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Factors associated with more frequent diagnostic tests and procedures in patients with irritable bowel syndrome

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Abstract

Background: Irritable bowel syndrome (IBS) reduces quality of life and burdens healthcare systems. This study identified factors associated with frequent use of IBS diagnostic tests and procedures.

Methods: Using a United States claims database (2001–2012), tests and procedures in IBS patients occurring in the 2-year study period (12 months before/following the first IBS diagnosis) were analyzed: endoscopy, GI transit testing, anorectal procedures, and radiologic imaging. Patients were classified based on test/procedure frequency (3+, 1–2, or 0). Multivariate logistic regression identified factors associated with more frequent tests/procedures.

Results: Among 201,322 IBS patients, 41.7% had 3+ tests/procedures, 35.1% had 1–2, and 23.3% had 0. Patients with more tests/procedures were older [mean age 50.6 (3+ group), more likely to be female and had more comorbidities, including anxiety, depressive disorders, and somatization. Dyspepsia [odds ratio (95% confidence interval): 1.80 (1.72–1.87)], interstitial cystitis [1.60 (1.45–1.77)], gastroesophageal reflux disease [1.59 (1.55–1.63)], constipation [1.50 (1.45–1.54)], and dyspareunia [1.38 (1.25–1.52)] were significantly associated with more tests/procedures (3+ *versus* 1–2), while anxiety, depressive disorders, and somatization were not. Patients with more frequent specialist visits [emergency department (ED; 1.10 (1.09–1.11)) and gastroenterologists (1.26 (1.26–1.27))] or at least one GI-related ED visit or inpatient admission [1.95 (1.86–2.04) and 3.67 (3.48–3.87), respectively] were more likely to have more tests/procedures (all $p < 0.05$).

Conclusions: Test frequency in patients with IBS is strongly associated with demographic and clinical characteristics, especially comorbid conditions related to IBS. Presence of common overlapping comorbid conditions should increase clinicians' confidence in making the diagnosis of IBS, thus curtailing redundant testing and reducing healthcare costs.

Keywords: claims analysis, diagnostic tests, irritable bowel syndrome, procedures resource use

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Introduction

Irritable bowel syndrome (IBS) is a common gastrointestinal (GI) disorder that affects 10–15% of the United States (US) population,[1] with a higher prevalence among women and patients under 50 years of age.[2] IBS is characterized by recurrent abdominal pain and altered bowel habits; bloating and distension frequently coexist. Symptoms are frequently chronic, which can negatively impact patients' quality of life.[3,4]

Diagnosing IBS can be challenging due to the nonspecific nature of symptoms, overlapping upper and lower abdominal symptoms, and the frequent presence of somatic and psychological comorbidities.[3] The Rome IV guidelines state that diagnostic tests may be appropriate in the evaluation of a patient with IBS symptoms.[5] However, no validated algorithm for diagnostic tests exists. The Rome criteria are most often used during IBS diagnosis, and clinical guidelines on the management of IBS have been developed to help improve and standardize treatment.[6–8] Despite these guidelines, there remains low awareness and little consensus on the use of diagnostic tests and surgical procedures in IBS.[9,10] Furthermore, although surgery has no role in the recommended treatment approach for IBS,[8] multiple studies have reported that this patient population is predisposed to unnecessary surgical procedures,[11–14] suggesting a disconnect between the recommended best practices and real-world management of IBS.

IBS causes a significant burden on healthcare systems, due in part to the high level of healthcare resource utilization (HRU) associated with IBS.[15] Direct medical costs attributed to IBS in the US, excluding prescription and over-the-counter medicines, were estimated at US $1.5–$10 billion per year in 2005.[16] A portion of these costs may be related to unnecessary[17] and high-frequency tests,[14] although few studies have assessed the factors underlying frequent tests and procedures among patients with IBS. A claims study (2001–2012) reported large regional variation in levels of HRU among patients with IBS in the US;[15] however, the reasons for the differences are unclear. A systematic review and meta-analysis found that certain comorbidities, such as depression and anxiety, are prevalent among this patient population, which may contribute to higher HRU including tests and procedures.[18] However, prior studies have not adequately evaluated the demographic and clinical factors which influence the use, and overuse, of diagnostic tests and procedures among IBS patients.

This study assessed the demographic and clinical factors associated with high test frequency among adults with IBS in the US. We hypothesized that patients with more comorbid conditions overlapping with IBS, or psychological disorders such as anxiety, depression, or somatization, would be likely to undergo relatively frequent tests/diagnostic procedures.

Methods

Data source

Data were derived from the Truven Health Analytics MarketScan® databases (1 January 2001 to 31 December 2012, the latest period with US state-level data), a large retrospective US commercial claims database that is nationally representative of Americans with employer-provided health insurance and Medicaid.[19] The database contains information regarding patient demographics, health plan enrollment history, medical diagnoses, procedures performed, dates and places of service, and payment amounts as well as prescription drug claims for over 25 million covered lives annually.

Patient selection and groups

Patients were included in the study if they (1) had at least two separate and distinct diagnoses for IBS [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code 564.1x] recorded on different dates between 1 January 2001 and 31 December 2012; (2) had ⩾12 months of continuous healthcare plan enrollment before and after the first recorded IBS diagnosis; and (3) were aged ⩾18 years on the date of the first recorded IBS diagnosis, with no upper age limit.

Patients were categorized into three groups based on the frequency of tests/procedures received during the 2-year study period: the high-count group (⩾3 tests/procedures), the moderate-count group (1–2 tests/procedures), and the zero-count group (0 tests/procedures). Tests were summarized by category level (i.e. colonoscopy, anoscopy, Sitzmark test) and patients were permitted to have the same procedure once per day; the same test on different days or multiple tests with separate codes on the same day were considered to be separate procedures. Appendix A contains a list of included GI tests/procedures along with their corresponding diagnostic and procedural codes used to search the claims database. Physician specialty was recorded, identified based on a corresponding annotation in the data.

This study was not subject to review by an Institutional Review Board, and no informed consent was needed, as ethics approval was not required for this national database study.

Study period and measures

The study period was defined as the 2-year period surrounding the first recorded IBS diagnosis (i.e. 1 year before and on/after the first IBS diagnosis date). The index date was defined as the date of the first recorded IBS diagnosis. Data collected during the study period included patient demographics, including age at IBS diagnosis, sex, region of residence, and insurance plan type; clinical characteristics, including modified Charlson–Quan comorbidity index (CCI; a composite measure of patient's health)[20] and IBS-related comorbidities [e.g. dyspepsia, gastroesophageal reflux disease (GERD), interstitial cystitis, anxiety, depressive disorders, and somatization; see Appendix B; note that constipation, while clinically considered an IBS symptom, had to be computed as a comorbidity, as at the time of the study there was no specific coding for IBS with constipation]; and HRU, including all-cause medical visits stratified by provider type (e.g. family practice, internal medicine, emergency medicine), intestinal-related emergency department (ED) visits, and inpatient admissions. IBS medical procedures and tests were identified in the database using ICD-9-CM and Current Procedural Terminology (CPT) codes (see Appendix A). Types of healthcare plans included preferred provider organization (PPO), health maintenance organization (HMO), comprehensive coverage (i.e. total coverage for healthcare-related charges), point of service (POS)/POS with capitation, consumer-directed health plan (CDHP)/high-deductible health plan (HDHP), exclusive provider organization (EPO), and 'unknown.'

Statistical analysis

Pairwise comparisons of patient demographic and clinical characteristics were conducted across the high-, moderate-, and low-count groups using Chi-squared tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. Univariate and multivariate logistic regression models, comparing the high- and moderate-count groups, were estimated to identify factors associated with more frequent use of tests/procedures. The multivariate regression models used stepwise selection to choose the most relevant variables while generating a parsimonious model. Results were reported as an odds ratio (OR) and corresponding 95% confidence interval (CI). The proportions of patients with different combinations of comorbid conditions were summarized for the zero-, moderate-, and high-count groups. A p value of 0.05 was used to determine statistical significance.

Results

Demographic and clinical characteristics of patients with IBS

A total of 201,322 IBS patients met the inclusion criteria (Figure 1), with 83,852 (42%), 70,577 (35%), and 46,892 (23%) patients in the high-, moderate-, and zero-count test groups, respectively (Figure 2). Across all groups, patients were predominantly from the south (40.5–43.5%, including the following US states: Alabama, North Carolina, South Carolina, Georgia, Texas, Mississippi, Louisiana, Florida) and had PPO insurance (57.0–59.0%; Table 1).

Patients in the high-count group were older (50.6 years) and there was a larger proportion of females (79.5%) compared with the moderate-count (49.5 years and 76.7%, respectively) and zero-count (46.8 years and 74.0%) groups (all $p < 0.0001$; Table 1). The high-count group also had a higher CCI [mean 2.2 *versus* 1.4 (moderate-count) and 1.1 (zero-count); all $p < 0.0001$] and the highest prevalence of all observed IBS-related comorbidities. Pronounced trends of higher rates of comorbidity associated with higher numbers of tests were observed for dyspepsia (high-count: 13.0%, moderate-count: 5.8%, zero-count: 2.6%; all $p < 0.0001$), GERD (40.4%, 24.0%, and 15.2%, respectively; all $p < 0.0001$), constipation (25.6%, 15%, and 7.8%; all $p < 0.0001$), and depressive disorders (23.5%, 17.7%, and 17.5%; $p < 0.0001$ for high-count *versus* zero-count and moderate-count). Anxiety was significantly more prevalent in the high-count group (20.4%) compared with the moderate- or zero-count groups (15.5%, and 15.8%; both $p < 0.0001$ *versus* high-count). Somatization was significantly more prevalent among patients in the high-count group (0.2%) compared with the moderate-count and zero-count group (both 0.1%; both $p < 0.0001$ *versus* high-count).

Patient HRU and costs related to IBS. The high-count group had significantly higher mean numbers of annual medical visits to all provider types compared with the moderate-count and zero-count groups, as follows: family practice: 6.5, 4.5, and 3.9, respectively; internal medicine:

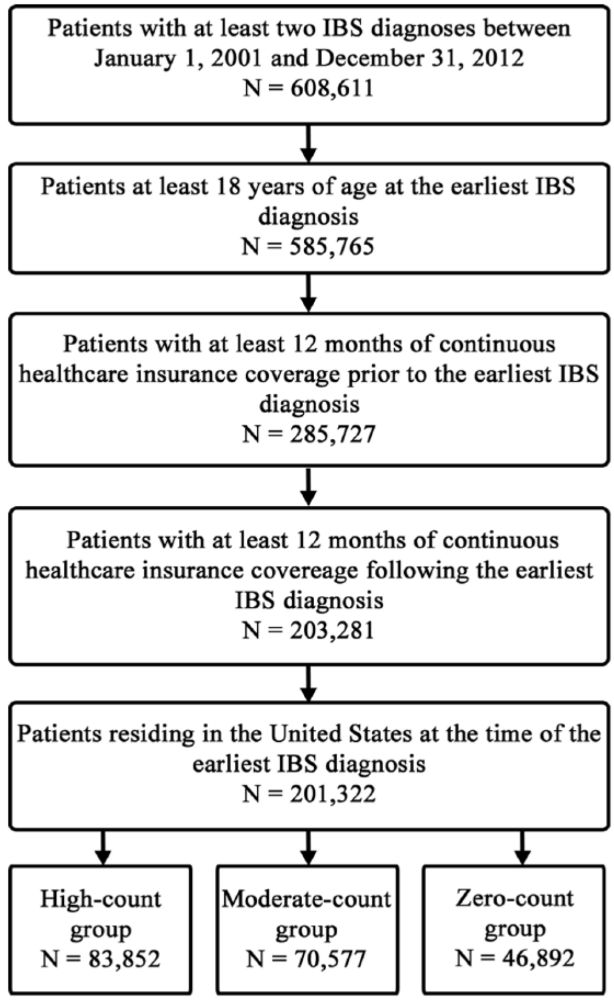

Figure 1. Sample selection of patients with IBS diagnosis in the United States.
Patients in the high-count group had ⩾3 tests/procedures in the 2-year study period, those in the moderate-count group had 1–2 tests/procedures, and those in the zero-count group had no tests/procedures. IBS diagnosis was identified by a claim with ICD-9 code 564.1x.
IBS, irritable bowel syndrome; ICD, International Classification of Diseases, ninth revision; *N*, number.

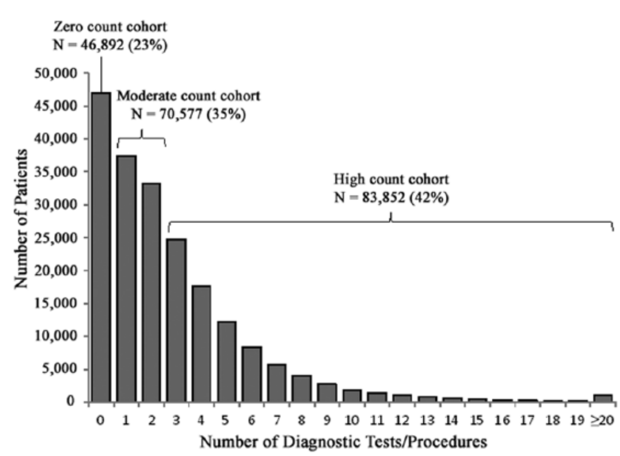

Figure 2. Number of diagnostic tests/procedures during the 2-year study period and definition of study cohorts.
N, number.

Table 1. Comparison of demographic and clinical characteristics among IBS patients stratified by multiple test/procedure counts.[a,b]

	High-count group (3+ tests) n = 83,853	Moderate-count group (1 or 2 tests) n = 70,577	Zero-count group n = 46,892	p value[c] High versus zero multiple test/procedure count	p value[c] Moderate versus zero multiple test/procedure count	p value[c] High versus moderate multiple test/procedure count
Demographics						
Age,[d] mean ± SD	50.6 ± 15.4	49.5 ± 15.1	46.8 ± 15.6	<0.0001	<0.0001	<0.0001
Female, n (%)	66,629 (79.5)	54,102 (76.7)	34,718 (74.0)	<0.0001	<0.0001	<0.0001
Male, n (%)	17,224 (20.5)	16,475 (23.3)	12,174 (26.0)	<0.0001	<0.0001	<0.0001
Region, n (%)						
South	36,191 (43.2)	29,235 (41.4)	19,002 (40.5)	<0.0001	0.0021	<0.0001
North-central	22,831 (27.2)	18,334 (26.0)	12,501 (26.7)	0.0265	0.0093	<0.0001
West	13,512 (16.1)	14,341 (20.3)	9931 (21.2)	<0.0001	0.0004	<0.0001
North-east	11,319 (13.5)	8667 (12.3)	5458 (11.6)	<0.0001	0.0009	<0.0001
Insurance plan type, n (%)						
PPO	47,834 (57.0)	40,642 (57.6)	27,684 (59.0)	<0.0001	<0.0001	0.0325
HMO	11,683 (13.9)	11,035 (15.6)	7584 (16.2)	<0.0001	0.0134	<0.0001
Comprehensive cover	10,946 (13.1)	7784 (11.0)	4339 (9.3)	<0.0001	<0.0001	<0.0001
POS/POS with capitation	8627 (10.3)	7339 (10.4)	4527 (9.7)	0.0003	<0.0001	0.4781
CDHP/HDHP	1796 (2.1)	1453 (2.1)	1135 (2.4)	0.0011	<0.0001	0.2570
EPO	1241 (1.5)	889 (1.3)	620 (1.3)	0.0209	0.3510	0.0002
Unknown	1726 (2.1)	1435 (2.0)	1003 (2.1)	0.3282	0.2132	0.7283
Year of earliest IBS diagnosis, n (%)						
2002	3369 (4.0)	3454 (4.9)	2056 (4.4)	0.0014	<0.0001	<0.0001
2003	4491 (5.4)	4173 (5.9)	2363 (5.0)	0.0138	<0.0001	<0.0001
2004	7214 (8.6)	6528 (9.2)	3934 (8.4)	0.1846	<0.0001	<0.0001
2005	5833 (7.0)	5348 (7.6)	3149 (6.7)	0.0988	<0.0001	<0.0001
2006	5358 (6.4)	4646 (6.6)	3078 (6.6)	0.2187	0.8984	0.1245
2007	10,387 (12.4)	9088 (12.9)	5953 (12.7)	0.1063	0.3617	0.0039
2008	9096 (10.8)	7441 (10.5)	4878 (10.4)	0.0125	0.4416	0.0539
2009	10,588 (12.6)	8926 (12.6)	6319 (13.5)	<0.0001	<0.0001	0.9047

(Continued)

Table 1. (Continued)

	High-count group (3+ tests) *n* = 83,853	Moderate-count group (1 or 2 tests) *n* = 70,577	Zero-count group *n* = 46,892	*p* value[c] High *versus* zero multiple test/procedure count	*p* value[c] Moderate *versus* zero multiple test/procedure count	*p* value[c] High *versus* moderate multiple test/procedure count
2010	12,564 (15.0)	9528 (13.5)	6923 (14.8)	0.2848	<0.0001	<0.0001
2011	14,944 (17.8)	11,440 (16.2)	8237 (17.6)	0.2455	<0.0001	<0.0001
2012	9 (0.0)	5 (0.0)	2 (0.0)	0.3476	0.7099	0.4531
Modified Charlson–Quan comorbidity index,[a] mean ± SD	2.2 ± 2.2	1.4 ± 1.6	1.1 ± 1.3	<0.0001	<0.0001	<0.0001
IBS-related comorbidities,[a,e] *n* (%)						
Anxiety	17,116 (20.4)	10,933 (15.5)	7388 (15.8)	<0.0001	0.2211	<0.0001
Depressive disorders	19,733 (23.5)	12,523 (17.7)	8211 (17.5)	<0.0001	0.3044	<0.0001
Somatization	203 (0.2)	52 (0.1)	31 (0.1)	<0.0001	0.6326	<0.0001
Migraines	10,408 (12.4)	6051 (8.6)	3823 (8.2)	<0.0001	0.0109	<0.0001
Interstitial cystitis	1594 (1.9)	656 (0.9)	266 (0.6)	<0.0001	<0.0001	<0.0001
Fibromyalgia	12,598 (15.0)	7099 (10.1)	3988 (8.5)	<0.0001	<0.0001	<0.0001
Chronic fatigue	1902 (2.3)	1213 (1.7)	779 (1.7)	<0.0001	0.4553	<0.0001
Dyspareunia	1494 (1.8)	802 (1.1)	351 (0.7)	<0.0001	<0.0001	<0.0001
Dyspepsia	10,864 (13.0)	4095 (5.8)	1224 (2.6)	<0.0001	<0.0001	<0.0001
GERD	33,893 (40.4)	16,964 (24.0)	7105 (15.2)	<0.0001	<0.0001	<0.0001
Constipation	21,437 (25.6)	10,555 (15.0)	3635 (7.8)	<0.0001	<0.0001	<0.0001
Number of comorbid conditions,[a,e] mean ± SD	4.3 ± 2.3	2.7 ± 1.9	1.7 ± 1.6	<0.0001	<0.0001	<0.0001
Average copayment for medical service (USD),[a] mean ± SD						
Inpatient	102.8 ± 524.5	109.0 ± 476.9	96.4 ± 300.7	<0.0001	0.3721	<0.0001
Outpatient	8.6 ± 30.3	8.3 ± 30.2	6.3 ± 37.5	<0.0001	<0.0001	<0.0001
Emergency department	37.2 ± 54.7	37.8 ± 55.2	38.3 ± 55.0	0.8105	0.6019	0.2880
Office	15.1 ± 25.2	14.7 ± 15.2	14.6 ± 19.7	0.0003	0.2829	0.0042
Other	13.1 ± 65.6	14.4 ± 60.2	9.6 ± 57.2	<0.0001	0.0001	0.9918

Table 1. (Continued)

	High-count group (3+ tests) n = 83,853	Moderate-count group (1 or 2 tests) n = 70,577	Zero-count group n = 46,892	p value[c] High versus zero multiple test/procedure count	p value[c] Moderate versus zero multiple test/procedure count	p value[c] High versus moderate multiple test/procedure count
Average deductible for medical service (USD),[a] mean ± SD						
Inpatient	113.3 ± 377.4	148.0 ± 503.2	181.7 ± 780.8	<0.0001	0.2803	<0.0001
Outpatient	36.4 ± 100.4	51.6 ± 139.5	38.5 ± 109.7	<0.0001	<0.0001	0.2956
ED	30.5 ± 123.8	44.4 ± 156.9	53.0 ± 174.5	<0.0001	<0.0001	<0.0001
Office	10.7 ± 19.1	14.4 ± 25.6	17.2 ± 31.0	<0.0001	<0.0001	<0.0001
Other	45.4 ± 167.3	66.3 ± 209.6	38.2 ± 172.6	0.2128	<0.0001	<0.0001
Number of medical visits by provider type,[a] mean ± SD						
Family practice	6.5 ± 10.6	4.5 ± 7.3	3.9 ± 6.4	<0.0001	<0.0001	<0.0001
Internal medicine (NEC)	5.6 ± 10.0	3.2 ± 5.9	2.4 ± 4.8	<0.0001	<0.0001	<0.0001
Gastroenterology	3.3 ± 4.3	1.4 ± 2.0	0.4 ± 1.1	<0.0001	<0.0001	<0.0001
Medical doctor (NEC)	3.8 ± 12.7	2.4 ± 8.4	1.8 ± 7.0	<0.0001	<0.0001	<0.0001
Multi-specialty physician group	2.3 ± 9.5	1.6 ± 6.7	1.2 ± 5.4	<0.0001	<0.0001	<0.0001
Emergency medicine	1.1 ± 3.2	0.4 ± 1.4	0.3 ± 1.1	<0.0001	<0.0001	<0.0001
At least one gastroenterology visit,[a] n (%)	56,022 (66.8)	35,095 (49.7)	9682 (20.6)	<0.0001	<0.0001	<0.0001
Intestinal-related medical care[a]						
ED visits, mean ± SD	0.2 ± 0.6	0.1 ± 0.2	0.0 ± 0.2	<0.0001	<0.0001	<0.0001
At least one ED visit, n (%)	9639 (11.5)	3149 (4.5)	941 (2.0)	<0.0001	<0.0001	<0.0001
IP admissions, mean ± SD	0.2 ± 0.6	0.0 ± 0.2	0.0 ± 0.1	<0.0001	<0.0001	<0.0001
At least one IP admission, n (%)	12,040 (14.4)	1961 (2.8)	700 (1.5)	<0.0001	<0.0001	<0.0001
Federal qualified health centers per 100,000 residents,[f] mean ± SD	3.6 ± 16.2	3.7 ± 17.0	3.7 ± 16.5	<0.0001	<0.0001	<0.0001
Provider density,[f] mean ± SD						
Number of hospitals per 100,000 residents	2.3 ± 9.1	2.3 ± 7.6	2.4 ± 7.1	0.0720	0.1535	0.7583

(Continued)

Table 1. (Continued)

	High-count group (3+ tests) *n* = 83,853	Moderate-count group (1 or 2 tests) *n* = 70,577	Zero-count group *n* = 46,892	*p* value[c] High *versus* zero multiple test/procedure count	*p* value[c] Moderate *versus* zero multiple test/procedure count	*p* value[c] High *versus* moderate multiple test/procedure count
Number of active MDs per 1000 residents	3.3 ± 8.7	3.2 ± 2.6	3.3 ± 10.1	<0.0001	0.5261	<0.0001
Number of gastroenterologists per 1000 residents	0.1 ± 0.6	0.2 ± 0.7	0.2 ± 0.7	0.0003	0.0551	<0.0001
Number of general internal med per 1000 residents	0.6 ± 3.2	0.6 ± 3.7	0.6 ± 4.0	<0.0001	0.6356	<0.0001
Neighborhood demographics,[f] mean ± SD						
% in poverty	14.6 ± 5.1	14.5 ± 5.0	14.5 ± 5.0	0.0614	0.1013	<0.0001
Median household income (USD)	50,940.6 ± 12,685.9	50,869.4 ± 12,538.3	51,069.4 ± 12,567.7	0.0030	0.0026	0.8505
% with college-level education	29.5 ± 10.1	29.4 ± 10.1	29.6 ± 10.2	0.0376	0.0157	0.6269
% without high school-level education	14.5 ± 5.3	14.6 ± 5.4	14.5 ± 5.4	0.0021	0.5940	<0.0001

CDHP, consumer-directed health plan; ED, emergency department; EPO, exclusive provider organization; GERD, gastroesophageal reflux disease; HDHP, high-deductible health plan; HMO, health maintenance organization; IBS, irritable bowel syndrome; IP, inpatient; Med, medicine; MD, medical doctor; *N*, number; NEC, not elsewhere classifiable; POS, point of service; PPO, preferred provider organization; SD, standard deviation; USD, United States dollars.
[a]Evaluated during the 2-year study period which includes the 12 months prior to the earliest IBS diagnosis and the 12 months following the earliest IBS diagnosis.
[b]See Supplemental File-Appendix A for a comprehensive list of tests and procedures counted.
[c]*p*-values were calculated using Chi-squared tests for categorical variables (or Fisher's exact test for sample <5 patients) and Wilcoxon rank-sum tests for continuous variables.
[d]Age was calculated as of the earliest IBS diagnosis.
[e]See Supplemental File-Appendix B for a comprehensive list of comorbid conditions.
[f]Provided by Area Health Resources Files at the index year. Reference: Area Health Resources Files. http://ahrf.hrsa.gov/categories.htm. Data were available for 201,315 patients.

5.6, 3.2, and 2.4; gastroenterology: 3.3, 1.4, and 0.4; medical doctor: 3.3, 2.4, and 1.8; multi-specialty physician group: 2.3, 1.6, and 1.2; and emergency medicine: 1.1, 0.4, and 0.3 (all $p < 0.0001$; Table 1). Furthermore, 66.8%, 11.5%, and 14.4% of the high-count group had at least one gastroenterology visit, ED visit, and inpatient admission, respectively, compared with 49.7%, 4.5%, and 2.8% of the moderate- and 20.6%, 2.0%, 1.5% of the zero-count groups (all $p < 0.0001$).

The mean number of federal qualified health centers per 100,000 residents, which may indicate a higher standard of care, was lower for the high-count group (3.6) compared with the moderate-count and zero-count groups (both 3.7; all $p < 0.0001$).

Multivariable analysis. In the multivariable analyses comparing the demographic and clinical characteristics of the high-count and moderate-count groups, female sex [OR (CI): 1.1170 (1.0867–1.1481); $p <$

0.001], region [e.g. north-central: 1.1587 (1.1240–1.1946); north-east 1.1239 (1.0806–1.1690); both $p < 0.001$], and type of coverage [HMO: 1.0385 (1.0036–1.0746); $p = 0.03$; comprehensive coverage: 1.1271 (1.0825–1.1737); $p < 0.001$] were associated with more frequent (⩾3) tests (Table 2). Age at the index date was statistically associated with fewer tests but had a small effect [0.9938 (0.9930–0.9947); $p < 0.001$]. Patients in areas with more active medical doctors (MDs) per 1000 residents were slightly more likely to have a higher number of tests/procedures [1.0079 (1.0033–1.0125); $p < 0.001$], while patients in areas with more general internal medicine practitioners were slightly less likely [0.9955 (0.9912–0.9998); $p = 0.041$]. In addition, patients were slightly less likely to have more tests if they resided in an area with higher proportions of people with a college-level education [0.9939 (0.9923–0.9956)] or without a high school-level education [0.9964 (0.9932–0.9997); $p = 0.034$].

Patients with a high CCI score were significantly more likely to have more tests/procedures [1.1452 (1.1365–1.1540); $p < 0.001$; Table 2]. In addition, patients with the following IBS-related comorbidities were significantly more likely to have ⩾3 tests: dyspepsia (1.7960 [1.7230–1.8720]), interstitial cystitis [1.5998 (1.4450–1.7711)], GERD [1.5933 (1.5542–1.6335)], constipation [1.4967 (1.4538–1.5408)], dyspareunia [1.3810 (1.2545–1.5203)], fibromyalgia [1.1150 (1.0759–1.1555)], and migraines [1.1043 (1.0627–1.1476), all $p < 0.001$]. The presence of a depressive disorder was statistically associated with fewer tests but had a small effect [0.9352 (0.9071–0.9641); $p < 0.001$].

The number of visits to the following provider types was associated with a higher test frequency: family practice [1.0210 (1.0195–1.0226)], internal medicine [1.0240 (1.0221–1.0260)], gastroenterology [1.2623 (1.2556–1.2690)], MDs [1.0264 (1.0250–1.0279)], multi-specialty physician groups [1.0222 (1.0205–1.0239)], and emergency medicine [1.0996 (1.0894–1.1099); all $p < 0.001$]. Patients with ⩾1ED visit [1.9507 (1.8608–2.0449)] or inpatient (IP) admission [3.6681 (3.4785–3.8680); both $p < 0.001$] were much more likely to have a higher number of tests/procedures.

Comparison of IBS-related comorbidity counts among patient groups. Overall, patients with GERD, dyspepsia, dyspareunia, and interstitial cystitis were highly concentrated in the group that received ⩾3 tests/procedures, and there was a trend towards fewer tests as comorbidity burden decreased (Table 3). GERD was the most common comorbidity of the four considered. Of the 57,962 patients with GERD, 58.5% had ⩾3 tests, 29.3% had 1–2 tests, and 12.3% had zero tests. A total of 16,183 patients had dyspepsia, and of these, 67.1% had ⩾3 tests, 25.3% had 1–2 tests, and 7.6% had zero tests. Of the 2647 patients with dyspareunia, 56.4% had ⩾3 tests, 30.3% had 1–2 tests, and 13.3% had zero tests, and of the 2516 patients with interstitial cystitis, the proportions were 63.4%, 26.1%, and 10.6%, respectively.

In addition, the proportions of the high-count, moderate-count, and zero-count groups with two of these four comorbidities were as follows: dyspareunia and dyspepsia (overall $n = 295$; 76.6%, 21.0%, and 2.4%, respectively); dyspareunia and GERD (936; 68.7%, 24.8%, and 6.5%); dyspareunia and interstitial cystitis (186; 73.7%, 21.5%, 10.2%); dyspepsia and GERD (8214; 73.7%, 21.8%, and 4.5%); dyspepsia and interstitial cystitis (257; 82.9%, 14.0%, and 3.1%); and GERD and interstitial cystitis (946; 74.8%, 18.9%, and 6.2%; Table 3). When including patients with three or all of these comorbidities, the proportions were even more greatly skewed towards the high- *versus* the moderate-count or zero-count groups: dyspareunia, dyspepsia, and GERD (overall $n = 169$; 81.1%, 17.8%, and 1.2%, respectively); dyspareunia, dyspepsia, and interstitial cystitis (30; 90.0%, 10.0%, and 0%); dyspareunia, GERD, and interstitial cystitis (74; 73%, 17.6%, and 9.5%); dyspepsia, GERD, and interstitial cystitis (150; 88.7%, 9.3%, and 2.0%); and dyspareunia, dyspepsia, GERD, and interstitial cystitis (20; 90.0%, 10.0%, and 0%; Table 3 and Figure 3).

Discussion

IBS is a common, chronic and complex GI disorder associated with a significant burden to the healthcare system. The negative financial impact of IBS is related, in part, to the large number of diagnostic tests and procedures performed on IBS patients despite the lack of evidence supporting their need or clinical utility. In this retrospective claims database study of 201,322 patients with IBS, we found that most (41.7%) patients had at least IBS-related diagnostic tests/procedures. After assessing factors associated with frequent use of IBS-related diagnostics tests/procedures, we

Table 2. Comparison of risk factors among IBS patients stratified by multiple test/procedure counts.[a,b]

	High-count group (⩾3 tests/procedures) *versus* Moderate-count group (1–2 tests/procedures)			
	Univariate model		Multivariate model	
	OR[c] (95% CI)	*p* value	OR[c] (95% CI)	*p* value
Demographics				
Age[d]	1.0047 (1.0041–1.0054)	<0.001*	0.9938 (0.9930–0.9947)	<0.001*
Female	1.0620 (1.0366– 1.0880)	<0.001*	1.1170 (1.0867– 1.1481)	<0.001*
Region				
South	1.0738 (1.0522– 1.0958)	<0.001*	ǂ	
North-central	1.0661 (1.0422– 1.0906)	<0.001*	1.1587 (1.1240– 1.1946)	<0.001*
West	0.7533 (0.7339– 0.7731)	<0.001*	0.9262 (0.8949– 0.9586)	<0.001*
North-east	1.1147 (1.0818– 1.1486)	<0.001*	1.1239 (1.0806– 1.1690)	<0.001*
Insurance plan type				
Preferred provider organization	0.9782 (0.9586– 0.9982)	0.033*	ǂ	
Health maintenance organization	0.8735 (0.8492– 0.8984)	<0.001*	1.0385 (1.0036– 1.0746)	0.030*
Comprehensive coverage	1.2111 (1.1742– 1.2492)	<0.001*	1.1271 (1.0825– 1.1737)	<0.001*
Point of service/point of service with capitation	0.9882 (0.9562– 1.0212)	0.478	1.0066 (0.9684– 1.0463)	0.739
Consumer-directed health plan/high-deductible health plan	1.0412 (0.9710– 1.1166)	0.257	1.0168 (0.9394– 1.1005)	0.680
Exclusive provider organization	1.1776 (1.0798– 1.2842)	<0.001*	1.0813 (0.9795– 1.1936)	0.121
Unknown	1.0126 (0.9435– 1.0868)	0.728	1.0626 (0.9813– 1.1507)	0.135
Modified Charlson–Quan comorbidity index[a, 20]	1.2707 (1.2630– 1.2785)	<0.001*	1.1452 (1.1365– 1.1540)	<0.001*
IBS-related comorbidities[a,e]				
Anxiety	1.3991 (1.3627– 1.4366)	<0.001*	1.0295 (0.9975– 1.0625)	0.071
Depressive disorders	1.4267 (1.3914– 1.4629)	<0.001*	0.9352 (0.9071– 0.9641)	<0.001*
Somatization	3.2913 (2.4266– 4.4642)	<0.001*	1.2615 (0.8831– 1.8021)	0.202
Migraines	1.5112 (1.4615– 1.5625)	<0.001*	1.1043 (1.0627– 1.1476)	<0.001*
Interstitial cystitis	2.0654 (1.8849– 2.2633)	<0.001*	1.5998 (1.4450– 1.7711)	<0.001*
Fibromyalgia	1.5809 (1.5327– 1.6307)	<0.001*	1.1150 (1.0759– 1.1555)	<0.001*
Chronic fatigue	1.3272 (1.2341– 1.4273)	<0.001*	ǂ	
Dyspareunia	1.5782 (1.4476– 1.7206)	<0.001*	1.3810 (1.2545– 1.5203)	<0.001*

Table 2. (Continued)

	High-count group (⩾3 tests/procedures) *versus* Moderate-count group (1–2 tests/procedures)			
	Univariate model		Multivariate model	
	OR[c] (95% CI)	*p* value	OR[c] (95% CI)	*p* value
Dyspepsia	2.4165 (2.3277– 2.5087)	<0.001*	1.7960 (1.7230– 1.8720)	<0.001*
GERD	2.1440 (2.0972– 2.1919)	<0.001*	1.5933 (1.5542– 1.6335)	<0.001*
Constipation	1.9531 (1.9032– 2.0042)	<0.001*	1.4967 (1.4538– 1.5408)	<0.001*
Number of comorbid conditions[e]	1.4406 (1.4325– 1.4488)	<0.001*	ǂ	
Average copayment for medical service (USD)[a]				
Inpatient	1.0011 (1.0010– 1.0012)	<0.001*	ǂ	
Outpatient	1.0006 (1.0003– 1.0010)	<0.001*	ǂ	
ED	1.0048 (1.0045– 1.0050)	<0.001*	ǂ	
Office	1.0013 (1.0007– 1.0019)	<0.001*	ǂ	
Other	1.0010 (1.0007– 1.0012)	<0.001*	ǂ	
Average deductible for medical service (USD)[a]				
Inpatient	1.0007 (1.0007– 1.0008)	<0.001*	ǂ	
Outpatient	0.9990 (0.9989– 0.9991)	<0.001*	ǂ	
ED	1.0002 (1.0001– 1.0003)	0.002*	ǂ	
Office	0.9922 (0.9917– 0.9927)	<0.001*	ǂ	
Other	0.9999 (0.9998– 1.0000)	0.009*	ǂ	
Number of medical visits by provider type[a]				
Family practice	1.0290 (1.0276– 1.0304)	<0.001*	1.0210 (1.0195– 1.0226)	<0.001*
Internal medicine (NEC)	1.0444 (1.0427– 1.0461)	<0.001*	1.0240 (1.0221– 1.0260)	<0.001*
Gastroenterology	1.2735 (1.2677– 1.2793)	<0.001*	1.2623 (1.2556– 1.2690)	<0.001*
Medical doctor (NEC)	1.0141 (1.0129– 1.0152)	<0.001*	1.0264 (1.0250– 1.0279)	<0.001*
Multi-specialty physician group	1.0112 (1.0099– 1.0126)	<0.001*	1.0222 (1.0205– 1.0239)	<0.001*
Emergency medicine	1.2527 (1.2422– 1.2633)	<0.001*	1.0996 (1.0894– 1.1099)	<0.001*
At least one gastroenterology visit[a]	2.0351 (1.9936– 2.0775)	<0.001*	ǂ	
Intestinal-related medical care[a]				
ED visits	2.2831 (2.2047– 2.3642)	<0.001*	ǂ	

(Continued)

Table 2. (Continued)

	High-count group (⩾3 tests/procedures) *versus* Moderate-count group (1–2 tests/procedures)			
	Univariate model		Multivariate model	
	OR[c] (95% CI)	*p* value	OR[c] (95% CI)	*p* value
At least one ED visit	2.7811 (2.6679– 2.8991)	<0.001*	1.9507 (1.8608– 2.0449)	<0.001*
IP admissions	4.7579 (4.5452– 4.9806)	<0.001*	ǂ	
At least one IP admission	5.8664 (5.5866– 6.1602)	<0.001*	3.6681 (3.4785– 3.8680)	<0.001*
Federal qualified health centers per 100,000 residents[f]	0.9994 (0.9988– 1.0000)	0.067	0.9994 (0.9985– 1.0002)	0.156
Provider density[f]				
Number of hospitals per 100,000 residents	0.9998 (0.9986– 1.0010)	0.751	ǂ	
Number of active MDs per 1000 residents	1.0099 (1.0059– 1.0139)	<0.001*	1.0079 (1.0033– 1.0125)	<0.001*
Number of gastroenterologists per 1000 residents	0.9808 (0.9659– 0.9961)	0.014*	1.0231 (0.9970– 1.0499)	0.084
Number of general internal med per 1000 residents	0.9975 (0.9946– 1.0004)	0.097	0.9955 (0.9912– 0.9998)	0.041*
Neighborhood demographics[f]				
% in poverty	1.0031 (1.0011– 1.0051)	0.002*	0.9976 (0.9945– 1.0008)	0.148
Median household income (USD)	1.0000 (1.0000– 1.0000)	0.269	ǂ	
% with college-level education	1.0003 (0.9993– 1.0013)	0.573	0.9939 (0.9923– 0.9956)	<0.001*
% without high school-level education	0.9965 (0.9946– 0.9984)	<0.001*	0.9964 (0.9932– 0.9997)	0.034*

*Significant at the 5% level. ǂVariable not selected by stepwise selection procedure.
CI, confidence interval; ED, emergency department; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; IP, inpatient; MD, medical doctor; Med, medicine; N, number; NEC, not elsewhere classifiable; OR, odds ratio; SD, standard deviation; USD, United States dollars.
[a]Evaluated during the 2-year study period which includes the 12 months prior to the earliest IBS diagnosis and the 12 months following the earliest IBS diagnosis.
[b]See Supplemental File-Appendix A for a comprehensive list of tests and procedures counted.
[c]The reported OR, CIs, and *p* values were calculated using logistic regression models. An OR >1 indicates that exposure associated with higher odds of utilization.
[d]Age was calculated as of the earliest IBS diagnosis.
[e]See Supplemental File-Appendix B for a comprehensive list of comorbid conditions.
[f]Provided by Area Health Resources Files at the index year. Reference: Area Health Resources Files (http://ahrf.hrsa.gov/categories.htm). Data were available for 201,315 patients.

observed that test/procedure frequency was significantly associated with older age, female sex, GI-related ED or inpatient visits, high overall comorbidity burden, and certain individual comorbidities (GERD, dyspepsia, interstitial cystitis, constipation, and dyspareunia).

Our findings also suggest that the overall health of patients in the high-count group was generally worse than in the others (higher mean CCI) and thus may provide a rationale for the increased number of tests/procedures. Similar to prior studies, we found high comorbidity burden in this population of patients with IBS, particularly anxiety, depressive disorders, and somatization,[14,18,21] although these comorbidities were not associated with a higher test frequency. This is important clinically, as it suggests that coexisting

Table 3. Comparison of multiple test/procedure counts among patients with IBS-related comorbidities.[a,b,c]

IBS-related comorbidities	Total patients with comorbidity (*n*)	High-count group, *n* (%)		Moderate-count group, *n* (%)		Zero-count group, *n* (%)	
		(3+ tests)		(1, 2 tests)			
		n = 83,853		*n* = 70,577		*n* = 46,892	
Dyspareunia	2647	1494	(56.4%)	802	(30.3%)	351	(13.3%)
Dyspepsia	16,183	10,864	(67.1%)	4095	(25.3%)	1224	(7.6%)
GERD	57,962	33,893	(58.5%)	16,964	(29.3%)	7105	(12.3%)
Interstitial cystitis	2516	1594	(63.4%)	656	(26.1%)	266	(10.6%)
Dyspareunia and dyspepsia	295	226	(76.6%)	62	(21.0%)	7	(2.4%)
Dyspareunia and GERD	936	643	(68.7%)	232	(24.8%)	61	(6.5%)
Dyspareunia and interstitial cystitis	186	127	(68.3%)	40	(21.5%)	19	(10.2%)
Dyspepsia and GERD	8214	6056	(73.7%)	1791	(21.8%)	367	(4.5%)
Dyspepsia and interstitial cystitis	257	213	(82.9%)	36	(14.0%)	8	(3.1%)
GERD and interstitial cystitis	946	708	(74.8%)	179	(18.9%)	59	(6.2%)
Dyspareunia, dyspepsia, and GERD	169	137	(81.1%)	30	(17.8%)	2	(1.2%)
Dyspareunia, dyspepsia, and interstitial cystitis	30	27	(90.0%)	3	(10.0%)	0	(0.0%)
Dyspareunia, GERD, and interstitial cystitis	74	54	(73.0%)	13	(17.6%)	7	(9.5%)
Dyspepsia, GERD, and interstitial cystitis	150	133	(88.7%)	14	(9.3%)	3	(2.0%)
Dyspareunia, dyspepsia, GERD, and interstitial cystitis	20	18	(90.0%)	2	(10.0%)	0	(0.0%)

GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome.
[a]Evaluated during the 2-year study period which includes the 12 months prior to the earliest IBS diagnosis and the 12 months following the earliest IBS diagnosis.
[b]See Supplemental File-Appendix B for a comprehensive list of comorbid conditions.
[c]See Supplemental File-Appendix A for a comprehensive list of tests and procedures counted.

anxiety and depression are not driving factors in ordering tests or procedures. In the multivariable analysis, the two comorbidities most strongly associated with a high test frequency were dyspepsia and interstitial cystitis. Dyspepsia and interstitial cystitis are notable in that they involve subjective feelings of abdominal pain, arise from multiple and diverse etiologies, and are often interrelated.[22,23] Abdominal pain is a primary predictor of increased HRU among patients with IBS,[4] and quality of life is highly associated with patient-perceived IBS severity.[24] Our results suggest that abdominal pain arising from multiple overlapping upper and lower abdominal causes (e.g. dyspepsia and IBS and dyspareunia) is a driving factor in providers ordering tests and procedures. The picture that emerges from our study, taken together with prior observations, is one in which functional bowel disorders often present together,[25] leading to diagnostic testing approaches that become additive in burden, but not necessarily in benefit.

The current findings have implications for patients, care providers, and payers. Given the lack of consensus on the therapeutic value and clinical utility of tests and procedures in the diagnosis and treatment of IBS, our study indicates that many patients

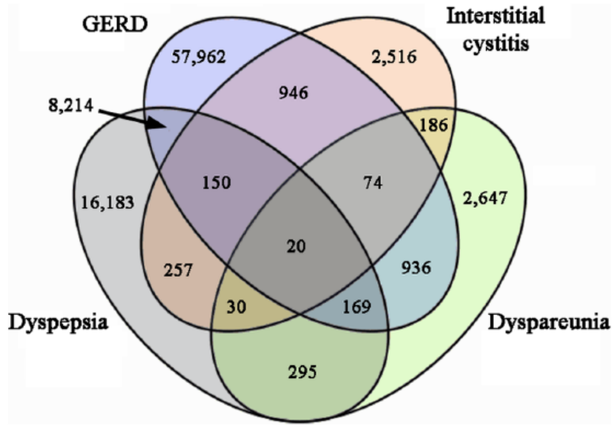

Figure 3. Overall distribution and overlap of patients with IBS and GERD, interstitial cystitis, dyspepsia, and dyspareunia.
All digits refer to the number of patients with a single or combination of overlapping comorbidities.
GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome.

with IBS are subjected to diagnostic tests and procedures which are neither required nor essential or beneficial.[6] Unfortunately, this strategy is expensive to both patients and payers,[26] and carries significant risks, including adverse events during these procedures. The large proportion of patients receiving multiple tests/procedures over the study period provides strong evidence for the need to increase awareness of physician practice guidelines for the diagnosis and treatment of IBS.[9,10] Common practices for IBS management begin with diet and lifestyle modification, and in more severe cases, pharmacotherapy (e.g. antidepressants, smooth muscle antispasmodics, or secretagogues).[27] However, in the real world, several studies have noted the high utilization of surgical procedures, related or unrelated to IBS, among patients with IBS.[11–14] For example, an analysis of the medical records (1995–2000) of a large cohort of patients with IBS showed that the incidence of abdominopelvic surgery (excluding gallbladder) was 87% higher among these patients *versus* control patients.[13]

At least one inpatient admission or ED visit was a highly significant risk factor for ⩾3 *versus* 1–2 tests/procedures among this study sample. Prior studies have consistently found that patients with IBS undergo frequent hospitalizations, which appears to be a driver of increased test frequency. For example, a prior survey of HMO participants with IBS found that, over 2 years, these patients had significantly more outpatient and inpatient visits, as well as more ED visits, compared with patients without IBS.[26] Similarly, a large managed-care cohort study reported that patients with IBS were more likely than control patients to have blood, stool, endoscopic, and radiologic tests, and to undergo abdominal/pelvic surgery.[14] Higher rates of HRU together with higher frequencies of tests (which may be related to inpatient admissions and frequent provider visits) may compound the cost of IBS treatment. The reasons behind the higher HRU among patients with IBS are not well known. Patients with IBS and high levels of somatization are not more likely to seek out GI tests/procedures; however, once they are evaluated for IBS, they expend significantly more healthcare costs compared with matched controls.[28] Region of residence has also been reported to impact HRU among IBS patients. A claims database study of HRU in patients with IBS (2001–2012) identified considerable regional variation across the US and noted that 36.3% of patients had ⩾3 different types of GI medical tests/procedures in the a 2-year period surrounding IBS diagnosis.[15]

In summary, care providers for patients with IBS face a complex decision landscape, where an interplay of underlying patient characteristics, possibly including aspects of their psyche and behaviors, such as their tendency (or not) to seek frequent medical attention, may compound the challenges posed by the presentation of IBS symptoms that frequently overlap with a number of IBS-related comorbidities (Figure 4). In the midst of these factors, healthcare professionals

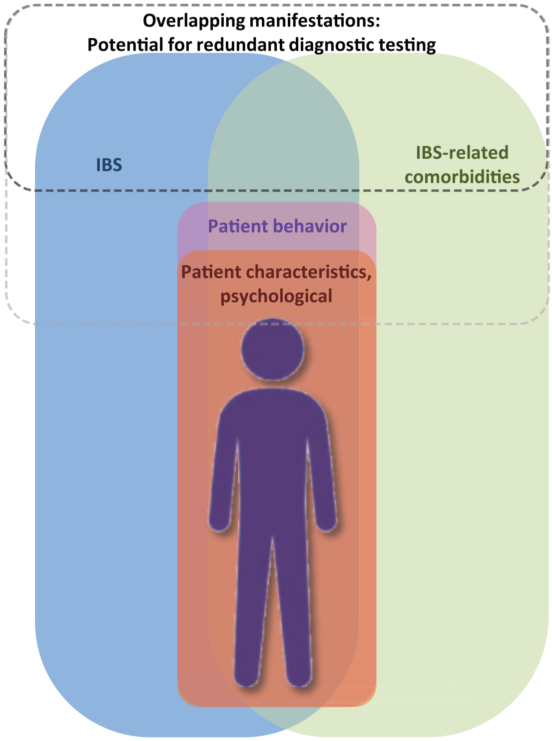

Figure 4. Interplay of factors that complicate the full diagnostic process for patients with IBS.
IBS, irritable bowel syndrome.

have to make cost-effective decisions about appropriate diagnostic tests and interventions, creating a fertile ground that may foster over-testing and redundant procedures.

Future prospective studies could help gain a better understanding of the reasons why diagnostic tests are ordered and evaluate the clinical utility of these tests/procedures regarding the diagnosis and treatment of IBS. This information should strengthen clinical practice guidelines and potentially reduce the economic burden of IBS on the healthcare system. In addition, future studies could expand upon the current analysis by stratifying outcomes by IBS subtype, which could not be performed in this study, as separate ICD-9 codes for IBS subtypes did not exist at the time of data collection.

This study is subject to several limitations. Overall, our study only included patients with IBS and did not provide a matched comparison with a non-IBS reference population. Prior studies have already shown high HRU rates specific to IBS,[14,25] and this is a premise that we did not further investigate in our study in the context of diagnostic tests. While we believe that our observations suggest that these patients often undergo excessive testing and are diagnosed by exclusion, an approach inconsistent with the current Rome IV criteria,[5] it is true that our study does not close this particular question. A matched comparison to quantify the volume of diagnostic tests with negative results in this population relative to non-IBS individuals would go a long way to more definitively answer the question of whether the excess in diagnostic testing that we observe in IBS patients is truly unwarranted. Given the substantial economic impact of IBS[16,29] (a combination of productivity losses, increased interventions and, according to our study, diagnostic procedures), this becomes a pressing question to follow up. There are also specific limitations. First, as with any claims data analysis, this analysis relied on ICD-9-CM and CPT codes to identify diagnoses and procedures within the database, as opposed to actual observance of diagnoses and resource use. However, patients required two separate diagnoses of IBS, which minimizes the possibility of coding errors; in addition, as a byproduct of following the coding system, constipation, which is clinically an IBS symptom (for the disease subtype IBS-C), had to be counted as a comorbidity because IBS subtypes were not coded as such. Second, this study was based on a population of commercially-insured beneficiaries in the US, and the generalizability to other patient populations (e.g. Medicaid, which would include mostly low-income patients younger than 65 years) is unknown. In addition, a large proportion of the included patients were from the southern US (40.5–43.5%), which may limit the representativeness of the sample; race or ethnicity was not included as a variable in the analysis. Third, the results of this study should be interpreted as correlations which may not have causal interpretations. For instance, because tests and hospitalizations were assessed over the same study period, the findings do not imply that hospitalizations or emergency room (ER) visits are associated with future tests that are not directly related to the hospitalization/ER visit; indeed, the association may be mainly due to tests during the hospitalization or ER visit. Or, in another example, we document that patients with higher test counts tend to be older or have higher CCI; it is possible that at least some of those 'excess' tests could be directly driven by those factors, more so than the IBS diagnosis. However, many of the concurrent comorbidities specific to the high-count group were IBS-related and associated with abdominal pain symptoms, an observation that strongly suggests the underlying IBS pathology was an important (and redundant) trigger for a substantial proportion of those tests. Therefore, considering our findings and our study limitations, we are not proposing that clinicians radically curtail diagnostic tests in patients presenting with multiple functional bowel and abdominal symptoms, particularly in elderly patients. We would favor an approach in which clinicians are proactively judicious, weighing all the factors present in a given patient as they decide a diagnostic strategy for them, rather than reacting narrowly to individual symptoms.

Conclusion

This study provides real-world evidence that the frequency of IBS-related diagnostic tests/procedures is strongly associated with a patient's demographic and clinical profile, especially their comorbidity profile. In the clinical setting, healthcare providers equipped with the knowledge that overlapping comorbid conditions of GERD, dyspepsia, and dyspareunia are not just common in IBS patients, but likely explain many of the symptoms reported by IBS patients, should enable clinicians to minimize redundant diagnostic tests and procedures and instead focus on initiating individualized treatment. This should reduce healthcare costs globally and improve patients' quality of life.

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Conflict of interest statement

BL is a scientific advisory board member with Takeda Pharmaceuticals, Ironwood, and Salix. RA, AG, and SS are employees of Analysis Group, Inc., and AL is a former employee of Analysis Group, Inc., which has received consultancy fees from Takeda Pharmaceuticals. ML is an employee of Takeda Pharmaceuticals and owns stock/stock options.

Supplemental material

Supplemental material for this article is available online.

References

1. International Foundation for Functional Gastrointestinal Disorders. Statistics, http://www.aboutibs.org/site/what-is-ibs/facts/statistics (2013, accessed 29 November 2016).
2. Lovell RM and Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol* 2012; 10: 712–721.e4.
3. Lacy BE, Mearin F, Chang L, *et al*. Bowel disorders. *Gastroenterology* 2016; 150: 1393–1407.
4. Creed F, Ratcliffe J, Fernandez L, *et al*. Health-related quality of life and health care costs in severe, refractory irritable bowel syndrome. *Ann Intern Med* 2001; 134: 860–868.
5. Drossman DA and Hasler WL. Rome IV-functional GI disorders: disorders of gut-brain interaction. *Gastroenterology* 2016; 150: 1257–1261.
6. Ford AC, Moayyedi P, Lacy BE, *et al*. American college of gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. *Am J Gastroenterol* 2014; 109(Suppl. 1): S2–S26; quiz S27.
7. Rubin G, De Wit N, Meineche-Schmidt V, *et al*. The diagnosis of IBS in primary care: consensus development using nominal group technique. *Fam Pract* 2006; 23: 687–692.
8. Drossman DA and Dumitrascu DL. Rome III: new standard for functional gastrointestinal

disorders. *J Gastrointestin Liver Dis* 2006; 15: 237–241.

9. Spiegel BM, Farid M, Esrailian E, *et al.* Is irritable bowel syndrome a diagnosis of exclusion?: a survey of primary care providers, gastroenterologists, and IBS experts. *Am J Gastroenterol* 2010; 105: 848–858.
10. Mearin F and Lacy BE. Diagnostic criteria in IBS: useful or not? *Neurogastroenterol Motil* 2012; 24: 791–801.
11. Longstreth GF and Yao JF. Irritable bowel syndrome and surgery: a multivariable analysis. *Gastroenterology* 2004; 126: 1665–1673.
12. Hasler WL and Schoenfeld P. Systematic review: abdominal and pelvic surgery in patients with irritable bowel syndrome. *Aliment Pharmacol Ther* 2003; 17: 997–1005.
13. Cole JA, Yeaw JM, Cutone JA, *et al.* The incidence of abdominal and pelvic surgery among patients with irritable bowel syndrome. *Dig Dis Sci* 2005; 50: 2268–2275.
14. Ladabaum U, Boyd E, Zhao WK, *et al.* Diagnosis, comorbidities, and management of irritable bowel syndrome in patients in a large health maintenance organization. *Clin Gastroenterol Hepatol* 2012; 10: 37–45.
15. Lacy BE, Patel H, Guerin A, *et al.* Variation in care for patients with irritable bowel syndrome in the United States. *PLoS One* 2016; 11: e0154258.
16. Cash B, Sullivan S and Barghout V. Total costs of IBS: employer and managed care perspective. *Am J Manag Care* 2005; 11: S7–S16.
17. Irritable bowel syndrome: a mild disorder; purely symptomatic treatment. *Prescrire Int* 2009; 18: 75–79.
18. Fond G, Loundou A, Hamdani N, *et al.* Anxiety and depression comorbidities in irritable bowel syndrome (IBS): a systematic review and meta-analysis. *Eur Arch Psychiatry Clin Neurosci* 2014; 264: 651–660.
19. Hansen L and Chang S. Health research data for the real world: the Marketscan databases, http://truvenhealth.com/portals/0/assets/PH_11238_0612_TEMP_MarketScan_WP_FINAL.pdf (2011, accessed 30 November 2016).
20. Charlson M, Charlson R, Peterson J, *et al.* The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. *J Clin Epidemiol*; 61: 1234–1240.
21. Faresjo A, Grodzinsky E, Hallert C, *et al.* Patients with irritable bowel syndrome are more burdened by co-morbidity and worry about serious diseases than healthy controls–eight years follow-up of IBS patients in primary care. *BMC Public Health* 2013; 13: 832.
22. Fujiwara Y and Arakawa T. Overlap in patients with dyspepsia/functional dyspepsia. *J Neurogastroenterol Motil* 2014; 20: 447–457.
23. Chelimsky G, Heller E, Buffington CA, *et al.* Co-morbidities of interstitial cystitis. *Front Neurosci* 2012; 6: 114.
24. Hahn BA, Kirchdoerfer LJ, Fullerton S, *et al.* Patient-perceived severity of irritable bowel syndrome in relation to symptoms, health resource utilization and quality of life. *Aliment Pharmacol Ther* 1997; 11: 553–559.
25. Aziz I, Palsson OS, Tornblom H, *et al.* The prevalence and impact of overlapping Rome IV-diagnosed functional gastrointestinal disorders on somatization, quality of life, and healthcare utilization: a cross-sectional general population study in three countries. *Am J Gastroenterol* 2018; 113: 86–96.
26. Longstreth GF, Wilson A, Knight K, *et al.* Irritable bowel syndrome, health care use, and costs: a US-managed care perspective. *Am J Gastroenterol* 2003; 98: 600–607.
27. Wald A, Talley N and Grover S. Treatment of irritable bowel syndrome in adults, https://www.uptodate.com/contents/treatment-of-irritable-bowel-syndrome-in-adults?source=search_result&search=irritable%20bowel%20syndrome&selectedTitle=1~150 (2016, accessed 5 December 2016).
28. Spiegel BM, Kanwal F, Naliboff B, *et al.* The impact of somatization on the use of gastrointestinal health-care resources in patients with irritable bowel syndrome. *Am J Gastroenterol* 2005; 100: 2262–2273.
29. Canavan C, West J and Card T. Review article: the economic impact of the irritable bowel syndrome. *Aliment Pharmacol Ther* 2014; 40: 1023–1034.