The initial decision between empirical IBS treatment and testing for CS is depicted by a square "decision node." In each strategy the patient has a probability of underlying IBS and a probability of underlying CS, which is governed by a circular "chance node." There are 2 possible results from empirical therapy: (1) IBS therapy is appropriately prescribed for underlying IBS, or (2) IBS therapy is inappropriately prescribed for underlying CS (i.e., missed diagnosis of CS). There are 4 possible results from CS testing: (1) IBS therapy is appropriately prescribed on a timely basis for underlying IBS as a result of a true negative diagnostic test, (2) IBS therapy is inappropriately delayed for underlying IBS as a result of a false positive diagnostic test leading to additional confirmatory testing (i.e., endoscopy with mucosal biopsy reveals no CS despite positive diagnostic test), (3) gluten-free diet is appropriately prescribed for underlying CS as a result of a true positive diagnostic test, or (4) IBS therapy is inappropriately prescribed for underlying CS as a result of a false-negative diagnostic test (i.e., missed diagnosis of CS).

We based our assumptions about patient and physician behavior on patient-centered outcomes rather than surrogate end points such as histologic abnormalities or mucosal healing rates. To capture the full range of downstream costs generated by each strategy, we included the ongoing cost of care associated with IBS and CS, including physician follow-up visits, treatment costs, and laboratory costs (see Cost Estimates section below), along with the probability of developing recurrent symptoms over the course of the 10-year model time horizon.

Competing Management Strategies

Empirical therapy. In this strategy, patients with Rome II–positive IBS-D were not tested for the presence of CS and instead began empiric treatment for presumed IBS. Because the objective of our analysis was to test the cost-effectiveness of CS testing alone rather than to test specific available therapies for IBS, we assumed that patients in this strategy received a generic standard therapy for IBS in lieu of a specific named treatment (i.e., antidiarrheals, antidepressants, tegaserod, dynamic psychotherapy, fiber, and others). To model the spectrum of available therapies for IBS, we performed sensitivity analysis over a wide range of cost and effectiveness estimates derived from a systematic review of the medical literature (see below). Patients rendered asymptomatic with generic IBS therapy were followed clinically, and those with persistent or relapsing symptoms despite IBS therapy received further treatment for IBS. The clinical probability estimates governing this strategy are described in the Model Assumptions section below.

CS testing. All patients in this strategy received an initial serologic diagnostic test for CS. Because the objective of our analysis was to investigate the cost-effectiveness of CS testing in general rather than to test specific screening tests, we assumed that patients in this strategy received a generic diagnostic test in lieu of a specific named test (i.e., anti-gliadin antibody, anti-EMA antibody, anti-TTG antibody). To model the spectrum of available diagnostic test for CS, we performed sensitivity analysis over a wide range of sensitivity, specificity, and cost estimates (see below). All patients with positive tests subsequently received a confirmatory upper endoscopy with small-bowel biopsy. We assumed that patients with a normal small-bowel biopsy had a false positive diagnostic test and underlying IBS, and those with an abnormal small-bowel biopsy (i.e., villous atrophy) had a true positive diagnostic test and underlying CS. We further assumed that a subset of patients had "latent" or "potential" CS (i.e., had the genetic susceptibility and symptoms of CS but a normal small bowel biopsy) that was undetectable by serologic testing (see Model Assumptions section below). Patients with histologically documented CS were prescribed a gluten-free diet. Noncompliance with the gluten-free diet was modeled using intention-to-treat analysis, as described below. Patients with symptomatic improvement remained on the gluten-free diet for the remainder of the analysis, and those with persistent symptoms were referred for second-line therapy. The clinical probability estimates governing this strategy are described in the Model Assumptions section below.

Data Sources

Our model incorporated 13 probability estimates derived from a systematic review of the medical literature (Table 1). We performed a structured search of published reports from the MEDLINE bibliographic database along with a CD-ROM-assisted (Digestive Disease Week Abstracts-on-Disc; AGA, Bethesda, MD) review of published abstracts to identify relevant English language publications from January 1980 to September 2003. When there was a range of data, we chose estimates that would tend to favor the empiric IBS therapy strategy and therefore biased the model against CS testing.

Model Assumptions

To systematically bias our analysis in favor of the empiric IBS therapy, we designed our model to support a study hypothesis that it is *not* cost-effective to test for CS in IBS-D. This "best case" model for empiric therapy was based on the following explicitly biased assumptions.

Assumptions regarding prevalence of CS in IBS. Our review identified 6 studies evaluating the prevalence of CS in patients with IBS symptoms (Table 2).[11,12,14–17] These studies vary in terms of their baseline patient population, country of origin, definition of IBS, and serologic testing used. None of the studies present results stratified by IBS subtype (i.e., diarrhea vs. constipation-predominant IBS). It is therefore difficult to determine whether the prevalence rates vary by subgroup. However, in the absence of stratified data there is a priori reason to believe that the prevalence of CS is highest in patients with IBS-D. For purposes of this analysis we therefore applied these data to IBS-D.

The mean prevalence of CS weighted by sample size among the 5 studies was 3.4%. The prevalence of CS in studies that relied on validated symptom criteria was 4.5%,[12,15–17] and the prevalence in studies conducted in nonuniversity primary care settings was 4.5%.[14–17] To bias the model against the testing strategy, we adopted the overall weighted mean of 3.4% (rather than the higher subgroup means) as our base-case point estimate. Of note, the large sample size of the series by Fasano et al.[11] anchors this base-case estimate to a large degree. However, the study by Fasano et al.[11] was not designed to evaluate the prevalence of CS in patients with IBS but instead presented data stratified by symptom type. The prevalence of CS in the subset of patients with "IBS-like" symptoms was 3.27%—a value *below* our base-case estimate of 3.4%. Therefore, if we removed these data from our base-case estimate calculation, the prevalence estimate would swell to 3.9%. We have therefore explicitly included the data from Fasano et al.[11] to help depress the base-case estimate of underlying CS. By minimizing the prevalence of CS in the hypothetic patient population with IBS symptoms, we explicitly minimized the potential effectiveness of testing for CS in IBS. However, because the prevalence of CS varies greatly in different patient

Table 1. Base-Case Clinical Probability Estimates

Variable	Base-Case Estimate	Range in literature	Range tested in sensitivity analysis	References
Prevalence of underlying CS in hypothetical cohort with Rome-positive IBS symptoms	3.4%	0%–11.4%	0%–100%	11,12,14–17
Sensitivity of serologic test for CS	85%	85%–98%	50%–100%	10
Specificity of serologic test for CS	94%	94%–100%	50%–100%	10
Probability that CS is latent/potential	35%	No range	0%–50%	18
Probability that CS is associated with IgA deficiency	5%	2%–10%	0%–20%	10
Probability of compliance with gluten-free diet	50%	50%–80%	30%–90%	10
Probability that gluten-free diet improves CS bowel symptoms	70%	70%–80%	50%–90%	10,19
Probability of initial symptomatic improvement with generic IBS therapy	75%	35%–75%	50%–90%	20
Probability of recurrent symptoms following initial symptomatic improvement with generic IBS therapy	50%	No range	30%–90%	21
Proportion of physicians who test for CS following failure with IBS therapy	25%	No range	10%–90%	Assumption
Mean diagnostic delay time between failed IBS therapy and testing for CS	6 months	12 months	1–120 months	9
Frequency of physician visits for ongoing IBS symptoms	Every 3 months	No range	Every 1–12 months	Assumption
Frequency of physician visits for resolved IBS symptoms	Once yearly	No range	Once yearly to once every 3 years	Assumption

populations, we varied the estimate over a wide range in sensitivity analysis to determine the prevalence threshold at which CS testing might become the dominant strategy (i.e., more effective and less expensive than empirical IBS therapy).

Assumptions regarding CS diagnostic tests in IBS. There are several available serologic tests for CS, including the anti-gliadin IgA antibody, anti-EMA IgA antibody, and anti-TTG IgA antibody.[10] Because the anti-gliadin antibody is only moderately sensitive and far less specific than anti-EMA or anti-TTG,[10] it has progressively fallen out of favor in testing for CS. We therefore limited our analysis to anti-EMA and anti-TTG antibodies. The sensitivity and specificity of anti-EMA ranges between 85%–98% and 97%–100%, respectively.[10] Similarly, the sensitivity and specificity of anti-TTG ranges between 95%–98% and 94%–95%, respectively.[10] To bias the model against the testing strategy, we selected the low values from these ranges and adopted a sensitivity of 85% and specificity of 94% as the base-case estimates for our modeled generic diagnostic test. We then varied each estimate between 50% and 100% in sensitivity analysis.

These estimates are confounded by recent data indicating that up to one third of patients with IBS may have underlying "latent" or "potential" CS (i.e., have the genetic susceptibility and symptoms of CS but a normal small bowel biopsy) and that this subgroup may derive symptomatic benefit from a gluten-free diet.[18] However, these patients may only be diagnosed by sampling the duodenal aspirate for intestinal (rather than serum) anti-EMA and anti-TTG,[18] thereby questioning the role of serologic testing in IBS. In one recent series of 102 patients with IBS symptoms, 35% had latent or potential CS, of whom none tested positive with anti-EMA or anti-TTG serologies.[18] In addition, data suggest that 5% of CS patients have concurrent IgA deficiency, thereby rendering serologic screening with IgA antibodies ineffective (unless total IgA is concurrently measured).[10] In light of these data, we incorporated the following 4 assumptions to bias heavily the model against CS testing: (1) 35% of the hypothetical cohort had underlying latent or potential CS, as reported by Wahnschaffe et al.[18]; (2) 5% of the cohort had underlying IgA deficiency; (3) clinicians did not measure total IgA along with anti-IgA sprue titers; and (4) the sensitivity and specificity of serologic testing in latent CS, potential CS, and CS with IgA deficiency were 0%, thereby rendering serologic testing entirely ineffective in 40% of patients with CS. Because these estimates are based on limited data and are unlikely to be consistently reproduced in varying patient populations, we varied each over a wide range in sensitivity analysis.

Assumptions regarding gluten-free diet in sprue. Between 70% and 80% of CS patients who are compliant with a gluten-free diet achieve symptomatic improvement.[10,19] However, data suggest that only 50%–80% of CS patients are compliant with their dietary restrictions.[10] To incorporate intention-to-treat analysis, we assumed that noncompliant patients achieved no symptomatic improvement. We further assumed that 70% of compliant patients achieved symptomatic remission and that only 50% of CS patients were compliant. We then varied each estimate between 0% and 100% in sensitivity analysis.

Table 2. Studies Evaluating the Prevalence of Celiac Sprue in Cohorts With Symptoms Suggestive of Irritable Bowel Syndrome

Study (*yr*)	Country	Clinic type	IBS symptoms	Clinical evaluation	Serologic diagnostic test for CS	CS confirmed histologically?	Prevalence of CS
Fasano et al. (2003)[11]	US	University clinic	Not stated[a]	Not stated	Anti-gliadin Anti-EMA Anti-TTG	Yes	3.27% (166/5073)
Hin et al. (1999)[14]	UK	Primary care	Not stated	H&P, CBC	Anti-EMA	Yes	0.0% (0/132)
Holt et al. (2001)[15]	UK	Primary care	Rome I	Not stated	Anti-EMA	No	0.7% (1/138)
Sanders et al. (2001)[12]	UK	University clinic	Rome II	H&P, CBC, CRP, ESR, chemistry panel, TSH, structural colon evaluation	Anti-gliadin Anti-EMA	Yes	4.7% (14/300)
Sanders et al. (2003)[16]	UK	Primary care	Rome II	H&P	Anti-gliadin Anti-EMA	Yes	3.3% (4/123)
Shahbazkhani et al. (2003)[17]	Iran	Primary care	Rome II	H&P, CBC, electrolytes, U/A, Stool studies, TSH, structural colon evaluation	Anti-gliadin Anti-EMA	Yes	11.4% (12/105)

H&P, history and physical examination; UK, United Kingdom; US, United States; CBC, complete blood count; U/A, urinanalysis.
[a]Includes patients with chronic diarrhea, abdominal pain, or constipation.

Assumptions regarding IBS therapy. There is a wide spectrum of available therapies for IBS. A recent systematic review revealed that most of the data supporting therapies in IBS are limited by methodologic shortcomings, including inadequate sample size, inadequate case-finding definitions for IBS, inadequate follow-up periods, inadequate control groups, and heterogeneous outcome measures.[20] Moreover, with the exception of alosetron and tegeserod, no therapy has demonstrated significant improvement in global IBS symptoms vs. placebo, and placebo itself may provide benefits in up over 50% of IBS patients.[20] Despite these indicting data, we nonetheless assumed that standard IBS therapy provided an initial therapeutic benefit in 75% of patients with IBS-D (based on data from highly effective IBS therapies such as alosetron) and modeled the cost of therapy to be only $45 per month. This base-case estimate is similar to the monthly cost of less effective, although inexpensive, therapies such as loperamide, fiber supplements, or antispasmotics and is only one fourth the cost of therapies proven effective such as alosetron. By adopting estimates that maximized effectiveness and minimized costs for IBS therapy, we further biased the model against the CS testing strategy. To model the wide range of available therapies, we varied the effectiveness of IBS therapy between 50% and 90% and the monthly cost between $10 and $300 in sensitivity analysis.

There are limited data regarding the incidence of recurrent symptoms following initial symptom improvement in IBS. Data from patients receiving tegeserod reveal that up to 85% develop symptomatic recurrence after discontinuing a successful therapeutic course, of whom 80% achieve symptomatic remission following a *second* therapeutic course.[21] Although these data apply to patients with constipation-predominant IBS (IBS-C), we adopted these favorable results to our hypothetic cohort of IBD-D patients. To bias the model against CS testing, we further assumed that only 50% (instead of 85%) of IBS-D patients developed symptomatic recurrence following successful therapy and adopted the tegaserod data of 80% remission following a second therapeutic course. These estimates regarding the natural history of IBS and response to sequential therapeutic courses are highly favorable for empiric IBS therapy and therefore biased the model against the CS testing strategy. Figure 2 displays the Markov state diagram governing patient transitions between symptom improvement and remission over the model time horizon.

Assumptions regarding provider behavior. The actions and inactions of health care providers are likely to influence the cost-effectiveness of competing strategies in IBS and CS. A critical variable is the proportion of clinicians who pursue a diagnosis of CS in patients with persistent IBS-D despite empiric therapy. Survey data in the United States

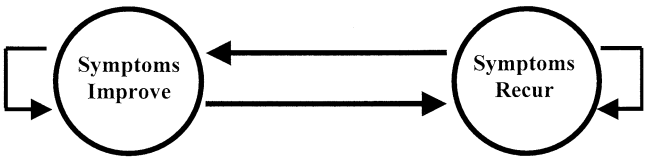

Figure 2. Two-Stage Markov Diagram of Cohort with Rome-positive IBS. During each 1-month cycle, individual patients either remain in their assigned health state (*recursive arrows*) or progress to a new health state (*straight arrows*). Patients entered the Markov cycle after achieving symptomatic improvement with therapy and subsequently either remained in remission or developed recurrent symptoms. The base-case time horizon included 120 cycles (10 years).

indicate that the median time to diagnosis in CS patients is 12 months[9] and that over 20% of patients have symptoms for 10 years before diagnostic testing is performed.[9] However, the true denominator of undiagnosed CS is unknown, and evolving epidemiologic data from both Europe and the United States indicate that most CS patients probably remain undiagnosed.[11,22–24] These data suggest that most clinicians do *not* routinely test for CS in patients with long-standing IBS-D symptoms, much less in CS patients with overt symptoms of steatorrhea or wasting. Nonetheless, to bias the model against the testing strategy, we assumed that 1 in 4 providers in the empiric therapy strategy had the insight eventually to test for CS in patients with persistent IBS-D symptoms (an estimate that is likely much higher than current community practice). We further assumed that the diagnostic delay was only 6 months (rather than 12 months). These assumptions improved the effectiveness and reduced the cost of empiric IBS therapy by ensuring that a subset of patients ultimately received the proper diagnosis despite failing to receive up-front CS testing.

Outcomes

The health-economic outcome most relevant to patients with IBS is unknown. Although guidelines on economic analyses suggest that quality-adjusted life years (QALYs) are the most appropriate unit for cost-effectiveness analysis,[25] others contend that global symptom relief most closely mirrors clinical reality for patients with IBS.[26] In the absence of validated utilities for IBS (which precludes the calculation of QALYs), the main outcome measure was the proportion of patients with symptomatic improvement at the end of the time horizon. Our analysis reports the incremental cost per additional symptomatic improvement between the competing strategies.

Time Horizon

Because IBS is a chronic condition that follows a dynamic path of symptom exacerbations and remissions, we adopted a base-case time horizon of 10 years. Throughout the 10-year period, patients cycled between symptomatic health states on a monthly basis as displayed in Figure 2. We varied the time horizon between 6 months and 20 years in sensitivity analysis.

Cost Estimates

We conducted our analysis from the perspective of a third-party payer, considering only direct health care costs (Table 3). We obtained costs for physician services from the 2003 American Medical Association Current Procedural Terminology codebook and the 2003 Medicare Fee Schedule and derived our base-case pharmaceutical costs from the average wholesale prices (AWP) listed in the Red Book.[27] Our base-case analysis discounted cost and effectiveness at 3% as rec-

Table 3. Cost Estimates

Variable	Base-case cost estimate ($)	Range tested ($)
Cost of initial general medicine office visit	99	25–150
Cost of follow-up general medicine office visit	52	25–150
Cost of generic screening test for CS	80	20–150
Cost of diagnostic upper endoscopy for positive CS test		
Endoscopist's consultation fee	160	
Endoscopist's procedure fee	231	
Facility fee	433	
Biopsy interpretation fee	150	
Total cost	974	400–1500
Cost of inpatient admission of ulcer perforation from upper endoscopy (probability of perforation = 0.03%):		
Medicare DRG for bowel perforation	13,531	
Cost of emergency room fee	168	
Initial surgical consultation	97	
Surgeon's fee	710	
Anesthesiologist's fee	299	
Surgeon's follow-up visit	53/day × 10 follow-up days	
Total cost	15,335	5000–20,000
Cost per month of generic IBS therapy (see text for details)	45	10–300

NOTE. Costs obtained from the 2002 American Medical Association Current Procedural Terminology codebook, the 2002 Medicare Fee Schedule, and the 2002 Red Book of Average Wholesale Drug Prices.

Table 4. Base-Case Results

Strategy	Cost[a]	Effectiveness[b]	Incremental cost/ effectiveness[c]
Empiric IBS therapy	$4023	.509	—
CS Testing	$4100	.516	$11,000

[a]Average cost per patient.
[b]Measured as proportion of cohort with symptomatic improvement at the end of 10-year time horizon.
[c]Cost per additional symptomatic improvement.

ommended by the National Panel on Cost-Effectiveness in Health and Medicine.[25]

Sensitivity Analyses: Base-Case Sensitivity Analysis

Table 1 lists our base-case probability estimates with the plausible range of values for each estimate. To test the influence of all variables on the model results, we performed a multivariable sensitivity ("tornado analysis") to rank order the most influential variables.[28] We then performed 1-way sensitivity analyses on the most influential variables and report the threshold values at which CS testing became dominant (i.e., became more effective and less expensive than empiric IBS therapy).

Whereas 1-way sensitivity analyses provide information regarding the robustness of a model, they are inadequate to simulate real-world conditions. To acknowledge the reality that each individual carries a unique composition of clinical probabilities, we conducted a probabilistic (Monte Carlo) simulation under the assumption that all variables were triangular in distribution.[28] The triangular distribution assumes that a parameter's base-case value is most likely to occur and that the minimum and maximum values are least likely to occur. The probability of observing a value between the base-case and extreme value is linearly interpolated. We evaluated 1000 trials through this simulation and report the median, 2.5, and 97.5 percentile values of the incremental cost-effectiveness ratio (ICER) between the competing strategies. Because different third-party payers have different willingness-to-pay thresholds, we also report the percentage of trials falling below 3 ICER thresholds: $100,000, $50,000, and $20,000 per additional symptomatic improvement.

Results

Table 4 displays the results of the analysis. Under base-case conditions (assuming a 3% discount rate), the empiric IBS therapy strategy cost $4023 per average patient treated and resulted in 50.9% of the cohort achieving symptomatic remission at the end of 10 years. The CS testing strategy cost $4100 per average patient treated and resulted in 51.6% of the cohort achieving symptomatic remission at the end of 10 years. Therefore, testing for CS instead of starting empiric IBS therapy cost an incremental $11,000 to achieve 1 additional symptomatic improvement.

Multivariable sensitivity analysis of all parameters revealed that the model was sensitive to the following variables, in descending order of influence: prevalence of underlying CS, specificity of diagnostic test for CS, probability that gluten-free diet improves the symptoms of CS, and the cost of IBS therapy. Table 5 displays the results of 1-way sensitivity analysis for each of these parameters and lists the thresholds at which the CS testing strategy became dominant. The remaining probability estimates did not impact the model when varied over a wide range.

Figure 3 displays the results of 1000 trials through a probabilistic Monte Carlo simulation. The median ICER of these trials was $12,983 per additional symptomatic improvement (the 2.5 and 97.5 percentiles = −$32,520, $41,031, respectively). The percentage of trials beneath the $20,000, $50,000, and $100,000 willingness-to-pay thresholds were 78.0%, 89.1%, and 94.7%, respectively. For example, if a third-party payer were willing to pay $50,000 per symptomatic improvement for CS testing, 89.1% of the patients in this simulation would fall within the budget.

Table 5. Results of 1-way Sensitivity Analyses

Variable	Base-case estimate	Threshold	Comment
Prevalence of underlying CS in patients with Rome-positive IBS	3.4%	8%	If greater than threshold, then CS testing strategy becomes dominant
Specificity of CS test	85%	98%	If greater than threshold, then CS testing strategy becomes dominant
Probability that gluten-free diet improves symptoms of CS	70%	95%	If greater than threshold, then CS testing strategy becomes dominant
Cost per month of IBS therapy	$45	$135	If greater than threshold, then CS testing strategy becomes dominant

NOTE. The listed thresholds are the values at which the CS testing strategy becomes dominant (i.e., becomes more effective and less expensive than the empiric IBS therapy strategy).

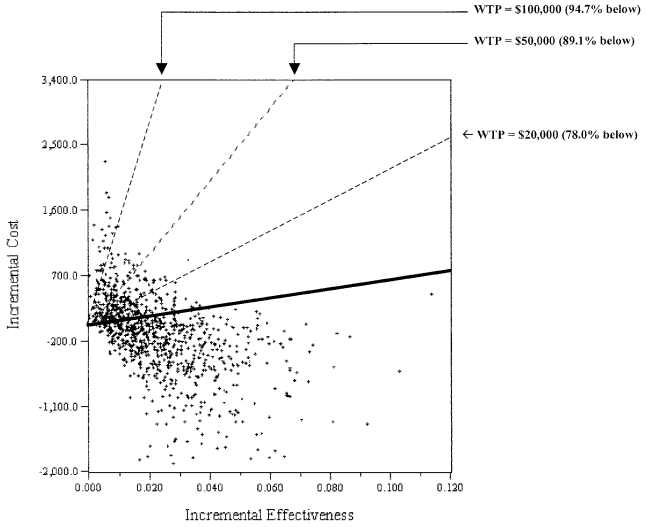

Figure 3. Probabilistic sensitivity analysis using 1000 trials. This analysis simultaneously varies all parameters over the full range of plausible values. Each point represents the incremental cost effectiveness ratio (ICER) generated by one trial through the simulation. The *bold line* delineates the median ICER of $12,000 per additional symptomatic improvement and, by definition, 50% of the trials fall on either side of the line. The remaining 3 *diagonal lines* represent willingness-to-pay (WTP) thresholds. Points below and to the right of each line represent trials that generated an ICER below the specified threshold. For example, if a third-party payer were willing to pay $50,000 per additional symptomatic improvement for CS screening, then 89.1% of the patients in this simulation would fall within the budget.

Discussion

This analysis indicates that testing for CS may be cost-effective vs. empiric IBS therapy in most patients with diarrhea-predominant IBS. Specifically, in a hypothetical IBS-D cohort with a CS prevalence of 3.4%, our analysis reveals that CS testing instead of empirical therapy costs an additional $11,000 to provide one additional symptomatic improvement—an incremental cost that compares favorably with commonly accepted medical interventions. Moreover, CS testing is likely to be cost-effective across a wide range of health care budgets from the most conservative to the most liberal (Figure 3). These findings emerge despite constructing a model that is explicitly biased in favor of empirical IBS therapy. If our analysis were not designed to reflect a "best case" scenario for empirical therapy, the incremental cost-effectiveness of the CS testing strategy would be even lower.

Because the cost-effectiveness of CS testing in IBS-D depends on the prevalence of underlying CS, the optimal strategy will vary among different populations. The decision to test may depend on the patients' ethnicity (i.e., Northern European), medical history (i.e., insulin-dependent diabetes, inflammatory arthritis), clinical syndromes (i.e., osteoporosis, unexplained infertility), and family history of CS. Figure 4 represents a 1-way sensitivity analysis comparing the incremental cost of CS-testing with the underlying prevalence of CS. These results may serve as a nomogram to help clinicians in selecting the most cost-effective strategy for their own IBS population. For example, clinicians caring for a predominantly African-American IBS population with a low (<1%) prevalence of underlying CS might consider using empiric IBS therapy instead of testing for CS (incremental cost >$100,000). In contrast, clinicians caring for a predominantly Northern European IBS population with a high (>1%) prevalence of underlying CS might consider initial CS testing instead of empirical IBS therapy. Our analysis indicates that testing for CS becomes more effective at a lower cost than empiric therapy when the prevalence of CS exceeds 8%. Moreover, the incremental cost of CS testing remains under $50,000 (a commonly accepted threshold for "cost-effective"[29]) for all populations with a prevalence above 1%. In short, CS testing is associated with an acceptable incremental cost in all populations with a prevalence above 1% and becomes the preferred strategy when the prevalence exceeds 8%.

Our analysis is directed toward patients with IBS-D. However, it is difficult to determine whether the prevalence of CS varies by subtype in the absence of data comparing the prevalence in IBS-D vs. IBS-C. Nonetheless, it seems reasonable to believe that CS is more prevalent in patients with IBS-D than IBS-C. Clinicians may want to downplay the relative importance of testing for CS (albeit in the absence of data) in patients with IBS-C. Future research should aim to measure the prev-

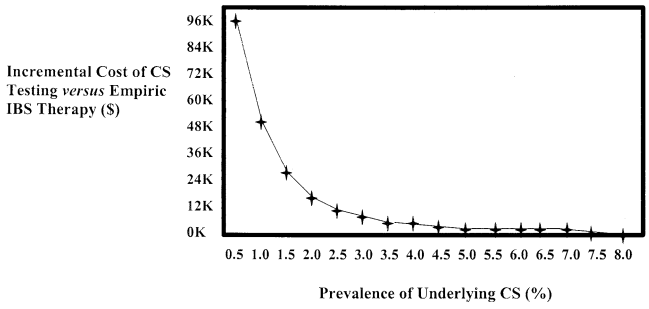

Figure 4. Cost-effectiveness of testing for celiac sprue (CS) in varying populations. Under base-case conditions (3.4% prevalence of underlying CS), the testing for CS costs an additional $11,000 per additional symptomatic improvement compared with empiric IBS therapy. However, the incremental cost falls rapidly as the baseline prevalence of underlying CS increases and reaches $0.00 when the prevalence is 8%. In contrast, the incremental cost approaches $100,000 when the prevalence of underlying CS falls below 1.0%.

alence of CS stratified by IBS subgroup. Once these data are available, a formal analysis should compare the cost-effectiveness of testing for CS by IBS subtype.

Testing for CS is likely to be cost-effective because it fulfills the 5 basic criteria for a successful screening strategy.[30,31] First, the mean prevalence of CS in IBS is 3.4% in published series, indicating that CS is not uncommon in IBS.[11,12,14–17] Second, emerging data indicate that CS rarely presents with advanced clinical symptoms and more often presents with insidious and nonspecific symptoms that render early detection difficult without diagnostic testing.[9] Third, diagnosing CS early in its clinical course may prevent years of expense and morbidity while minimizing potentially mortal complications (i.e., lymphoma). Fourth, there is a readily available, generally affordable, and highly successful treatment option for CS. Fifth, current diagnostic tests for CS are inexpensive, widely available, and highly sensitive and specific. Despite adopting unfavorable estimates for the sensitivity (85%) and specificity (94%) of CS diagnostic tests, our analysis indicates that CS testing is likely to be cost-effective. Moreover, our analysis reveals that CS testing becomes the dominant strategy when the specificity exceeds 98%—a value that falls well within the documented range for anti-EMA and anti-TTG IgA antibody tests.[10] Taken together, these features of CS suggest that it is worthwhile to test for CS in IBS despite the fact that most IBS patients have no detectable organic disease to account for their symptoms. The increased cost incurred by diagnostic CS tests and endoscopic confirmation is almost entirely offset by the years of expense avoided by unnecessarily treating misdiagnosed IBS.

There has been a trend in recent years to find organic explanations for IBS, including small intestinal bacterial overgrowth,[32,33] undiagnosed thyroid disorders,[34] and underlying colitis,[35,36] among others. This "organification" runs contrary to accumulating data that IBS is a discrete condition arising from defined physiologic, psychologic, and social abnormalities.[7] In light of this evolving insight into the pathophysiologic basis of IBS, it is not surprising that most attempts to uncover an organic etiology are met with failure.[8] Nonetheless, these facts do not preclude conducting a balanced, rational, and cost-effective set of selected diagnostic tests early in the management of IBS. Whereas data do not consistently support routine testing for most organic disorders in IBS,[8] testing for CS may be an exception. Acknowledging that patients with CS may fulfill the Rome criteria does not undermine the evolving disease paradigm of IBS but rather acknowledges that the positive predictive value of the Rome criteria is not 100% and that clinical decision making is a fallible process.

There are several limitations to this analysis. As with any decision analysis, the results depend on the validity of the base-case estimates. Because our base-case point estimates are unlikely to reflect all populations, our results are unlikely to be precisely reproduced in all populations. Moreover, several of our estimates are based on studies of varying design, patient population, follow-up, and quality. However, we have attempted to guard against inaccurate base-case results by systematically reviewing the literature and relying on preexisting systematic reviews when available. When there was a range of data, we selected conservative estimates that tended to bias the model in favor of empiric IBS therapy and therefore systematically biased the model against testing for CS. In addition, we performed a probabilistic sensitivity analysis to acknowledge that each estimate is likely to vary widely in clinical practice. Despite this conservative approach, our model indicates that the up-front costs associated with CS testing are almost entirely offset by the improved effectiveness afforded by identifying the small subset of undiagnosed CS in IBS.

Although we based our probability estimates on the available published data, there is reason to argue that our prevalence estimate of CS in IBS-D (3.4%) may be overstated. In particular, we assumed that patients entered the model only after receiving an extensive diagnostic evaluation including biochemical testing for common organic conditions and a structural evaluation of the colon. This diagnostic battery may screen out many patients with CS without requiring a serologic test for CS (on the basis of finding anemia, hypoalbuminemia, or malabsorption). The remaining cohort might therefore be less likely to have underlying CS than a cohort without diagnostic testing. However, our base-case estimate of 3.4% is based largely on studies that performed extensive screening for organic conditions (Table 2). Of note, the 2 studies with the most extensive screening criteria (including structural colon evaluations) produced the *highest* estimates for CS prevalence (Sanders et al.,[12] 4.7%; Shahbazkhani et al.,[17] 11.4%). In contrast, the studies that failed to report specific biochemical screening tests produced lower estimates for CS prevalence (Sanders et al.,[16] 3.3%; Holt et al.,[15] 0.7%). Therefore, our assumption of a 3.4% prevalence following a diagnostic battery appears consistent with the published data. If we relied solely on the studies that performed the most extensive diagnostic evaluations, our estimate

would be significantly *higher* than 3.4%. Nonetheless, future research should aim to define better the prevalence of CS in a cross-sectional sample of IBS patients stratified by subtype following a diagnostic battery.

Our analysis may also have overstated the cost-effectiveness of testing for CS on the basis of faulty assumptions regarding the test characteristics of serologic assays for CS. Although accumulated data indicate that the sensitivity and specificity of serologic tests for CS are in the 95%–100% range, data by Sanders et al.[16] found the anti-EMA test to be only 79% sensitive and 44% specific for the diagnosis of CS in patients with IBS symptoms (when compared with the gold standard of histology). Explanations for this potential anomaly include variations in the study laboratory, variations in the histologic criteria for diagnosing CS, or a potentially inadequate biopsy protocol (only 4 biopsy specimens were obtained), among others. However, another real possibility is that the anti-EMA is neither sufficiently sensitive nor specific in the subset of CS patients presenting with IBS symptoms. If this were true, it would negatively impact the cost-effectiveness of screening for CS in IBS. When the specificity of the screening test for CS falls to 44% in our analysis (the rate achieved by Sanders et al.[16]), the incremental cost of testing for CS exceeds $100,000 vs. usual care. In light of this possibility, future research should aim to characterize better the performance of screening tests for CS in the subset of patients presenting with IBS symptoms. In the meantime, there are inadequate data to assume that anti-EMA (or anti-TTG) behaves differently in this subset of CS patients.

Our analysis does not consider all possible clinical outcomes, including personal discomfort as a result of an invasive procedure or a complication of therapy. Health-related quality of life (HRQOL) is an important consideration in all areas of medicine because it may affect costs in a manner that is not accounted for by simple economic modeling. Testing for CS may decrease HRQOL compared with empiric therapy because patients diagnosed with CS are subjected to endoscopic examinations and burdensome dietary regulations. In contrast, empiric IBS therapy may decrease HRQOL compared with CS testing because patients with undiagnosed CS are subjected to preventable morbid symptoms and long-term complications (i.e., lymphoma, iron-deficiency anemia, nutritional deficiencies).[10] However, there has been no attempt to elicit and validate utilities for health states in CS or IBS. Therefore, in the absence of validated utility measures derived from patients with these conditions, we believe that it is not possible to perform a reliable or meaningful cost-utility analysis. Future research should aim to define utilities in IBS and thereby allow the calculation of quality-adjusted life years for cost-utility analyses.

We assumed the perspective of a third-party payer and used Medicare reimbursement costs. This approach is limited because it does not account for indirect or societal costs including transportation costs for physician visits, opportunity costs from missed work, or out-of-pocket expenses for maintaining a gluten-free diet. Although indirect costs may impact the cost-effectiveness of strategies in IBS and CS, there are limited data regarding these costs among cohorts. In light of this shortcoming, we could not use a societal perspective without relying on conjectural cost estimates. Moreover, because data indicate that IBS patients consume a disproportionate amount of health care resources compared with matched controls,[37] there is reason to expect that their indirect costs are higher as well. If we included these indirect costs, it would likely bias the model in favor of the CS testing strategy by further penalizing patients with ongoing IBS symptoms (which are more common in the empiric IBS treatment strategy). The indirect costs associated with undiagnosed CS are likely to exceed the out-of-pocket expenses incurred for a gluten-free diet.

Our results reveal that the cost and effectiveness of CS testing are almost equivalent to those of empiric IBS therapy (Table 4). Therefore, our interpretation that CS testing is "cost-effective" may be criticized because the data might instead be interpreted to indicate that the decision between strategies is akin to a coin flip. However, we believe that our interpretation is accurate for the following 3 reasons: (1) Decision analysis is concerned with the *relative* differences between strategies rather than the *absolute* values that are generated.[13,25,38] Therefore, the incremental cost-effectiveness (Δ costs/Δ effectiveness) between strategies is the primary measure of "cost-effectiveness," and the incremental cost of CS testing in this analysis is highly favorable. (2) Because we explicitly biased our analysis in favor of empiric IBS therapy, the model mandates that CS testing is only marginally more effective than not testing (51.6% vs. 50.9% effective, respectively). If we removed this bias, CS testing would become much more effective than our results indicate. (3) In clinical situations in which decision making is akin to a coin flip, the more effective of competing strategies is generally selected.[25,28,38] Therefore, despite the nearly equivalent cost and effectiveness between the competing strategies, our results indicate

that CS testing is likely to be a highly cost-effective approach in most patients with IBS.

In conclusion, this analysis reveals that testing for CS is likely to be cost-effective in IBS-D cohorts with a prevalence of CS exceeding 1%. Because recent data indicate that CS is more prevalent in the United States than previously assumed[11] and is 7 times more common in patients with IBS than matched controls,[12] testing for CS may be worthwhile not only in Northern European populations with IBS-D but also in North American populations with IBS-D. The decision to test should be based on a careful consideration of the pretest likelihood for underlying CS, the operating characteristics of the screening test, and the cost of proposed therapy for IBS (Table 5). In light of this analysis, using the best data available at this time, we suggest that further research include a prospective trial comparing the accrued cost and effectiveness of these competing management strategies stratified by IBS subgroup. Additional comparators may also include the use of an empiric gluten-free diet and "test and treat" for CS without endoscopic confirmation.

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