*Original Research*

# A Predictive Model to Estimate Cost Savings of a Novel Diagnostic Blood Panel for Diagnosis of Diarrhea-predominant Irritable Bowel Syndrome

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## ABSTRACT

**Purpose:** A high incidence of irritable bowel syndrome (IBS) is associated with significant medical costs. Diarrhea-predominant IBS (IBS-D) is diagnosed on the basis of clinical presentation and diagnostic test results and procedures that exclude other conditions. This study was conducted to estimate the potential cost savings of a novel IBS diagnostic blood panel that tests for the presence of antibodies to cytolethal distending toxin B and anti-vinculin associated with IBS-D.

**Methods:** A cost-minimization (CM) decision tree model was used to compare the costs of a novel IBS diagnostic blood panel pathway versus an exclusionary diagnostic pathway (ie, standard of care). The probability that patients proceed to treatment was modeled as a function of sensitivity, specificity, and likelihood ratios of the individual biomarker tests. One-way sensitivity analyses were performed for key variables, and a break-even analysis was performed for the pretest probability of IBS-D. Budget impact analysis of the CM model was extrapolated to a health plan with 1 million covered lives.

**Findings:** The CM model (base-case) predicted $509 cost savings for the novel IBS diagnostic blood panel versus the exclusionary diagnostic pathway because of the avoidance of downstream testing (eg, colonoscopy, computed tomography scans). Sensitivity analysis indicated that an increase in both positive likelihood ratios modestly increased cost savings. Break-even analysis estimated that the pretest probability of disease would be 0.451 to attain cost neutrality. The budget impact analysis predicted a cost savings of $3,634,006 ($0.30 per member per month).

**Implications:** The novel IBS diagnostic blood panel may yield significant cost savings by allowing patients to proceed to treatment earlier, thereby avoiding unnecessary testing. (*Clin Ther*. 2016;38:1638–1652) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

**Key words:** budget impact analysis, colonoscopy, cost-minimization, diarrhea-predominant irritable bowel syndrome, IBS diagnostic blood panel.

## INTRODUCTION

Irritable bowel syndrome (IBS) is a common relapsing gastrointestinal (GI) disorder characterized by abdominal pain and discomfort, bloating, and changes in bowel habit.[1,2] IBS is the most common functional GI disorder in the population and has a prevalence that ranges from 5% to 15%.[3–8] The prevalence of IBS was 10.5% in a large survey of patients from community-based practices,[8] and a recent meta-analysis reported a pooled global prevalence of 11.2%.[7] Within the overall prevalence, IBS is subclassified according to the predominant bowel habit to include diarrhea-predominant IBS (IBS-D), constipation-predominant IBS, mixed subtype IBS, or unclassified IBS.[4] In the large survey of patients in community-based practices, symptom profiles were evenly divided between those patients with predominant diarrhea (25.4%) and constipation (24.1%), with more women than men typically affected by IBS.[8]

*Accepted for publication May 3, 2016.*
http://dx.doi.org/10.1016/j.clinthera.2016.05.003
0149-2918/$ - see front matter

Chronic diarrhea associated with IBS-D may also be common among individuals with celiac disease or inflammatory bowel disease (IBD). The anti-tissue transglutaminase antibody is a reliable biomarker selective for celiac disease[9]; however, differentiating IBS from IBD relies on excluding organic disease origins. Although the diagnosis of IBS is based on clinical findings that meet Rome criteria (eg, Rome III),[10] these common criteria do not distinguish IBS from IBD.[11] Importantly, the process of exclusion used for a definitive IBS-D diagnosis can be laborious, time-consuming, and costly.[12]

Common diagnostic testing for IBS can include laboratory tests (thyroid and liver function, C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], celiac panel, and complete blood cell [CBC] counts) and procedures, such as endoscopy, hydrogen breath test, ultrasound, and/or abdominal/pelvic computed tomography (CT) scans.[12] In a retrospective cohort study of patients diagnosed with IBS, blood tests were performed in 49% of patients, imaging and endoscopic procedures in 47%, colon tests in 37%, and sigmoidoscopy in 18%.[13] Although the current battery of laboratory tests is useful for the differentiation of IBD and IBS-D, none is associated with biomarkers that have been linked to IBS-D. ESR and CRP are used to investigate biomarkers associated with inflammation and thereby are tests of exclusion for IBS-D.

A recent systematic review reported evidence suggesting that CRP level has significant utility for the differential diagnosis of IBS-D and IBD whereas ESR did not. If the CRP level was $\leq 0.5$, the probability that the patient had IBD was then $\leq 1\%$.[14] A prospective study investigated the performance of several laboratory tests for the diagnosis of IBS-D; this study found the sensitivity and specificity of CRP to be 64% and 92%, respectively, for the discrimination of IBS-D and IBD.[15] Including (and beyond just considering) the costs associated with reaching a definitive diagnosis, the health care burden of IBS is substantial.[16] It contributes 3.5 million physician office visits, even though a low proportion (10%–25%) of patients with IBS seek medical treatment. According to 1 study, annual direct and indirect costs of IBS exceed $20 billion.[17] Unfortunately, IBS is a heterogeneous disease, and, until now, there has been no reliable biomarker (organic) that is selective for IBS.[4,11]

Increased understanding of the pathophysiology of IBS by the lead author and others has helped lead to the development of a novel IBS diagnostic blood panel (Commonwealth Laboratories, Inc, Salem, MA).[18–24] The biomarker consists of a simple blood test measurement of circulating antibodies to cytolethal distending toxin B (anti-CdtB) and vinculin (anti-vinculin). Studies in a postinfectious animal model have shown that an IBS-like phenotype was produced when host antibodies to CdtB cross-reacted with vinculin in the host gut.[25] This IBS diagnostic blood panel was recently validated in a large study that enrolled patients with IBS-D (n = 2375), IBD (n = 142), or celiac disease (n = 121) and healthy control subjects (n = 43).[21] In that study, anti-CdtB and anti-vinculin titers were significantly higher in patients with IBS-D than in patients with IBD, celiac disease, and healthy subjects (all comparisons, $P < 0.001$). In that study, optimization demonstrated that for anti-CdtB (optical density $\geq 2.80$), the sensitivity, specificity, and likelihood ratio were 43.7%, 91.6%, and 5.2, respectively. For anti-vinculin, optimization demonstrated (optical density $\geq 1.68$) that the sensitivity, specificity, and likelihood ratio were 32.6%, 83.8%, and 2.0. This diagnostic test is currently available to providers who are responsible for diagnosing and managing patients with various GI disorders.

The IBS diagnostic blood panel may have beneficial economic implications for the diagnosis and management of patients suspected of having IBS-D; however, this possibility has not been studied. Indeed, a reduction in the time interval or number of diagnostic procedures used from symptom presentation to treatment initiation for a definitive IBS-D diagnosis may reduce patient morbidity and cost burden associated with performing a battery of exclusionary tests.[26,27] The objective of the present study, therefore, was to apply a cost-minimization (CM) decision tree model to compare the costs associated with 2 diagnostic pathways: the novel IBS diagnostic blood panel pathway and the exclusionary diagnostic pathway (current standard of care).

## MATERIALS AND METHODS

### Physician Surveys

Two surveys were developed and completed by expert gastroenterologists in the United States. The physician characteristics are reported (see **Supplemental Table I** in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.05.003). The first survey addressed physician characteristics, patient characteristics, patient insurance type, distribution of patients with IBS according to

subtype, time to diagnosis, diagnostic tests, diagnostic procedures, treatments for IBS, and the use of (or agreement with) the Rome criteria III. Frequency of diagnostic testing and procedure utilization was also captured. The second survey was circulated among the same group of physicians and addressed some of the same variables as the first survey, albeit in a more detailed manner. This survey also addressed the time to diagnosis and the sequence of diagnostic testing. Both surveys were analyzed in Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington).

## CM Model

A CM model for gastroenterology practices in the United States was constructed to compare 2 different diagnostic strategies for IBS-D. The time horizon was not specified; the intent of the model was to sum the health care resources and associated costs during the diagnostic process. The decision tree begins with patients who present with the symptoms of "chronic diarrhea, pain and bloating" and who do not present with alarm symptoms. After this symptomatic presentation, there were 2 differing strategies: the IBS diagnostic blood panel pathway versus the "exclusionary diagnostic pathway." The tests for the 2 biomarkers were modeled independently; the likelihood ratios, sensitivity, and specificity of the biomarkers were taken from the validation study.[21] The exclusionary diagnostic pathway was based on a literature review as well as expert clinical guidance; this pathway depicts what typically happens in the diagnostic process in an attempt to exclude other organic conditions (eg, celiac disease or IBD). The overall decision tree model is depicted in Figure 1A.

The exclusionary diagnostic pathway consists of 2 stages of testing (Figures 1B and 1C): a first stage that comprises mostly laboratory tests (and 1 procedure [upper endoscopy]), and a second stage that consists entirely of procedures (eg, colonoscopy, CT scans, ultrasound). The testing stages were modeled by using "summation nodes." The probabilities for the utilization of these tests and procedures were derived from the surveys. The summation nodes allow the probability that each test is utilized to be modeled independently. The survey also addressed the pretest probability that the patient population is positive for IBS-D disease (based on symptom presentation only).

The costs for these tests and procedures were derived from publically available sources (see Supplemental Table II in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.05.003). The costs are derived from Centers for Medicare & Medicaid Services and private payer sources. Only diagnostic costs were considered for this analysis. Office visit costs were included in the overall cost of diagnosis. The expert clinicians advised the focus to be only on diagnostic costs because there is no consensus on IBS-D treatment; hence, it would be difficult to model both the diagnostic and treatment model within the same model framework. During the survey, the physicians were asked to specify a time frame for diagnosing a patient with suspected IBS-D; the responses ranged from 1 week to 6 months. Therefore, there is no specified time frame for this decision tree; the focus is to summarize the costs during the diagnostic process. Because the diagnostic process will likely conclude within 1 year, there was no discounting. The decision tree was modeled in TreeAge Pro 2014 (TreeAge Software, Inc, Williamstown, MA).

One of the key parameters using the CM model is the probability that a patient will avoid further testing after receiving the IBS diagnostic blood panel results. Because this probability is unknown, it is modeled as the posttest probability of IBS-D (based on the pretest probability of disease and characteristics of the biomarker tests). A table of pretest and posttest probabilities has been provided (see Supplemental Table III in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.05.003). The posttest probability of disease is computed by using standard equations as follows:

$$Post\text{-}test\ odds(D+) = Pre\text{-}test\ odds(D+) * LR(CdtB) * LR(vinculin) \quad [1]$$

$$Post\text{-}test\ \Pr(D+) = \frac{Post\text{-}test\ odds(D+)}{1+Post\text{-}test\ odds(D+)} \quad [2]$$

A matrix of probabilities relating the pretest and posttest probabilities was developed. The probability that a patient will avoid further testing after the initial symptomatic presentation in the exclusionary diagnostic pathway ranges from 0.0 to 0.7 (base-case, 0.2); these values were provided by consultation with currently practicing gastroenterologists. One-way sensitivity analyses were performed for all cost and utilization variables. A separate scenario analysis was performed in which the posttest probability of disease is calculated by using the formulas (formulas 1 and 2) for the posttest probability of disease for both treatment arms.

A probabilistic sensitivity analysis (PSA) was performed to estimate the variability for the cost outcomes

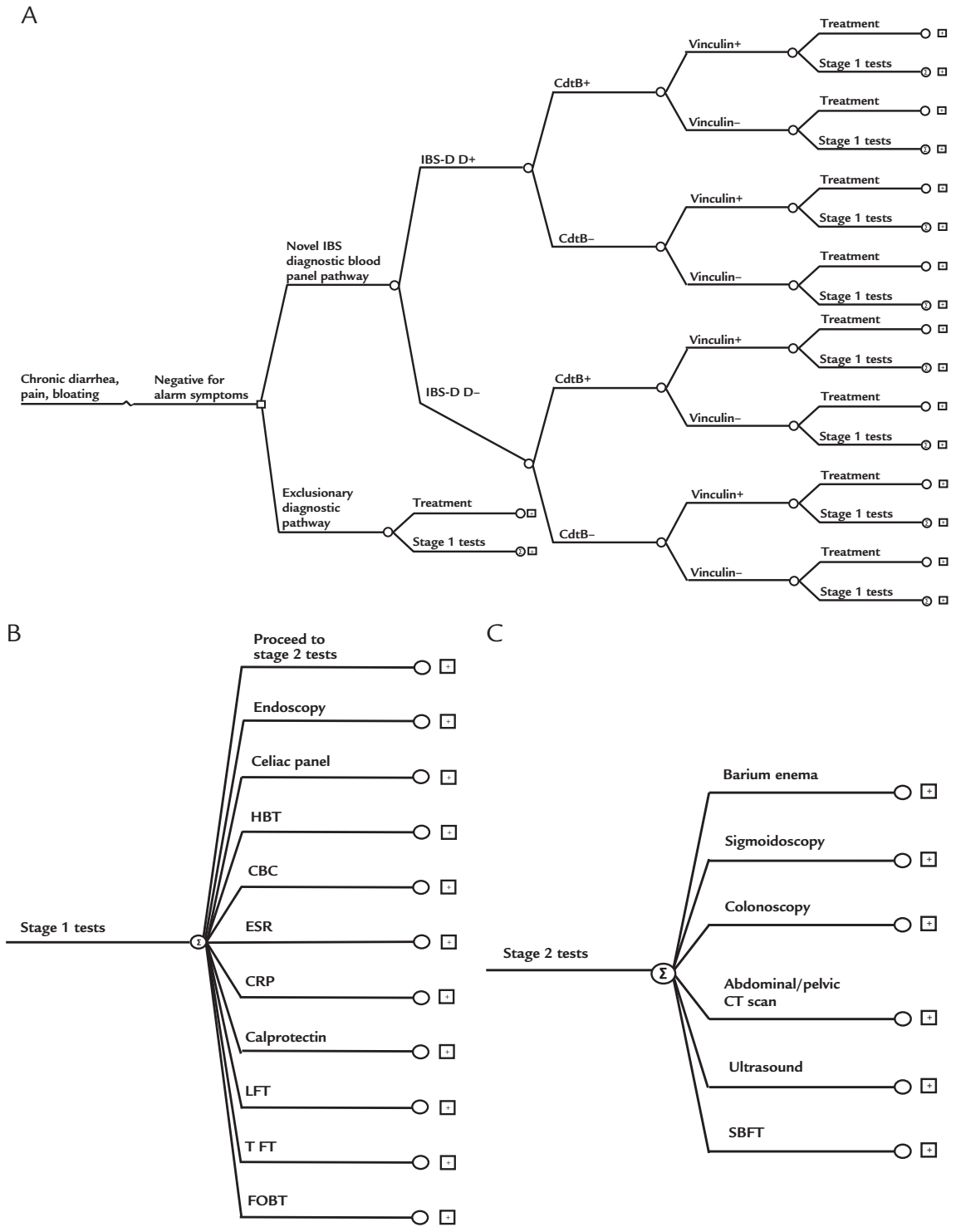


Figure 1. Schema of (A) cost-minimization model design, (B) diagnostic tests, and (C) procedures in the exclusionary arm. + = positive; – = negative; CBC = complete blood cell count; CdtB = cytolethal distending toxin B; CRP = C-reactive protein; CT = computed tomography; ESR = erythrocyte sedimentation rate; FOBT = fecal occult blood test; HBT = hydrogen breath test; IBS = irritable bowel syndrome; IBS-D D+ = diarrhea-predominant IBS disease-positive; LFT = liver function test; SBFT = small-bowel follow-through; TFT = thyroid function test.

for each diagnostic approach. A Monte-Carlo simulation was performed with 20,000 iterations. Cost variables were modeled with log-normal distributions; probability variables were modeled with β distributions (see Supplemental Tables V and VI in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.05.003). The distributions were chosen to have the same expected value as the corresponding variable probabilities; the variability of the distributions was estimated because reliable data were unavailable. A cumulative distribution function plot summarized the differences between the strategies.[28] The cumulative distribution function plot was prepared by using SAS version 9.2 (SAS Institute, Inc, Cary, North Carolina). Per simulated iteration, the differences were defined as:

$$differences = x_i - y_i;\ where\ x_i\ is\ the\ simulated\ value\ for\ the\ IBS\ diagnostic\ bloodpanel\ pathway\ and\ y_i\ is\ the\ simulated\ value\ for\ the\ exclusionary\ pathway$$

### Budget Impact Analysis

A budget impact analysis was performed for a hypothetical health plan with 1 million covered lives. The prevalence of IBS was estimated from the medical literature; the analysis was performed for the US population aged 18 to 64 years.[29] The relative prevalence of the IBS-D subtype was derived from the physician survey. The net impact to the health plan was calculated by extrapolating the results of the CM model. The analysis computes the difference in net costs for 2 scenarios: (1) 100% of eligible patients are diagnosed with the exclusionary pathway; and (2) 50% of eligible patients are diagnosed with the exclusionary pathway and 50% of eligible patients are diagnosed with the IBS diagnostic blood panel pathway. Using the net difference in costs, per-member per-month (PMPM) costs (or savings) are computed. The published research suggests that a significant proportion of the population with IBS symptoms do not seek care; therefore, the budget impact results were reported for a range of probabilities for this variable (0.10–1.0).[16] A sensitivity analysis was performed for the budget impact analysis with respect to the pretest probability of disease (IBS-D).

## RESULTS

### Survey Outcomes

Nine gastroenterologists from primarily academic centers and with a median tenure in their current department of at least 7 years were surveyed; survey results are summarized in Table I. Pretest probability of IBS-D diagnosis based on in-office symptom presentation was 0.763. According to survey results, physicians were most likely to use celiac tests, CRP, CBC, liver function, and colonoscopy diagnostic tests. Survey participants were least likely to use barium enema,

Table I. Summary of test/procedure utilization, sequence, and estimated cost.

| Diagnostic Test/Procedure | Percent Utilization | Sequence Ranking* | Estimated Cost, US $ |
|---|---|---|---|
| IBS diagnostic blood panel | NA | NA | 500 |
| Celiac test | 0.888 | 5 | 450 |
| Complete blood count | 0.875 | 1 | 149 |
| C-reactive protein | 0.775 | 3 | 90 |
| Thyroid function test | 0.688 | 4 | 257 |
| Liver function test | 0.644 | 7 | 31 |
| Colonoscopy | 0.625 | 8 | 2727 |
| ESR | 0.531 | 2 | 36 |
| Fecal calprotectin | 0.438 | 6 | 92 |
| Upper endoscopy | 0.400 | 13 | 1,375 |
| FOBT | 0.369 | 10 | 21.70 |
| Computed tomography scan | 0.306 | 15 | 2175 |
| Ultrasound | 0.294 | 12 | 370.50 |
| SBFT | 0.294 | 11 | 189 |
| Hydrogen breath test | 0.250 | 9 | 175 |
| Sigmoidoscopy | 0.200 | 16 | 1215 |
| Barium enema | 0.188 | 14 | 359 |

ESR = erythrocyte sedimentation rate; FOBT = fecal occult blood test; IBS = irritable bowel syndrome; NA = not applicable; SBFT = small-bowel follow-through.
*Gastroenterologists were asked to rank-score the sequence that tests/diagnostics are requested (higher scores implied earlier utilization).

sigmoidoscopy, hydrogen breath test, and ultrasound. The sequence of diagnostic tests was generally consistent with the probability of using a diagnostic test or procedure. Physicians were more likely to test CBC, ESR, CRP, thyroid function, and celiac panel before performing procedures such as a colonoscopy, ultrasound, enema, and sigmoidoscopy. Time to diagnosis was generally <1 month, although some physicians estimated a time frame up to 6 months.

### CM Model Outcomes

Estimated costs of diagnostic tests and procedures are summarized in Table I and Supplemental Table II (given in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.05.003). Not including the cost of the IBS diagnostic blood panel, blood diagnostic test costs ranged from approximately $22 for a fecal occult blood test to $450 for a celiac test; procedures costs ranged from $189 for small-bowel follow-through to $2727 for a colonoscopy. The per-visit costs of a new office visit or an established office visit were $109.05 and $72.94, respectively.

A schematic of the CM model for the 2 diagnostic pathways (IBS diagnostic blood panel vs exclusionary) is shown in Figure 1**A**. The exclusionary diagnostic pathway included stage 1 (early) diagnostic tests (Figure 1**B**) and stage 2 procedures (Figure 1**C**), in conjunction with probability of utilization. The IBS diagnostic blood panel pathway considered all biomarker outcomes and included the possibility that further testing would be likely in a patient without a diagnosis of IBS-D. Table II provides a summary of CM model outcomes. For this model, the probability that a physician will send a patient to treatment after the IBS diagnostic blood panel was set to be the posttest probability for the patient being IBS-D disease positive. The total expected cost in this case was $3490. For the base-case, the probability of sending the patient to treatment was 0.20 in the exclusionary pathway arm. The total expected cost according to the exclusionary pathway was $3999, compared with $3490 for the IBS diagnostic blood panel pathway, representing an expected cost savings of $509. Cost savings increase inversely with the probability that the exclusionary pathway sends patients to treatment, with potential cost savings of $735 for a probability of 0.0. Conversely, cost savings associated with the IBS diagnostic blood panel pathway narrow as the probability of sending a patient to treatment increases in the exclusionary pathway arm (Table III). The break-even for this variable occurs when the probability of treatment in the exclusionary pathway is equal to 0.652 (Figure 2). A summary of stage 1 and stage 2 diagnostic costs is presented for tests and procedure (see Supplemental Table IV in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.05.003)

A sensitivity analysis was performed for the pretest probability of disease (IBS-D) (Table IV, Figure 3). The pretest probability of disease ranged from 0.363 to 0.963 (base-case, 0.763). The estimated cost savings increase as the pretest probability of disease increases. The break-even for this variable occurs when the pretest probability of disease is equal to 0.451. If the pretest probability of disease is 0.363, the model predicts that the IBS diagnostic blood test pathway will cost $142 more than the exclusionary pathway. If the pretest probability of disease ranges up to 0.963, the model predicts a cost savings of $840 for the IBS diagnostic blood panel pathway.

Table II. Summary of the cost-minimization model (base-case).

| Diagnostic Pathway | Pretest Probability of Disease (IBS-D) | Probability (IBS Treatment) Exclusionary | Expected Cost, US $ | Cost Savings, US $* |
|---|---|---|---|---|
| IBS diagnostic blood panel | 0.763 | NA | 3490 | (509) |
| Exclusionary | NA | 0.200 | 3999 | |

IBS = irritable bowel syndrome; NA = not applicable.
*Parentheses indicate cost savings for IBS diagnostic blood panel pathway.

Table III. One-way sensitivity analysis for the probability of irritable bowel syndrome (IBS) treatment in the exclusionary arm.

| Diagnostic Pathway | Pretest Probability of Disease (IBS-D) | Probability (IBS Treatment) Exclusionary | Expected Cost, US $ | Cost Savings, US $* |
|---|---|---|---|---|
| IBS diagnostic blood panel | 0.763 | NA | 3490 | 54 |
| Exclusionary | NA | 70.0 | 3436 | |
| IBS diagnostic blood panel | 0.763 | NA | 3490 | (58) |
| Exclusionary | NA | 60.0 | 3548 | |
| IBS diagnostic blood panel | 0.763 | NA | 3490 | (171) |
| Exclusionary | NA | 50.0 | 3661 | |
| IBS diagnostic blood panel | 0.763 | NA | 3490 | (284) |
| Exclusionary | NA | 40.0 | 3774 | |
| IBS diagnostic blood panel | 0.763 | NA | 3490 | (397) |
| Exclusionary | NA | 30.0 | 3887 | |
| IBS diagnostic blood panel | 0.763 | NA | 3490 | (509)† |
| Exclusionary | NA | 20.0 | 3999 | |
| IBS diagnostic blood panel | 0.763 | NA | 3490 | (622) |
| Exclusionary | NA | 10.0 | 4112 | |
| IBS diagnostic blood panel | 0.763 | NA | 3490 | (735) |
| Exclusionary | NA | 0.0 | 4225 | |

NA = not applicable.
*Parentheses indicate cost savings for IBS diagnostic blood panel pathway.
†Base-case results.

The posttest probability of having IBS-D according to pretest probability and outcomes for individual biomarkers measured with the IBS diagnostic blood panel are summarized in **Supplemental Table III** (given in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.05.003). As expected, the posttest probability of having IBS-D is proportional to the pretest probability and greatest when both CdtB and vinculin are elevated (positive results). The posttest probability of IBS-D declines when the 2 biomarkers fail to corroborate (1 positive and 1 negative), and IBS-D is least likely in patients negative (not elevated) for both biomarkers.

A scenario analysis has been performed that models the probability of IBS-D treatment as the posttest probability of IBS-D for both diagnostic arms (**Table V**). The cost savings for the IBS diagnostic blood panel arm ranges from $302 to ($159). If the pretest probability of IBS-D is equal to 0.50, the model predicts a cost savings of $117 for the IBS diagnostic blood panel arm.

One-way sensitivity analyses were performed for all cost and utilization variables for both treatment arms. For utilization probabilities and costs, the values ranged from ±25% (probabilities were restricted to [0, 1]). For the utilization probabilities,

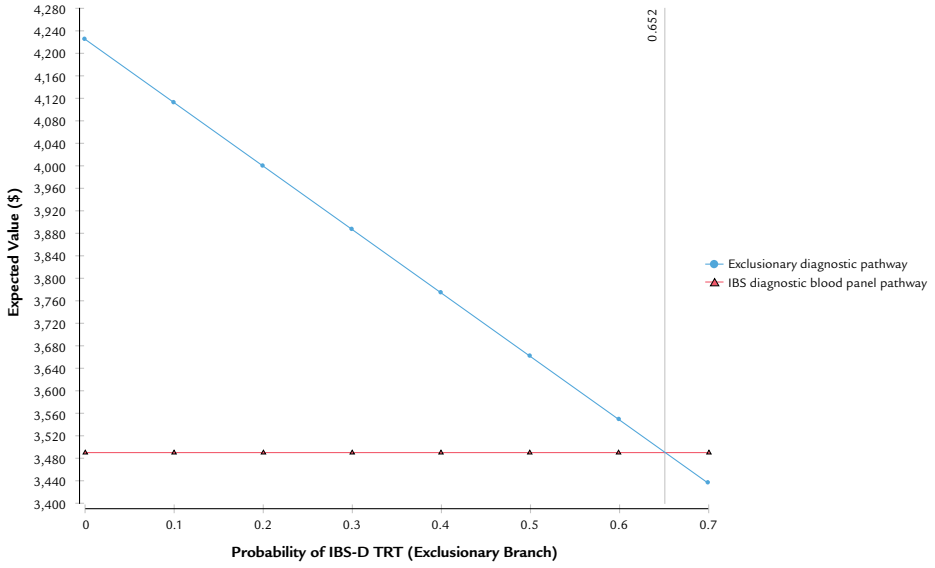


Figure 2. One-way sensitivity analysis for the probability of irritable bowel syndrome (IBS) treatment in the exclusionary branch. TRT = treatment.

these analyses indicate which variables had the most influence on the CM results: colonoscopy (1), CT scan (2), endoscopy (3), celiac test (4), sigmoidoscopy (5), and the thyroid function test (6) (see Supplemental Tables VII and VIII in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.05.003). For the cost sensitivity analyses, the following variables had the most influence on the CM results: colonoscopy (1), endoscopy (2), CT scan (3), celiac test (4), sigmoidoscopy (5), and the thyroid function test (6).

One-way sensitivity analysis for IBS treatment success with the IBS diagnostic blood panel pathway and with the exclusionary pathway is summarized in Figure 4. The probability of IBS treatment success was derived from the TARGET (Targeted Non-systemic Antibiotic Rifaximin Gut Selective Evaluation Treatment of Non-constipated IBS) studies for rifaximin (ie, 41% responded to the primary end point for TARGET 1/2; 72% responded to at least 1 dimension for TARGET 3).[21,30] The expected cost of the IBS diagnostic blood panel pathway is less than that of the exclusionary pathway for the entire range of the variable being investigated (ie, the probability of IBS treatment success). As the probability of IBS treatment success increased, the cost savings associated with the IBS diagnostic blood panel pathway increased from $509 to $1051 per patient.

## Budget Impact Analysis

A summary of the budget impact analysis for 1 million covered lives is shown in Table VI.[6,29,31] In this analysis, prevalence of IBS and IBS-D were set at 14.1%[6] and 32.2%, respectively (data on file). The proportion of patients seeking care was tested from 10% to 100%. The IBS diagnostic blood panel cost savings per patient and annual net cost savings to plan increase in proportion to the percentage of patients seeking care. For the base-case, in which the probability of sending a patient to IBS-D treatment in the exclusionary arm was 0.200 and the cost savings per patient was predicted to be $509, the IBS diagnostic blood panel would be estimated to save the plan a net savings of up to $3.6 million (annually). Annual plan cost savings surpass $7 million when 100% of the persons meeting the criteria for IBS-D seek care.

A sensitivity analysis was performed for the budget impact for the variable of the pretest probability of disease (IBS-D) (Table VII).[6,29,31] The pretest probability of disease ranged from 0.363 to 0.963. The estimated cost (savings) for the health plan ranged from $1.01 million to ($6.00 million). On a PMPM basis, the cost (savings) ranged from $0.08 to ($0.50).

The PSA estimated the variability for the base-case results of the cost-minimization model (Figure 5, Supplemental Table IX [in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.05.003]).

Table IV. One-way sensitivity analysis for the pretest probability of disease (diarrhea-predominant irritable bowel syndrome [IBS]).

| Diagnostic Pathway | Pretest Probability of Disease (IBS-D) | Probability (IBS Treatment) Exclusionary | Expected Cost, US $ | Cost Savings, US $* |
|---|---|---|---|---|
| IBS diagnostic blood panel | 0.363 | NA | 4141 | 142 |
| Exclusionary | NA | 20.0 | 3999 | |
| IBS diagnostic blood panel | 0.463 | NA | 3980 | (19) |
| Exclusionary | NA | 20.0 | 3999 | |
| IBS diagnostic blood panel | 0.563 | NA | 3817 | (182) |
| Exclusionary | NA | 20.0 | 3999 | |
| IBS diagnostic blood panel | 0.663 | NA | 3654 | (345) |
| Exclusionary | NA | 20.0 | 3999 | |
| IBS diagnostic blood panel | 0.763 | NA | 3490 | (509)† |
| Exclusionary | NA | 20.0 | 3999 | |
| IBS diagnostic blood panel | 0.863 | NA | 3325 | (674) |
| Exclusionary | NA | 20.0 | 3999 | |
| IBS diagnostic blood panel | 0.963 | NA | 3159 | (840) |
| Exclusionary | NA | 20.0 | 3999 | |

NA = not applicable.
*Parentheses indicate cost savings for IBS diagnostic blood panel pathway.
†Base-case results.

The majority of simulations (95.7%) indicated a positive cost savings associated with the IBS diagnostic blood panel pathway. For the differences between the simulated values for both diagnostic arms, the interval from the 10th to the 90th percentile was (–974.31, –99.15). The mean and SD of the simulated differences were –502.84 and 356.66.

## DISCUSSION

Symptoms of IBS adversely affect patient quality of life, including social and psychologic aspects, and are associated with considerable cost to the health care system.[4,16,32,33] Indeed, overutilization of diagnostic procedures represents a growing complaint among physicians and payers.[34–36] According to recent guidelines for the diagnosis and management of IBS issued by the National Institute for Health and Care Excellence,[12] colonoscopy, sigmoidoscopy, ultrasound, thyroid testing, and other diagnostic tests are not considered necessary to confirm a diagnosis in individuals who meet IBS diagnostic criteria. We also recognize that although the risks of diagnostic testing for IBS are small, they are not insignificant. Complications of invasive procedures, albeit infrequent, may include risk of bacterial infection, hemorrhage, and bowel perforation.[37,38] These procedures may require sedation, are sometimes painful, and are generally unpleasant and uncomfortable for patients. Eliminating tests and/or procedures currently used in the diagnosis by the exclusionary pathway may allow patients to start effective treatment earlier, saving health care dollars in the process.

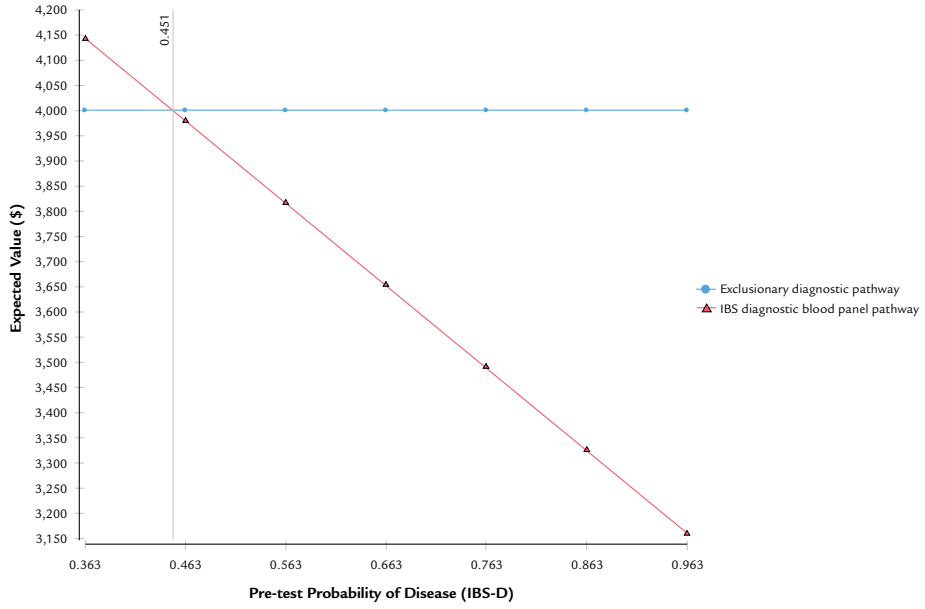


Figure 3. One-way sensitivity analysis for the pretest probability of diarrhea-predominant irritable bowel syndrome (IBS-D) disease positive.

In the current study using conservative assumptions (base-case), we estimated that the cost savings associated with the IBS diagnostic blood panel would be $509 per patient (Table II). The PSA suggests that it is highly likely (>95% of simulations) that the IBS diagnostic blood panel pathway is associated with a cost savings greater than zero. When the cost savings were amortized over 1 million lives, the IBS diagnostic blood panel was estimated to save the plan a net savings of up to approximately $3 million annually

Table V. Summary of cost-minimization model (scenario analysis).

| Diagnostic Pathway | Pretest Probability of Disease (IBS-D) | Expected Cost, US $ | Cost Savings, US $ |
|---|---|---|---|
| IBS diagnostic blood panel | 0.30 | 3585 | 302 |
| Exclusionary | 0.30 | 3887 | |
| IBS diagnostic blood panel | 0.40 | 3564 | 210 |
| Exclusionary | 0.40 | 3774 | |
| IBS diagnostic blood panel | 0.50 | 3544 | 117 |
| Exclusionary | 0.50 | 3661 | |
| IBS diagnostic blood panel | 0.60 | 3523 | 25 |
| Exclusionary | 0.60 | 3548 | |
| IBS diagnostic blood panel | 0.70 | 3503 | (67) |
| Exclusionary | 0.70 | 3436 | |
| IBS diagnostic blood panel | 0.80 | 3482 | (159) |
| Exclusionary | 0.80 | 3323 | |

IBS = irritable bowel syndrome.

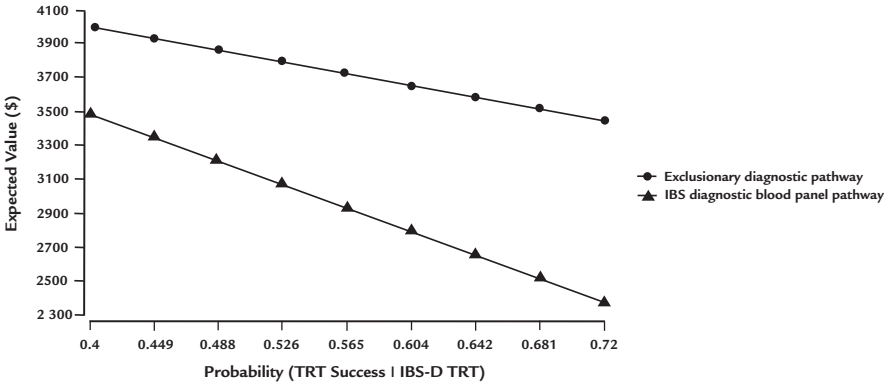


Figure 4. One-way sensitivity analysis for the success of diarrhea-predominant irritable bowel syndrome (IBS-D) treatment. TRT = treatment.

(Table VI). The per-patient and per-plan (annual) cost savings reached $840 and $6.00 million, respectively, when more optimistic assumptions for the pretest probability of disease were tested. As expected, cost savings associated with the IBS diagnostic blood panel were highly dependent on the probability that a given test result would lead to treatment in either treatment arm. Cost savings grew in proportion to level of "uncertainty" and "narrowed" with diagnostics that offer greater certainty (eg, higher probability of IBS-D

Table VI. Budget impact analysis summary for the proportion of patients seeking care.

| Covered Lives[*,†,‡,§,¶] | Proportion Seeking Care[‖] | No. of Individuals Seeking Care | Net Cost if 100% of Patients Diagnosed With Exclusionary Path | Net Cost if 50% Exclusionary Path, 50% IBS Diagnostic Blood Panel | Cost (Savings) | Cost (Savings) PMPM |
|---|---|---|---|---|---|---|
| 1,000,000 | 10% | 2856 | $11,421,144 | $10,694,292 | $(726,852) | $(0.06) |
| 1,000,000 | 20% | 5712 | $22,842,288 | $21,388,584 | $(1,453,704) | $(0.12) |
| 1,000,000 | 30% | 8567 | $34,259,433 | $32,079,132 | $(2,180,302) | $(0.18) |
| 1,000,000 | 40% | 11,423 | $45,680,577 | $42,773,424 | $(2,907,154) | $(0.24) |
| 1,000,000 | 50% | 14,279 | $57,101,721 | $53,467,716 | $(3,634,006) | $(0.30) |
| 1,000,000 | 60% | 17,135 | $68,522,865 | $64,162,008 | $(4,360,858) | $(0.36) |
| 1,000,000 | 70% | 19,991 | $79,944,009 | $74,856,300 | $(5,087,710) | $(0.42) |
| 1,000,000 | 80% | 22,846 | $91,361,154 | $85,546,847 | $(5,814,307) | $(0.48) |
| 1,000,000 | 90% | 25,702 | $02,782,298 | $96,241,139 | $(6,541,159) | $(0.55) |
| 1,000,000 | 100% | 28,558 | $114,203,442 | $106,935,431 | $(7,268,011) | $(0.61) |

HMO = health maintenance organization; IBS = irritable bowel syndrome; IBS-D = diarrhea-predominant irritable bowel syndrome; PMPM = per member per month.
[*]Assumption: HMO with 1 million covered lives.
[†]IBS Prevalence = 14.1%.[6]
[‡]IBS-D Prevalence within IBS =32.2%.[24]
[§]Proportion of US population within 18–64 age group (62.9%).[23]
[¶]Pretest probability of disease estimated to be 0.763 (from cost-minimization model).
[‖]Base-case assumption: proportion seeking care = 50%.

Table VII. Budget impact analysis summary for the pretest probability of disease (diarrhea-predominant irritable bowel syndrome [IBS-D]).

| Covered Lives[*,†,‡,§,¶] | Pretest Probability of Disease (IBS-D) | No. of Individuals Seeking Care | Net Cost if 100% of Patients Diagnosed With Exclusionary Path | Net Cost if 50% Exclusionary Path, 50% IBS Diagnostic Blood Panel | Cost (Savings) | Cost (Savings) PMPM |
|---|---|---|---|---|---|---|
| 1,000,000 | 36.3% | 14,279 | $57,101,721 | $58,115,530 | $1,013,809 | $0.08 |
| 1,000,000 | 46.3% | 14,279 | $57,101,721 | $56,966,071 | $(135,651) | $(0.01) |
| 1,000,000 | 56.3% | 14,279 | $57,101,721 | $55,802,332 | $(1,299,389) | $(0.11) |
| 1,000,000 | 66.3% | 14,279 | $57,101,721 | $54,638,594 | $(2,463,128) | $(0.21) |
| 1,000,000 | 76.3% | 14,279 | $57,101,721 | $53,467,716 | $(3,634,006) | $(0.30) |
| 1,000,000 | 86.3% | 14,279 | $57,101,721 | $52,289,698 | $(4,812,023) | $(0.40) |
| 1,000,000 | 96.3% | 14,279 | $57,101,721 | $51,104,541 | $(5,997,180) | $(0.50) |

HMO = health maintenance organization; PMPM = per member per month.
[*]Assumption: HMO with 1 million covered lives.
[†]IBS prevalence, 14.1%.[6]
[‡]IBS-D prevalence within IBS, 32.2%.[24]
[§]Proportion of US population within 18- to 64-year-old age group, 62.9%.[23]
[¶]Proportion of patients seeking care estimated to be 0.5 (assumption).

disease). When the importance (to decision-making) of individual laboratory and procedural tests was assessed, the cost of colonoscopy was the largest contributor to variability in cost-effectiveness outcome. Other diagnostics that contributed to variability included the costs associated with CT scanning and endoscopy.

A decision to send a patient to treatment based on an IBS diagnostic blood panel was also affected by individual biomarker outcomes. For example, an absence of corroboration between anti-CdtB and anti-vinculin results reduced the posttest probability of sending a patient to treatment (Table III). In the validation study, although both tests were effective in

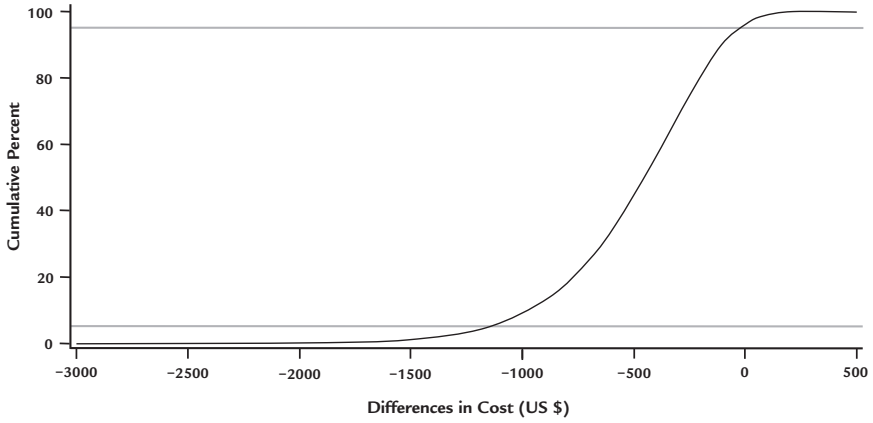


Figure 5. Cumulative distribution function for probability sensitivity analysis: (1) 95.7% of simulated differences were $<0$ (ie, indicating cost savings); and (2) Monte-Carlo simulation with 20,000 iterations.

discriminating IBS-D from IBD, the value of anti-CdtB was higher than that of anti-vinculin.[21] This finding was reflected in our model assumptions. From a mathematical perspective, the negative likelihood ratios (anti-CdtB, 0.6; anti-vinculin, 0.8) were not as influential as the positive likelihood ratios (anti-CdtB, 5.2; anti-vinculin, 2.0). Furthermore, the possibility that a patient who is negative for both biomarkers has IBS-D cannot be excluded. Indeed, the posttest probabilities for IBS-D remain fairly significant even when both test results were negative, ranging from 22% to 93%.

Cost savings were considered when the model was extended to assess the effect of treatment for IBS-D. Estimated cost savings increased as the probability of treatment success increased. Because there are few proven safe and effective agents for the treatment of IBS-D, we derived treatment success (ie, response rates) from the trials of rifaximin in this patient population.[30] In those studies, 41% of patients randomized to undergo active treatment experienced relief in global IBS symptoms. We recognize that, at least in part, the absence of a number of effective therapies may contribute to the participation rate of patients with IBS seeking medical treatment.[39] For the analyses assessed in this study, we provided a wide range of participation rates (ie, 10%–100%) that was likely to contain the actual rate of patients seeking medical attention in determining the budget impact of IBS diagnostic blood tests. In a study of the costs of IBS in the United States and United Kingdom, Maxion-Bergemann et al[16] reported that 10% to 25% of individuals with IBS seek medical treatment.

There were some limitations to the present study. Mean pretest probability of IBS disease based on symptom presentation was 0.763; however, there was a wide range of response among the surveyed physicians, and the sample size of 9 was relatively small. The model did not account for the small percentage of physicians who would initiate treatment before conducting a battery of diagnostic tests. Our model concluded with a positive IBS-D diagnosis (for all practical purposes, the model ended with referral for treatment). Although potential cost savings associated with the IBS diagnostic blood panel was demonstrated in the model, we recognize that the probability that a physician will send a patient to treatment after the test outcome is unknown at this early juncture. The additional scenario analysis (which used the posttest probability of disease as the probability of proceeding to treatment in both arms) predicted modest cost savings (for the IBS diagnostic blood panel) or modest additional costs, depending on the pretest probability of disease.

For the budget impact analysis, the proportion of patients diagnosed with the IBS diagnostic blood panel pathway was arbitrarily set at 50%, which may over- or underrepresent real-world utilization. In addition, the exclusionary pathway was estimated conservatively. For example, we did not consider repeated investigations (eg, multiple colonoscopies) and the potential for more invasive studies stemming from false-positive results of the investigations in the exclusionary pathway. Finally, the cost of pathology assessments was not considered in the construction of our model.

Thus, a model to estimate the cost savings associated with a novel biomarker diagnostic blood panel conservatively suggested that implementation will achieve cost savings in the diagnosis of IBS-D. Other benefits that may be realized but are more difficult to quantify include reduced loss of productivity and fewer days out of the office, lower risk for GI procedure–related complications, and lower morbidity for patients. In addition to the potential cost savings associated with the IBS diagnostic blood panel, integration of the blood panel into the process of care may align with current recommendations related to reducing the number of unnecessary diagnostic tests.[12] With the exception of patients who present with symptoms of alarm that may indicate a diagnosis of cancer, the application of the IBS diagnostic blood panel may result in greater efficiencies in patient management and associated cost savings to the health care system.

## CONCLUSIONS

As our knowledge about the pathophysiology of IBS grows, it will be important to determine how the IBS diagnostic blood panel is used in the real world, as well as to assess whether the panel outcomes alter our view of IBS as a functional disorder rather than an organic disease. Further studies of this novel assessment, and of others as they are introduced, are warranted inasmuch as they may streamline the management of various disorders.

## ACKNOWLEDGMENTS

Technical editorial and medical writing support was provided by LN, PhD, CMPP, of 4-Cite Medical Communications, LLC, and funded by AHRM Inc.

Dr. Pimentel contributed to the study design, data interpretation and writing. Dr. Rezaie contributed to the study design, data interpretation and writing. Mr. Magar contributed to the literature search, study design, data interpretation and writing. Mr. Purdy contributed to the literature search, figure creation, study design, data collection, and writing.

## CONFLICTS OF INTERESTS

Dr. Rezaie has participated in advisory board meetings for commonwealth laboratories; he has also served as a consultant for Actavis and as a speaker for Salix. Mr. Purdy is an employee of AHRM Inc, and Mr. Magar is an employee of CRO/Outcomes Research, AHRM Inc. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

## SUPPORTING INFORMATION

Supplemental tables accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.05.003.

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## SUPPLEMENTARY MATERIAL

Tables SI–SIX.

Table SI. Physician Characteristics (Survey) (US Respondents only)

| Variable | Level | Frequency | Percent |
|---|---|---|---|
| N | NA | 9 | 100.00% |
| Experience | < 1 year | 2 | 22.22% |
| | 1 – 4 years | 2 | 22.22% |
| | 5 – 7 years | 0 | 0.00% |
| | < 7 years | 5 | 55.56% |
| Practice Setting | University Hospital | 5 | 55.56% |
| | University Hospital / Community | 1 | 11.11% |
| | University Hospital / Government | 2 | 22.22% |
| | No Response | 1 | 11.11% |
| % Patients with IBS | ≤ 50% | 6 | 66.67% |
| | > 50% | 3 | 33.33% |

NA, Not Applicable

Table SII. *Supplemental Table II* List of cost references

| Diagnostic | Cost | Description | Source |
|---|---|---|---|
| Office Visit New | 109.05 | Average of HCPCS codes 99201 – 99205. (Accessed April 7, 2015) | https://www.cms.gov/apps/physician-fee-schedule/search/search-results.aspx?Y=0&T=0&HT=0&CT=3&H1=99201. (Accessed April 6, 2015) |
| Office Visit Established | 72.94 | Average of HCPCS codes 99211 – 99215. (Accessed April 7, 2015) | https://www.cms.gov/apps/physician-fee-schedule/search/search-results.aspx?Y=0&T=0&HT=0&CT=3&H1=99211. (Accessed April 6, 2015) |
| IBS Diagnostic Blood Panel | 500 | Provided by Sponsor | Commonwealth Laboratories, 39 Norman St. Ste 1, Salem, MA 01970 |
| Complete Blood Count | 149 | https://www.honorhealth.com/patients-visitors/average-pricing/laboratory-procedures-scottsdale85025 | Honor Health. https://www.honorhealth.com/patients-visitors/average-pricing/laboratory-procedures-scottsdale85025. (Accessed April 20, 2015) |

(continued)

Table SII. (continued).

| Diagnostic | Cost | Description | Source |
|---|---|---|---|
| ESR | 36 | http://www.walkinlab.com/catalogsearch/result/?order=relevance&dir=desc&q=erythrocyte&btnSearchSubmit= | Walk-In-Lab. http://www.walkinlab.com/catalogsearch/result/?order=relevance&dir=desc&q=erythrocyte&btnSearchSubmit=. (Accessed April 17, 2015) |
| C-Reactive Protein | 90 | https://www.honorhealth.com/patients-visitors/average-pricing/laboratory-procedures-scottsdale86140 | Honor Health. https://www.honorhealth.com/patients-visitors/average-pricing/laboratory-procedures-scottsdale86140. (Accessed April 20, 2015) |
| Faecal Calprotectin | 92 | https://www.clinicalkey.com/!/content/journal/1-s2.0-S1542356513010446 | Yang Z, Clark N, Park K.T. Effectiveness and cost-effectiveness of measuring fecal calprotectin in diagnosis of inflammatory bowel disease in adults and children. *Clin Gastroenterol Hepatol*. 2014;12(2). |
| Liver Function | 31 | www.healthcarebluebook.com | Healthcare Bluebook. http://www.healthcarebluebook.com. (Accessed April 24, 2015) |
| Thyroid Function | 257 | https://www.honorhealth.com/patients-visitors/average-pricing/laboratory-procedures-phoenix#84443 | Honor Health. https://www.honorhealth.com/patients-visitors/average-pricing/laboratory-procedures-phoenix#84443. (Accessed April 20, 2015) |
| FOBT | 21.7 | http://www.quidel.com/sites/default/files/Quidel%20All%20Products%20Reimbursement%201-pager%20%280914%29.pdf | Quidel. http://www.quidel.com/sites/default/files/Quidel%20All%20Products%20Reimbursement%201-pager%20%280914%29.pdf. (Accessed May 16, 2015) |
| Celiac Test | 450 | Expert Opinion | Discussions with practicing gastroenterologists |
| Hydrogen Breath Test | 175 | http://www.hydrogenbreathtesting.com/store.html | Commonwealth Laboratories Online Store. http://www.hydrogenbreathtesting.com/store.html. (Accessed May 7, 2015) |
| Endoscopy | 1,375 | https://www.healthcarebluebook.com/page_ProcedureDetails.aspx?id=340&dataset=MD&g=Upper+Gastrointestinal+Endoscopy+(no+biopsy) | Healthcare Bluebook. https://www.healthcarebluebook.com/page_ProcedureDetails.aspx?id=340&dataset=MD&g=Upper+Gastrointestinal+Endosco |

(continued)

Table SII. (continued).

| Diagnostic | Cost | Description | Source |
|---|---|---|---|
| | | | py+(no+biopsy). (Accessed April 24, 2015) |
| Sigmoidoscopy | 1,215 | https://www.healthcarebluebook.com/page_ProcedureDetails.aspx?id=518&dataset=MD&g=Sigmoidoscopy+(no+biopsy) | Healthcare Bluebook. https://www.healthcarebluebook.com/page_ProcedureDetails.aspx?id=518&dataset=MD&g=Sigmoidoscopy+(no+biopsy). (Accessed April 24, 2015) |
| Colonoscopy | 2,727 | https://www.honorhealth.com/patients-visitors/average-pricing/outpatient-procedures-phoenix | Honor Health. https://www.honorhealth.com/patients-visitors/average-pricing/outpatient-procedures-phoenix. (Accessed April 20, 2015) |
| Computed Tomography | 2,175 | In the range from national minimum (1,750) to national average (2,325) | http://www.newchoicehealth.com/procedures/ct-scan-of-abdomen. (Accessed August 3, 2015) |
| Barium Enema | 359 | https://www.healthcarebluebook.com/page_ProcedureDetails.aspx?id=366&dataset=MD&g=Barium+Enema | Healthcare Bluebook. https://www.healthcarebluebook.com/page_ProcedureDetails.aspx?id=366&dataset=MD&g=Barium+Enema. (Accessed April 24, 2015) |
| Ultrasound | 370.5 | https://www.healthcarebluebook.com/page_SearchResults.aspx?SearchTerms=abdominal+ultrasound | Healthcare Bluebook. https://www.healthcarebluebook.com/page_SearchResults.aspx?SearchTerms=abdominal+ultrasound. (Accessed April 24, 2015) |
| SBFT | 189 | https://www.healthcarebluebook.com/page_ProcedureDetails.aspx?id=374&dataset=MD&g=Lower+GI+Series | Healthcare Bluebook. https://www.healthcarebluebook.com/page_ProcedureDetails.aspx?id=374&dataset=MD&g=Lower+GI+Series. (Accessed April 24, 2015) |

ESR, erythrocyte sedimentation rate; IBS, irritable bowel syndrome; FOBT, faecal occult blood test; SBFT, small bowel follow-through.

Table SIII. Post-test probability of IBS-D

| Pre-test Pr(D+) | LR CdtB | LR VINC | LR- CdtB | LR- VINC | CdtB result | Vinculin result | Pr(D+) |
|---|---|---|---|---|---|---|---|
| 36.3 | 5.2 | 2 | 0.6 | 0.8 | P | P | 85.6% |
| 36.3 | 5.2 | 2 | 0.6 | 0.8 | P | I | 70.3% |
| 36.3 | 5.2 | 2 | 0.6 | 0.8 | I | P | 40.6% |
| 36.3 | 5.2 | 2 | 0.6 | 0.8 | I | I | 21.5% |
| 46.3 | 5.2 | 2 | 0.6 | 0.8 | P | P | 90.0% |
| 46.3 | 5.2 | 2 | 0.6 | 0.8 | P | I | 78.2% |
| 46.3 | 5.2 | 2 | 0.6 | 0.8 | I | P | 50.9% |
| 46.3 | 5.2 | 2 | 0.6 | 0.8 | I | I | 29.3% |
| 56.3 | 5.2 | 2 | 0.6 | 0.8 | P | P | 93.1% |
| 56.3 | 5.2 | 2 | 0.6 | 0.8 | P | I | 84.3% |
| 56.3 | 5.2 | 2 | 0.6 | 0.8 | I | P | 60.7% |
| 56.3 | 5.2 | 2 | 0.6 | 0.8 | I | I | 38.2% |
| 66.3 | 5.2 | 2 | 0.6 | 0.8 | P | P | 95.3% |
| 66.3 | 5.2 | 2 | 0.6 | 0.8 | P | I | 89.1% |
| 66.3 | 5.2 | 2 | 0.6 | 0.8 | I | P | 70.2% |
| 66.3 | 5.2 | 2 | 0.6 | 0.8 | I | I | 48.6% |
| 76.3 | 5.2 | 2 | 0.6 | 0.8 | P | P | 97.1% |
| 76.3 | 5.2 | 2 | 0.6 | 0.8 | P | I | 93.1% |
| 76.3 | 5.2 | 2 | 0.6 | 0.8 | I | P | 79.4% |
| 76.3 | 5.2 | 2 | 0.6 | 0.8 | I | I | 60.7% |
| 86.3 | 5.2 | 2 | 0.6 | 0.8 | P | P | 98.5% |
| 86.3 | 5.2 | 2 | 0.6 | 0.8 | P | I | 96.3% |
| 86.3 | 5.2 | 2 | 0.6 | 0.8 | I | P | 88.3% |
| 86.3 | 5.2 | 2 | 0.6 | 0.8 | I | I | 75.1% |
| 96.3 | 5.2 | 2 | 0.6 | 0.8 | P | P | 99.6% |
| 96.3 | 5.2 | 2 | 0.6 | 0.8 | P | I | 99.1% |
| 96.3 | 5.2 | 2 | 0.6 | 0.8 | I | P | 96.9% |
| 96.3 | 5.2 | 2 | 0.6 | 0.8 | I | I | 92.6% |

CdtB, cytolethal distending toxin B; IBS-D, diarrhoea predominant irritable bowel syndrome; LR+, laboratory result positive; LR-, laboratory result negative; N, negative; P, positive; Pr(D+), probability of disease (IBS-D); VINC, vinculin.

Table SIV. Summary of Stage 1 & Stage 2 Diagnostic Costs

| Stage | Procedure / Test | Cost per Test* | Avg Cost / Patient† |
|---|---|---|---|
| 1 | Endoscopy | $ 1,375.00 | $ 550.00 |
| 1 | Celiac Panel | $ 450.00 | $ 399.60 |
| 1 | Hydrogen Breath Test | $ 175.00 | $ 43.75 |
| 1 | Complete Blood Count | $ 149.00 | $ 130.38 |
| 1 | Erythrocyte Sedimentation Rate | $ 36.00 | $ 19.12 |
| 1 | C-Reactive Protein | $ 90.00 | $ 69.75 |
| 1 | Calprotectin | $ 92.00 | $ 40.30 |
| 1 | Liver Function Test | $ 31.00 | $ 19.96 |
| 1 | Thyroid Function Test | $ 257.00 | $ 176.82 |
| 1 | Fecal Occult Blood Test | $ 21.70 | $ 8.01 |
| 2 | Barium Enema | $ 359.00 | $ 67.49 |
| 2 | Sigmoidoscopy | $ 1,215.00 | $ 243.00 |
| 2 | Colonoscopy | $2,727.00 | $ 1,704.37 |
| 2 | Abdominal Pelvic CT Scan | $ 2,175.00 | $ 665.55 |
| 2 | Ultrasound | $ 370.50 | $ 108.93 |
| 2 | Small Bowel Follow Through | $ 189.00 | $ 55.57 |

*Cost per each test or procedure.
†Average cost per patient (equal to the product of the (cost per test) x (probability the patient receives the test)).

Table SV. Cost distributions for probability sensitivity analysis (PSA)

| Distribution type | Distribution variable | Parameter 1 = mu | Parameter 2 = sigma |
|---|---|---|---|
| LogNormal | Cost of Barium Enema | 5.778 | 0.459 |
| LogNormal | Cost of Calprotectin | 4.416 | 0.459 |
| LogNormal | Cost of CBC | 4.899 | 0.459 |
| LogNormal | Cost of Celiac Panel | 6.004 | 0.459 |
| LogNormal | Cost of Colonoscopy | 7.806 | 0.459 |
| LogNormal | Cost of CRP | 4.394 | 0.459 |
| LogNormal | Cost of CTSC | 7.579 | 0.459 |
| LogNormal | Cost of Endoscopy | 7.121 | 0.459 |
| LogNormal | Cost of ESR | 3.478 | 0.459 |
| LogNormal | Cost of FOBT | 2.972 | 0.459 |
| LogNormal | Cost of Follow-up Visit | 4.184 | 0.4589 |
| LogNormal | Cost of HBT Test | 5.059 | 0.459 |
| LogNormal | Cost of Initial Visit | 4.586 | 0.4589 |
| LogNormal | Cost of the Liver Function Test | 3.329 | 0.459 |
| LogNormal | Cost of SBFT | 5.136 | 0.459 |
| LogNormal | Cost of Sigmoidoscopy | 6.997 | 0.459 |
| LogNormal | Cost of TFT | 5.444 | 0.459 |
| LogNormal | Cost of Ultrasound | 5.809 | 0.459 |

CBC, complete blood count; CRP, C-reactive protein; CTSC, computed tomography scan; ESR, erythrocyte sedimentation rate; FOBT, faecal occult blood test; HBT, hydrogen breath test; SBFT, small bowel follow-through; TFT, thyroid function test.

Table SVI. Probability distributions (utilization) for probability sensitivity analysis (PSA)

| Distribution type | Distribution variable | Parameter 1 = alpha | Parameter 2 = beta |
|---|---|---|---|
| Beta | Probability of TRT (Exclusionary Branch) | 3.000 | 12.000 |
| Beta | Probability of Barium Enema | 2.682 | 11.5837 |
| Beta | Probability of Calprotectin | 10.344 | 13.272 |
| Beta | Probability of CBC | 8.695 | 1.2422 |
| Beta | Probability of Celiac Panel | 7.944 | 1.0019 |
| Beta | Probability of Colonoscopy | 14.023 | 8.4141 |
| Beta | Probability of CRP | 12.739 | 3.6984 |
| Beta | Probability of CTSC | 6.192 | 14.0441 |
| Beta | Probability of Endoscopy | 9.200 | 13.800 |
| Beta | Probability of ESR | 12.693 | 11.2109 |
| Beta | Probability of FOBT | 8.223 | 14.0611 |
| Beta | Probability of HBT | 4.438 | 13.3125 |
| Beta | Probability of IBS Positive | 13.034 | 4.0487 |
| Beta | Probability of IBS Treatment Success | 9.508 | 13.6821 |
| Beta | Probability of LFT | 14.121 | 7.8058 |
| Beta | Probability of SBFT | 5.808 | 13.948 |
| Beta | Probability of Sigmoidoscopy | 3.00 | 12.00 |
| Beta | Probability of TFT | 14.08 | 6.3853 |
| Beta | Probability of Ultrasound | 5.808 | 13.948 |
| Beta | Sensitivity of CdtB | 10.315 | 13.2885 |
| Beta | Sensitivity of Vinculin | 6.837 | 14.1354 |

CBC, complete blood count; CdtB, cytolethal distending toxin B; CRP, C-reactive protein; CTSC, computed tomography scan; ESR, erythrocyte sedimentation rate; FOBT, faecal occult blood test; HBT, hydrogen breath test; IBS, irritable bowel syndrome; LFT, liver function test; SBFT, small bowel follow-through; TFT, thyroid function test; TRT, treatment.

Table SVII. Sensitivity analysis for cost variables

| Input | Cost | Cost (-25%) | Cost (+25%) | Cost (savings) minimum | Cost (savings) maximum | Delta [1] |
|---|---|---|---|---|---|---|
| Colonoscopy | $ 2,727.00 | $ 2,045.25 | $ 3,408.75 | $ (427) | $ (591) | $ 164 |
| Endoscopy | $ 1,375.00 | $ 1,031.25 | $ 1,718.75 | $ (478) | $ (541) | $ 63 |
| Computed Tomography | $ 2,175.00 | $ 1,631.25 | $ 2,718.75 | $ (478) | $ (541) | $ 63 |
| Celiac Test | $ 450.00 | $ 337.50 | $ 562.50 | $ (487) | $ (532) | $ 45 |
| Sigmoidoscopy | $ 1,215.00 | $ 911.25 | $ 1,518.75 | $ (498) | $ (521) | $ 23 |
| Thyroid Function Test | $ 257.00 | $ 192.75 | $ 321.25 | $ (500) | $ (520) | $ 20 |
| Complete Blood Count | $ 149.00 | $ 111.75 | $ 186.25 | $ (502) | $ (517) | $ 15 |
| Ultrasound | $ 370.50 | $ 277.88 | $ 463.13 | $ (504) | $ (515) | $ 11 |
| C-Reactive Protein | $ 90.00 | $ 67.50 | $ 112.50 | $ (505) | $ (513) | $ 8 |
| Barium Enema | $ 359.00 | $ 269.25 | $ 448.75 | $ (506) | $ (513) | $ 7 |
| Faecal Calprotectin | $ 92.00 | $ 69.00 | $ 115.00 | $ (507) | $ (512) | $ 5 |
| SBFT | $ 189.00 | $ 141.75 | $ 236.25 | $ (507) | $ (512) | $ 5 |
| Hydrogen Breath Test | $ 175.00 | $ 131.25 | $ 218.75 | $ (507) | $ (512) | $ 5 |
| ESR | $ 36.00 | $ 27.00 | $ 45.00 | $ (508) | $ (511) | $ 3 |
| Liver Function Test | $ 31.00 | $ 23.25 | $ 38.75 | $ (509) | $ (511) | $ 2 |
| FOBT | $ 21.70 | $ 16.28 | $ 27.13 | $ (509) | $ (510) | $ 1 |

FOBT, faecal occult blood test; SBFT, small bowel follow-through.

Table SVIII. Sensitivity analysis for utilization variables

| Input | Probability of utilization | Prob (-25%) | Prob (+25%) | Cost (savings) minimum | Cost (savings) maximum | Delta |
|---|---|---|---|---|---|---|
| Colonoscopy | 0.625 | 0.469 | 0.781 | $ (428) | $ (591) | $ 163 |
| Computed tomography | 0.306 | 0.230 | 0.383 | $ (478) | $ (542) | $ 64 |
| Endoscopy | 0.4 | 0.300 | 0.500 | $ (478) | $ (541) | $ 63 |
| Celiac Test | 0.888 | 0.666 | 1.000 | $ (487) | $ (521) | $ 34 |
| Sigmoidoscopy | 0.2 | 0.150 | 0.250 | $ (498) | $ (521) | $ 23 |
| Thyroid Function Test | 0.688 | 0.516 | 0.860 | $ (499) | $ (520) | $ 21 |
| Complete Blood Count | 0.875 | 0.656 | 1.000 | $ (502) | $ (514) | $ 12 |
| Ultrasound | 0.294 | 0.221 | 0.368 | $ (504) | $ (515) | $ 11 |
| C-Reactive Protein | 0.775 | 0.581 | 0.969 | $ (505) | $ (513) | $ 8 |
| Barium Enema | 0.188 | 0.141 | 0.235 | $ (506) | $ (513) | $ 7 |
| Faecal Calprotectin | 0.438 | 0.329 | 0.548 | $ (507) | $ (512) | $ 5 |
| SBFT | 0.294 | 0.221 | 0.368 | $ (507) | $ (512) | $ 5 |
| Hydrogen Breath Test | 0.25 | 0.188 | 0.313 | $ (507) | $ (512) | $ 5 |
| Liver Function Test | 0.644 | 0.483 | 0.805 | $ (508) | $ (511) | $ 3 |
| ESR | 0.531 | 0.398 | 0.664 | $ (508) | $ (511) | $ 3 |
| FOBT | 0.369 | 0.277 | 0.461 | $ (509) | $ (510) | $ 1 |

ESR, erythrocyte sedimentation rate; FOBT, faecal occult blood test; SBFT, small bowel follow-through.

Table SIX. Summary for probability sensitivity analysis

| Statistic* | IBS diagnostic blood test path | Exclusionary path | Differences† |
|---|---|---|---|
| Mean | $ 3,499.04 | $ 4,001.87 | $ (502.84) |
| Standard Deviation | $ 763.69 | $ 867.38 | $ 356.66 |
| Minimum | $ 1,448.80 | $ 1,889.32 | $ (2,775.69) |
| 10% | $ 2,630.42 | $ 3,023.15 | $ (974.31) |
| Median | $ 3,397.11 | $ 3,881.84 | $ (451.53) |
| 90% | $ 4,485.65 | $ 5,129.95 | $ (99.15) |
| Maximum | $ 8,233.32 | $ 10,194.47 | $ 420.62 |

IBS, irritable bowel syndrome.
*Monte Carlo Simulation (20,000 iterations).
†Differences = IBS diagnostic blood panel – Exclusionary pathway.