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Cost Effectiveness of Biomarker Tests for Irritable Bowel Syndrome with Diarrhea – A Framework for Payers

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Abstract

BACKGROUND & AIMS—Diagnosis of diarrhea-predominant irritable bowel syndrome (IBS-D) relies on the Rome IV symptom-based criteria, which are imperfect for separating functional vs organic disease. Biomarker tests for IBS-D might be added to symptom data to allow clinicians to make more accurate and precise diagnoses in a cost-effective manner. We tested the economic consequences of using a range of hypothetical IBS-D biomarkers, and explored at what cost and level of accuracy a biomarker becomes cost effective. We produced a framework for payers to evaluate the return on an investment of implementing IBS-D biomarkers of varying accuracy and cost.

METHODS—We used decision analysis software to evaluate a hypothetical cohort of patients who met Rome IV criteria for IBS-D. We conducted cost utility and budget impact analyses of 2 competing approaches: usual care or an IBS biomarker-based diagnostic approach. Patients in the usual care group received empiric IBS treatment; non-responders received additional diagnostic tests for organic disease. In the group evaluated with a biomarker test, those with a positive result received IBS treatment before additional diagnostic analyses, whereas patients with a negative

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result underwent upfront diagnostic testing. Outcomes were incremental cost per quality-adjusted life year gained (third-party payer perspective) and incremental per-member per-month cost.

RESULTS—In the base case analysis, using a willingness-to-pay threshold of \$100,000/quality-adjusted life year, we found that biomarkers are not cost effective when the biomarker test costs more than \$846, even if the test is 100% accurate in detecting IBS-D. In probabilistic analysis using 1,000 simulations, most trials (75% or more) show that the biomarker-based diagnostic approach is cost effective above the following accuracy thresholds: a \$100 biomarker test with 51% accuracy, a \$200 test with 57% accuracy, a \$300 test with 63% accuracy, a \$400 test with 69% accuracy, a \$500 test with 76% accuracy, a \$600 test with 82% accuracy, a \$700 test with 89% accuracy, and a \$800 test with 94% accuracy.

CONCLUSIONS—In decision analysis of a hypothetical cohort of patients who met Rome IV criteria for IBS-D, we identified cost and accuracy thresholds that can guide investigators and payers as they develop, validate, price, and/or reimburse IBS-D biomarker tests for use in everyday clinical practice.

Keywords

QALY; modeling; budget impact; diagnostic

BACKGROUND & AIMS

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder (FGID) that is characterized by recurrent abdominal pain and altered bowel habits.¹ With an estimated worldwide prevalence of 11%, IBS is the most commonly diagnosed gastrointestinal condition.^{2, 3} Moreover, the economic burden of IBS is substantial with total costs estimated at \$30 billion annually in the U.S.⁴

Current diagnostic criteria for IBS are symptom-based, as the Rome IV criteria require recurrent abdominal pain 1 day per week in the last three months associated with 2 of the following: (i) related to defecation, (ii) change in stool frequency, (iii) change in stool form.¹ However, abdominal pain with altered bowel habits is not exclusive to IBS. Individuals with celiac disease, inflammatory bowel disease (IBD), and microscopic colitis, among other conditions, can present with similar symptoms to those with IBS.

The inability of symptom-based measures to differentiate between those with functional versus organic disease calls for a need to supplement symptom data with objective biomarkers. A clinically useful biomarker measures pathogenic processes specific to IBS, thereby enhancing diagnostic accuracy by distinguishing individuals with IBS from those who are healthy or have organic disease.^{5–7} The Rome IV Multidimensional Clinical Profile also recognizes the evolving utility of biomarkers, as they are part of the multi-component assessment system along with Rome diagnosis, clinical modifiers, personal impact, and psychosocial influences.⁸ IBS biomarkers may even allow clinicians to make more precise diagnoses in a cost-effective manner by allowing them to “rule-in” IBS and forgo usually fruitless and costly diagnostic testing for organic disease.⁹

Because of the high prevalence and large economic burden of IBS, along with the increasing number of existing and emerging IBS-D laboratory biomarkers – all of which will have different profiles of sensitivity, specificity, and cost – it is important to estimate the economic consequences of using these tests. In this study, we tested at what cost and accuracy a biomarker will become cost effective, as well as cost saving, in clinical practice. The result is a quantitative framework, supported by lookup tables and economic projection graphs, to guide investigators and payers as they develop, validate, price, and/or reimburse IBS-D biomarkers for use in everyday clinical practice.

METHODS

Model Overview

We used decision analysis software (TreeAge Pro 2016, TreeAge Software, Inc., Williamstown, MA) to evaluate a hypothetical cohort of patients who met Rome IV IBS-D criteria. Individuals entered the model without previous intervention and underwent one of two competing strategies: usual care or an IBS biomarker-based diagnostic approach. We followed the cohort over a one-year time horizon; all individuals were diagnosed with the correct underlying condition (IBS-D, celiac disease, IBD, or microscopic colitis) within one year.

Figure 1 displays the truncated decision model. In addition to meeting Rome IV IBS-D criteria, we also assumed patients did not have significant alarm symptoms (e.g., severe hematochezia, hematemesis, unintentional weight loss) that warrants expedited endoscopic evaluation. Of note, prior research has found that the diagnostic yield of non-severe alarm features in IBS and other FGIDs is low.^{10–13} Moreover, all individuals entered the model having a normal complete blood count (CBC), basic metabolic panel (BMP), and negative infectious stool studies. Celiac serologies were not included in the initial evaluation, as a meta-analysis revealed that the utility of universally screening for celiac disease in those with suspected IBS in the U.S. is not clear.¹⁴

Competing Strategies

Usual Care—Because all patients met Rome IV criteria and did not have worrisome features, those in the usual care arm first received empiric IBS-D therapy rather than additional diagnostic testing. As there is no accepted first-line IBS-D therapy along with the fact that there are variations in IBS severity at presentation, we emulated a community-based case-mix by assuming that one-third of patients received tricyclic antidepressant (TCA) therapy, one-third consulted with a dietician for a low FODMAP (fermentable oligo-, di-, mono-saccharides, and polyols) diet trial, and the remainder received anti-diarrheals/anti-spasmodics. Those who did not respond to first-line therapy then received a two-week course of rifaximin. Because there are many other variations in how IBS-D patients are managed by different providers, we varied these assumptions in subsequent sensitivity analyses via Monte Carlo simulations, which we describe below. Sensitivity analysis allows the model to incorporate a wide range of projected clinical benefits to simulate natural proactive variations in IBS-D management.

Individuals who did not respond to the first two lines of treatment underwent diagnostic testing with celiac serologies, C-reactive protein (CRP), and endoscopy with mucosal biopsies (esophagogastroduodenoscopy [EGD] for those with positive celiac antibodies and colonoscopy for those with negative antibodies) to screen for organic disease, as suggested by Rome IV for evaluation of persistently symptomatic patients.¹ Other workup such as liver and thyroid tests, lactase gene test, calcium, etc., were not included given findings by Begtrup and colleagues that limited testing was non-inferior and less costly versus a strategy of exclusion.¹⁵ Those found to have organic disease were treated accordingly, while patients with unrevealing tests received a third-line IBS-D therapy (modeled using eluxadoline).

Response rates for each line of therapy depended on the underlying condition. For those truly with IBS-D (i.e., no organic disease), the model reflected the traditional “adequate relief” response rates from IBS clinical trials – a validated and widely used endpoint in the published literature.¹⁶ All patients were seen by a gastroenterologist one month after initiation of therapy to determine whether they responded to the treatment. Finally, the model assumed that IBS-D patients who responded to a therapy remained in adequate relief over their remaining time in the model.

For those with true organic disease, our model accounted for a “placebo effect” from empiric IBS-D therapies; this value was modeled as the placebo response rate seen in IBS trials.¹⁷ We assumed that those who “responded” to an IBS-D therapy had symptom relief for one month. During the second month of treatment, patients became symptomatic again as their underlying disease was not being treated by the IBS therapy, requiring another gastroenterologist visit for further evaluation and management.

IBS Biomarker-Based Diagnostic Strategy—In the biomarker-based arm, individuals were first tested with a hypothetical IBS-D biomarker. Those with a positive test received up to three failed IBS-D treatments – as compared to two courses in usual care – before undergoing diagnostic testing to screen for organic disease. The model allowed for three treatment trials because the purpose of targeted biomarkers is to “rule-in” IBS-D with a positive test, thus reducing the need for additional exclusionary testing. Nonetheless, the model assumes that pragmatic clinicians will still question a positive IBS-D test if a patient has ongoing symptoms despite treatment, and will return to exclusionary testing in the face of repeated treatment failures. Thus, the model is designed to reflect judicious clinical practice and not bias the model in favor of the biomarker-based strategy.

Patients with a positive biomarker test who subsequently required and had negative diagnostic testing remained with an IBS-D diagnosis (i.e., true positive), while those with an alternative diagnosis identified through exclusionary testing were managed for the corresponding disease (i.e., false positive). Conversely, a negative biomarker test prompted upfront diagnostic testing, which dictated subsequent management. Individuals whose testing revealed organic disease (i.e., true negative) were treated accordingly. Those with negative diagnostic testing (i.e., false negative) were diagnosed with IBS and received up to three IBS-D treatments. Thus, the model penalizes false negative biomarker tests by incorrectly assuming the patient did not have IBS and triggering more testing for organic disease.

Clinical Probability Estimates

Our base-case model incorporated a wide range of estimates governing relevant clinical probabilities in the evaluation and management of Rome IV IBS-D positive patients (Table 1). To derive these estimates, we retrieved pertinent studies in MEDLINE and used a weighted average of estimates when multiple studies were identified.

Outcomes: Cost-Utility Approach

Using a cost-utility approach, we employed cost per quality-adjusted life years (QALYs) as our main outcome and reported the incremental cost per QALY gained between the two competing strategies. We used a willingness-to-pay (WTP) threshold of \$100,000/QALY gained since health economists have determined that the traditionally used \$50,000/QALY benchmark is too low for the U.S.¹⁸

Utility Estimates—The model included relevant health state utilities for those with untreated and treated IBS-D, celiac disease, IBD, and microscopic colitis. We searched the Tufts Cost-Effectiveness Analysis Registry to identify pertinent utilities (Table 1).^{19, 20} All patients entered the model without significant alarm features, so those with untreated celiac disease, IBD, and microscopic colitis were assumed to have the same utility as those with untreated IBS-D. The overall QALY calculated for each individual accounted for the amount of time spent in each state (i.e., untreated or treated). Since our study cohort was followed over a one-year period, discounting was not performed.

Cost Estimates—Our model accounted for total costs incurred from a third-party payer perspective. Table 2 depicts the base-case cost estimates and eAppendix 1 describes these estimates in detail. We obtained costs for procedures and physician services using the 2017 American Medical Association Current Procedural Terminology Codebook and the 2017 Centers for Medicare & Medicaid Services (CMS) Physician Fee Schedule. We incorporated the costs associated with lab testing using the 2017 CMS Clinical Laboratory Fee Schedule. Medication costs were obtained from UpToDate (Wolters Kluwer Health, Alphen aan den Rijn, Netherlands), which provides average wholesale U.S. dollar prices. Discounting was not performed as the time horizon was only one year.

Probabilistic Sensitivity Analyses—We conducted Monte Carlo probabilistic sensitivity analyses and assumed that all variables followed a triangular distribution with base-case, minimum, and maximum values listed in Tables 1 and 2. These analyses were carried out across varying biomarker costs and accuracies, and 1,000 second-order parameter samples were done for each cost and accuracy combination. Results from the Monte Carlo simulations were used to generate cost-effectiveness acceptability curve plots. Because there are many sensitivity and specificity combinations that lead to the same calculated accuracy, we opted to test scenarios where the biomarker's sensitivity, specificity, and thereby accuracy, were equal (i.e., a test that is 70% sensitive and 70% specific is also 70% accurate).

Outcome: Budget Impact Model Approach

Since the average effectiveness was similar between groups, we also performed a budget impact analysis. Per-member per-month (PMPM) cost served as the outcome and we calculated the incremental PMPM cost of adopting the IBS biomarker-based approach versus usual care in a hypothetical managed care organization (MCO) with 1,000,000 covered lives. To perform these calculations, we used a baseline annual incidence of Rome IV IBS-D positivity of 667 per 100,000 patients (assumes overall IBS incidence of 2,000 per 100,000 with one-third having diarrhea-predominant symptoms).^{21,22}

We calculated the average PMPM cost for each strategy – across a range of biomarker costs and accuracies – by multiplying the average monthly cost per patient with Rome IV positivity by the total number of patients with Rome IV positivity in the hypothetical MCO and then dividing this value by the total number of paying members. To calculate the incremental PMPM between strategies, we used the following expression:

$$\frac{\text{avg. monthly cost for Rome IV positive patients in biomarker arm} \times \text{no. patients positive for Rome IV in MCO}}{\text{total no. paying members in MCO}} - \frac{\text{avg. monthly cost for Rome IV positive patients in usual care arm} \times \text{no. patients positive for Rome IV in MCO}}{\text{total no. paying members in MCO}}$$

We also conducted sensitivity analyses by varying the Rome IV IBS-D annual incidence from 250 to 2,000 per 100,000 individuals.

RESULTS

Cost-Utility Analyses

Base-Case Results—Figure 2 and Supplementary Figures 1–7 present nomograms depicting the most cost-effective strategy across varying IBS-D biomarker costs, sensitivities, and specificities. We found that when using a WTP threshold of \$100,000/QALY, biomarkers are not cost effective when their price exceeds \$846, even when they are 100% accurate.

Probabilistic Sensitivity Analyses—Figure 3 depicts results from the probabilistic sensitivity analyses with 1,000 Monte Carlo simulations across several biomarker cost and accuracy combinations. With a WTP of \$100,000/QALY, the large majority of trials (75% or more) favor the biomarker arm above the following price and accuracy thresholds: \$100 biomarker–51% accurate, \$200–57%, \$300–63%, \$400–69%, \$500–76%, \$600–82%, \$700–89%, and \$800–94%. At \$900, most trials show that usual care is more cost effective across the tested biomarker accuracies.

Budget Impact Analyses

In the base case, the average annual cost for an individual in the usual care arm is \$3,159. Assuming a hypothetical MCO with 1,000,000 covered lives and a Rome IV IBS-D positivity annual incidence of 667 per 100,000 patients, the average PMPM cost for usual care is \$1.76.

Table 3 shows the incremental PMPM cost of the biomarker-based arm versus usual care stratified by biomarker prices and accuracies. For example, an MCO saves money when it employs a \$100 biomarker that is 75% accurate at detecting IBS-D. Conversely, a \$300 biomarker needs to be 100% accurate to save \$0.02 PMPM. Above \$344, regardless of the biomarker's diagnostic properties, its use no longer results in cost savings and there is an increased PMPM cost.

Supplementary Tables 1–8 show the incremental PMPM costs across several Rome IV IBS-D incidences. For instance, if an MCO has a Rome IV IBS-D incidence of 250 per 100,000 patients and employs a \$100 biomarker that is 80% accurate, the organization will save \$0.02 PMPM. Conversely, if the same biomarker is used at an MCO where 2,000 of every 100,000 meets criteria for Rome IV IBS-D, it will save \$0.13 on each member per month.

DISCUSSION

In light of recently approved and emerging objective IBS-D biomarkers in development,^{5–7} we tested the economic consequences of using a wide range of hypothetical biomarker tests with varying diagnostic properties and cost profiles. To our knowledge, this is the first study to detail the accuracy and cost combinations that are required for IBS-D biomarkers to be cost effective and cost saving in clinical practice. These data can serve as “economic blueprints” for guiding investigators and payers as they develop, validate, price and/or reimburse IBS-D biomarker tests.

We generated detailed lookup tables and projection graphs against which to check the projected cost effectiveness of hypothetical biomarker tests across a range of accuracies and prices, using the increasingly accepted \$100,000/QALY WTP threshold.¹⁸ As expected, increasing biomarker costs required improved accuracy at detecting IBS-D for it to remain cost effective. However, when a biomarker test is >\$846, it no longer is cost effective compared to usual care, even when 100% accurate.

Given that the overall effectiveness between arms was similar, we also performed our analyses from the budget impact perspective. With the increasing number of MCOs and companies with self-insured group health plans, it is important to distinguish cost effectiveness from budget impact. In contrast to cost-effectiveness analysis, which measures both cost and clinical utilities without considering the underlying disease prevalence, budget impact models focus exclusively on cost and consider the prevalence of disease. In our base case, we found that biomarker tests \$344 are potentially cost saving as long as they are accurate at detecting IBS-D. When they cost more than \$344, employing IBS-D biomarkers levy an increased PMPM cost, ranging from \$0.01 to \$0.53. Still, this value is lower compared to incremental PMPM costs for other common interventions in gastroenterology/hepatology: (i) \$2.86 for intravenous versus oral proton pump inhibitor after high-risk peptic ulcer hemorrhage²³ and (ii) \$3.40 for rifaximin versus lactulose for hepatic encephalopathy.²⁴ For IBS-D biomarkers that are not cost saving, but remain cost effective versus usual care (i.e., incremental cost/QALY <\$100,000), MCO executives will need to balance the additional PMPM costs with the QALY benefits gained by its members when considering whether to implement the biomarker test in practice.

This analysis has several strengths. First, our study reports both the cost effectiveness and budgetary impact of hypothetical IBS-D biomarker tests across varying diagnostic and cost profiles. As a result, we developed detailed lookup tables against which to check the projected cost effectiveness of existing and evolving biomarkers for IBS-D. These data are relevant and actionable for investigators developing, validating, and ultimately pricing biomarkers for use in everyday clinical practice. They are also valuable for executives in MCOs and companies with self-insured group health plans, as we recast the clinical data in an economic form that may assist in determining whether to introduce IBS biomarkers into health systems. Second, our model reflects the everyday challenges in the evaluation and management of those with Rome IV IBS-D positivity. Namely, it addresses the possibility that those who meet Rome IV IBS-D criteria may have an underlying organic disease. The model also accounts for a placebo effect among those with organic disease receiving IBS therapies. By accounting for these practical issues, our analysis is more likely to reflect the health economic consequences of everyday practice.

There are limitations to our analysis. First, no two MCOs are the same, so our base-case budget impact results cannot apply across the wide spectrum of healthcare settings. However, we addressed this limitation by calculating incremental PMPM costs across a broad range of incidences for Rome IV IBS-D positivity. Second, no two clinicians are the same; clinicians often approach IBS-D management with their own styles and strategies. This can make any IBS decision analysis difficult to model, but is not a reason to dismiss these models altogether. Instead, the model must account for natural variations in practice, which we accomplish here through multivariable sensitivity analysis in Monte Carlo modeling, allowing for 1,000 different clinical scenarios, treatment effect estimates, and patients. Third, the response rates to treatments were modeled as independent and not contingent on prior therapies; this was done due to a lack of relevant studies to inform base-case estimates of conditional treatment response rates. It is unclear, though, whether this differentially impacts the arms, as the model was largely driven by the performance of the biomarker test. Fourth, our findings may not be generalizable to sites outside of the U.S. given that our model included a low celiac disease prevalence (<1%) and U.S. healthcare costs. Fifth, it was beyond the scope of this current study to account for societal costs associated with untreated IBS and organic diseases. Inclusion of indirect costs such as loss in work productivity, transportation expenses, and caregiver costs, among many other factors, may amplify the cost savings related to biomarkers, provided they are accurate at detecting IBS-D. Finally, while not necessarily a methodologic limitation, the study did not account for the heterogeneous etiologies of IBS.⁵ A biomarker targeting only one disease mechanism will likely be suboptimal for use in clinical practice. However, our results can be extrapolated to determine the accuracy and cost thresholds required for a multicomponent biomarker panel to become either cost effective or cost saving.

In conclusion, our analyses determined the combinations of price, sensitivity, and specificity required for IBS-D biomarker tests to become cost effective as well as cost saving. Investigators, industry, and MCO healthcare executives can use these data to guide them as they develop, validate, price, and ultimately decide whether to employ biomarkers in everyday clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMP	basic metabolic panel
CBC	complete blood count
CMS	Centers for Medicare & Medicaid Services
CRP	C-reactive protein
EGD	esophagogastroduodenoscopy
FGID	functional gastrointestinal disorder
FODMAP	fermentable oligo-, di-, mono-saccharides, and polyols
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IBS-D	diarrhea-predominant irritable bowel syndrome
IgA	immunoglobulin A
MCO	managed care organization
PMPM	per-member per-month
QALY	quality-adjusted life year
TCA	tricyclic antidepressant
tTG	tissue transglutaminase
WTP	willingness-to-pay

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FIGURE 1.

Truncated decision model. Individuals in the usual care arm first received empiric IBS-D therapy and needed to fail two treatment courses before undergoing additional diagnostic testing with endoscopy, celiac serologies, and CRP. Those in the IBS-D biomarker-based approach first had a biomarker test. Individuals with a positive test received IBS-D therapy and diagnostic testing was only performed after three failed treatment courses. On the other hand, those with a negative biomarker test had immediate diagnostic testing, which determined whether the patient was treated for organic disease (celiac disease, IBD, or microscopic colitis) or IBS-D. □=decision node; ○=probability node; ◀=terminal node.

FIGURE 2.

Nomogram depicting the preferred strategy when the IBS-D biomarker costs \$100 and at a WTP threshold of \$100,000/QALY gained. For example, a biomarker that is 80% sensitive and 40% specific is not cost effective versus usual care. However, when increasing the specificity of the same biomarker to 50%, its use becomes cost effective.

FIGURE 3.

At varying biomarker costs and accuracies, we performed probabilistic sensitivity analyses using 1,000 trials and determined the proportion of trials within the \$100,000/QALY WTP threshold. For example, if a \$300 biomarker is 60% accurate, then 54.8% of trials would fall within the budget. Conversely, when increasing the accuracy to 75%, 99.6% of trials found that it is cost effective versus usual care. Note: tested scenarios included those where the biomarker's sensitivity, specificity, and thereby accuracy, were equal.

TABLE 1

Base-case clinical probability and utility estimates.*

Variable	Base-case estimate (range tested in Monte Carlo analysis)
Clinical probabilities, %	
Celiac disease if meets Rome IV criteria	4.1% (1.9%–7.0%)
IBD if meets Rome IV criteria	1.3% (1.0%–10%)
Microscopic colitis if meets Rome IV criteria	9.8% (4.4%–17%)
IBS-D patient responds to amitriptyline	54% (28%–71%)
IBS-D patient responds to low-FODMAP diet	63% (50%–79%)
IBS-D patient responds to anti-spasmodic/anti-diarrheal [†]	57% (13%–89%)
IBS-D patient responds to rifaximin	41% (31%–51%)
IBS-D patient responds to eluxadoline	56% (46%–66%)
Organic disease patient responds to IBS-D therapy [‡]	38% (34%–40%)
Utility estimates, QALY	
Untreated IBS-D	0.73 (0.67–0.75)
Treated IBS-D	0.78 (0.76–0.80)
Untreated celiac disease [§]	0.73 (0.67–0.75)
Treated celiac disease	0.90 (0.84–0.98)
Untreated IBD [§]	0.73 (0.67–0.75)
Treated IBD	0.79 (0.76–0.94)
Untreated microscopic colitis [§]	0.73 (0.67–0.75)
Treated microscopic colitis ^{//}	0.90 (0.84–0.98)

FODMAP, fermentable, oligo-, di-, mono-saccharides and polyols; IBS-D, diarrhea-predominant irritable bowel syndrome; IBD, inflammatory bowel disease; QALY, quality-adjusted life year.

* See eAppendix 2 for the associated references supporting the base-case estimates and ranges tested in Monte Carlo analysis.

[†] Assumed to be the response rate to anti-spasmodics due to limited anti-diarrheal data.

[‡] Assumed to be the placebo response rate seen in IBS clinical trials.

[§] Assumed to be the same as untreated IBS-D, since all patients met Rome IV criteria and did not have significant alarm features.

^{//} Assumed to be the same as treated celiac disease.

TABLE 2

Base-case cost estimates.

Cost	Base-case estimate (range tested in Monte Carlo analysis)*
CRP	\$10 (\$7–\$12)
tTG IgA	\$22 (\$17–\$28)
Total IgA	\$13 (\$10–\$16)
EGD with biopsies [†]	\$369 (\$277–\$462)
Colonoscopy with biopsies [†]	\$451 (\$338–\$564)
Initial dietician visit (60 mins)	\$137 (\$103–\$171)
Follow-up dietician visit (30 mins)	\$58 (\$44–\$73)
Initial gastroenterologist visit (60 mins)	\$177 (\$133–\$221)
Follow-up gastroenterologist visit (45 mins)	\$82 (\$62–\$103)
Amitriptyline 1-month supply	\$9 (\$7–\$12)
Loperamide 1-month supply	\$19 (\$14–\$24)
Hyoscyamine 1-month supply	\$62 (\$47–\$78)
Rifaximin 2-week treatment course	\$1,690 (\$1,268–\$2,113)
Eluxadoline 1-month supply	\$599 (\$449–\$749)
Budesonide 2-month treatment course	\$3,702 (\$2,777–\$4,628)
IBD treatment for 1 month ^{25, 26, ‡}	\$247 (\$7–\$952)

CRP, C-reactive protein; EGD, esophagogastroduodenoscopy; IBD, inflammatory bowel disease; IgA, immunoglobulin A; tTG, tissue transglutaminase.

Current Procedural Terminology codes: CRP 86140; tTG IgA 83516; total IgA 82784; EGD 43239; colonoscopy 45380; pathologist fee 80502; dietician initial visit 97802; dietician follow-up visit 97803; gastroenterologist initial visit 99205; gastroenterologist follow-up visit 99214.

* The ranges tested in Monte Carlo analysis are $\pm 25\%$ of the base-case cost estimate. The one exception is for IBD treatment costs, which reflect the interquartile range reported in the literature.^{25, 26}

[†] Cost includes the fees for the proceduralist, anesthesiologist, and pathologist.

[‡] Includes costs for prescriptions and inpatient, outpatient, emergency room, office, and home health services.

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TABLE 3
Budget impact model incremental PMPM cost estimates with a Rome IV IBS-D incidence of 667 per 100,000.

Biomarker accuracy	Biomarker cost									
	\$100	\$200	\$300	\$400	\$500	\$600	\$700	\$800	\$900	\$900
50%	\$0.09	\$0.14	\$0.20	\$0.25	\$0.31	\$0.36	\$0.42	\$0.47	\$0.53	\$0.53
55%	\$0.06	\$0.12	\$0.17	\$0.23	\$0.29	\$0.34	\$0.40	\$0.45	\$0.51	\$0.51
60%	\$0.04	\$0.10	\$0.15	\$0.21	\$0.26	\$0.32	\$0.38	\$0.43	\$0.49	\$0.49
65%	\$0.02	\$0.08	\$0.13	\$0.19	\$0.24	\$0.30	\$0.35	\$0.41	\$0.47	\$0.47
70%	\$0.00	\$0.05	\$0.11	\$0.17	\$0.22	\$0.28	\$0.33	\$0.39	\$0.44	\$0.44
75%	-\$0.02	\$0.03	\$0.09	\$0.14	\$0.20	\$0.26	\$0.31	\$0.37	\$0.42	\$0.42
80%	-\$0.04	\$0.01	\$0.07	\$0.12	\$0.18	\$0.23	\$0.29	\$0.35	\$0.40	\$0.40
85%	-\$0.07	-\$0.01	\$0.05	\$0.10	\$0.16	\$0.21	\$0.27	\$0.32	\$0.38	\$0.38
90%	-\$0.09	-\$0.03	\$0.02	\$0.08	\$0.14	\$0.19	\$0.25	\$0.30	\$0.36	\$0.36
95%	-\$0.11	-\$0.05	\$0.00	\$0.06	\$0.11	\$0.17	\$0.22	\$0.28	\$0.34	\$0.34
100%	-\$0.13	-\$0.07	-\$0.02	\$0.04	\$0.09	\$0.15	\$0.20	\$0.26	\$0.31	\$0.31

Data are presented as the incremental PMPM costs of the biomarker-based arm versus usual care. IBS-D, diarrhea-predominant irritable bowel syndrome; PMPM, per-member per-month.