

FUNCTIONAL DISORDERS

A Diagnosis of Irritable Bowel Syndrome Using Rome IV Criteria and Limited Investigations is Durable in Secondary Care



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BACKGROUND & AIMS: Irritable bowel syndrome (IBS) is a positive diagnosis, made using symptom-based criteria and limited, judicious, investigation. However, this may lead to uncertainty on the part of clinicians regarding potential for a missed diagnosis of organic gastrointestinal disease. Few studies have examined durability of a diagnosis of IBS, and none have used the current gold standard to diagnose IBS, the Rome IV criteria.

METHODS: We collected complete symptom data from 373 well-characterized adults meeting Rome IV criteria for IBS referred to a single UK clinic between September 2016 and March 2020. All patients underwent relatively standardized work-up to exclude relevant organic disease before diagnosis. We followed these individuals up to December 2022, assessing rates of rereferral, reinvestigation, and missed organic gastrointestinal disease.

RESULTS: During a mean follow-up of 4.2 years per patient (total follow-up in all patients, 1565 years), 62 (16.6%) patients were rereferred. Of these, 35 (56.5%) were rereferred for IBS and 27 (43.5%) for other gastrointestinal symptoms. Among the 35 rereferred with IBS this was caused by a change in symptoms in only 5 (14.3%). Reinvestigation was undertaken in 21 (60.0%) of 35 rereferred with IBS and 22 (81.5%) of 27 rereferred with other symptoms ($P = .12$). Only 4 (9.3% of those reinvestigated and 1.1% of the entire cohort) new cases of relevant organic disease, which may have been responsible for IBS symptoms at baseline, were identified (1 case of chronic calcific pancreatitis among those rereferred with IBS and 1 case each of inflammatory bowel disease–unclassified, moderate bile acid diarrhea, and small bowel obstruction among those rereferred with other gastrointestinal symptoms).

CONCLUSIONS: Despite rereferral for gastrointestinal symptoms among 1 in 6 patients overall, with almost 10% rereferred with ongoing IBS symptoms, and substantial reinvestigation rates, missed organic gastrointestinal disease occurred in only 1%. A diagnosis of Rome IV IBS after limited investigation is safe and durable.

Keywords: Irritable Bowel Syndrome; Rome IV Criteria; Durability; Misdiagnosis.

Irritable bowel syndrome (IBS) is a highly prevalent disorder of gut-brain interaction,¹⁻³ characterized by abdominal pain, in association with altered stool form or frequency.⁴ National guidelines recommend a diagnosis of IBS is made using symptom-based criteria in combination with limited, judicious, investigations.^{5,6} However, physicians find IBS challenging to diagnose, because symptoms overlap with those of organic gastrointestinal conditions, such as celiac disease,^{7,8} inflammatory bowel disease (IBD),⁹ microscopic colitis,¹⁰ or bile acid diarrhea (BAD).¹¹ This can result in diagnostic uncertainty on the part of the doctor and the patient, particularly because symptoms are chronic and

fluctuating,^{12,13} and treatments are not effective in all patients.¹⁴⁻¹⁷ This may lead to unnecessary investigations, which are associated with increased health care

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Abbreviations used in this paper: BAD, bile acid diarrhea; CT, computed tomography; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; SeHCAT, 23-seleno-25-homo-tauro-cholic acid.

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expenditure and exposure of patients to potential harm, which can be anxiety-provoking.¹⁸

The current gold standard symptom-based diagnostic criteria are the Rome criteria, which were developed in the 1990s.¹⁹ These have undergone 3 subsequent revisions, the most recent being the Rome IV criteria in 2016,⁴ which have been validated previously. In an initial validation study, performed by the Rome Foundation, sensitivity of the Rome IV criteria was assessed in more than 800 patients with a disorder of gut-brain interaction, estimated at 63%.²⁰ In a separate cohort of almost 6000 people from the general population, specificity was reported to be 97%.²⁰ Another diagnostic accuracy study performed by our group, in which patients with suspected IBS underwent relatively standardized work-up to exclude organic gastrointestinal disease before a diagnosis of IBS being made, demonstrated a good performance in secondary care,²¹ with sensitivity and specificity of 82.4% and 82.9%, respectively.

However, most validation studies of diagnostic criteria for IBS are performed during the patient's first clinical contact and episode of care.²² It may be, therefore, that during extended follow-up, an organic gastrointestinal condition that was not considered during the initial work-up is detected. Unfortunately, there are few data confirming that a diagnosis of IBS in routine clinical care is durable. To our knowledge, only 3 studies have examined this issue previously.²³⁻²⁵ Two were relatively small and used historical definitions of IBS,^{23,24} and 1 was conducted in a convenience sample of men and women during military service, so may not be generalizable to clinical practice.²⁵ If clinicians are to have confidence in diagnosing IBS based on only symptom-based criteria and limited investigations then evidence that such an approach is safe, and that the diagnosis is durable, is needed. We, therefore, performed longitudinal follow-up in all patients recruited into our diagnostic accuracy study of the Rome IV criteria to assess rates of rereferral, reinvestigation, and missed organic gastrointestinal disease.²¹

Methods

Participants and Setting

In the initial study, between September 2016 and March 2020, we recruited all unselected, consecutive, patients aged ≥ 16 years from primary care newly referred to our specialist IBS clinic in Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom.²¹ The hospital serves a local population of 800,000, and the clinic provides a pathway to rapid diagnosis and treatment for patients referred from primary care locally. Tertiary referrals from other centers of patients with IBS symptoms that are refractory to medical therapies are not accepted. Four experienced gastroenterologists provided input into this clinic during recruitment. Patients

What You Need To Know

Background

The durability and safety of a diagnosis of irritable bowel syndrome (IBS) made using accepted symptom-based criteria and limited investigations, in line with current management guidelines, is uncertain.

Findings

Among 373 patients meeting Rome IV criteria without organic disease on limited diagnostic testing, only four (1.1%) were diagnosed with a subsequent new relevant organic disease, during an average of 4 years of follow-up.

Implications for patient care

A diagnosis of Rome IV IBS after limited investigation is safe and durable, supporting recommendations from management guidelines.

attend an initial clinic visit to confirm the diagnosis and are offered treatment and follow-up. Our usual practice is to see patients at the initial visit to confirm the diagnosis and they are offered a maximum of 3 follow-up appointments to institute treatment and assess their response. Thereafter, they are returned to their primary care physician. There were no exclusion criteria, other than inability to understand written English. All patients were provided with a detailed questionnaire as part of their assessment at their first appointment. Symptom data were captured using the Rome IV questionnaire for IBS in all patients.⁴ The presence or absence of Rome IV-defined IBS was assigned according to the scoring algorithm proposed for use with the questionnaire.^{4,26} Because these data were collected to guide routine clinical practice, ethical approval was not required. We followed up individuals recruited into the study in December 2022. Patients underwent relatively standardized work-up, as described previously,²¹ and detailed in the [Supplementary Materials](#).

Data Collection and Synthesis

Demographic, Symptom, and Mood Data. Demographic, symptom, and mood data were collected prospectively at the initial clinic visit, before referral for investigations, and the date of the initial consultation. We assessed symptom severity using the IBS Severity Scoring System.²⁷ The maximum score is 500 points: <75 indicates remission of symptoms, 75–174 mild, 175–299 moderate, and 300–500 severe symptoms. Anxiety and depression data were collected using the Hospital Anxiety and Depression Scale,²⁸ with a total score ranging from 0 to 21 for either anxiety or depression. Severity for each was categorized into normal (total Hospital Anxiety and Depression Scale

depression or anxiety score 0–7), borderline abnormal (8–10), or abnormal (≥ 11). We collected extraintestinal symptom data using the Patient Health Questionnaire-12,²⁹ derived from the validated Patient Health Questionnaire-15,³⁰ with a total score ranging from 0 to 24.

Assessment of Rates of Rereferral, Reinvestigation, and Missed Organic Gastrointestinal Disease. One investigator (MK) reviewed electronic medical records for all patients. We recorded whether the patient was rereferred, the date of rereferral, and whether rereferral was with continuing symptoms of IBS or with other gastrointestinal symptoms. If the latter, we recorded the reason for rereferral. Among those rereferred, we recorded whether they were reinvestigated as part of their new care episode and, if so, what further investigations were requested. We also documented any new organic gastrointestinal diseases that were detected after these investigations. Finally, we recorded whether any patients had further investigations requested as part of their ongoing first episode of care after their initial appointment. Again, any new organic gastrointestinal diseases detected after these investigations were documented.

Statistical Analysis

We calculated mean follow-up duration between the date of the initial clinic visit and date of either rereferral, or final review of electronic medical records in those who were not rereferred, and total duration of follow-up in all recruited patients. We compared baseline characteristics of patients who were rereferred with those who were not using a Pearson chi-square test for categorical data and an independent samples *t*-test for continuous data. We performed logistic regression, controlling for baseline data to examine factors associated with rereferral, reporting results with odds ratios with 95% confidence intervals. Because of multiple comparisons, we considered a 2-tailed *P* value of $< .01$ as statistically significant. We used SPSS for Windows version 26.0 (SPSS Inc, Chicago, IL) for all analyses.

Results

There were 577 patients recruited into the aforementioned diagnostic accuracy study, of whom 373 who met Rome IV criteria for IBS with no organic gastrointestinal disease after the investigations outlined previously (see [Supplementary Table 1](#) for investigations performed during initial work-up).²¹ In total, 286 (76.7%) were female and mean age at study entry was 34.8 (standard deviation, 14.0) years ([Table 1](#)). Two-thirds of patients had severe symptoms at baseline, according to the IBS Severity Scoring System, and there were high levels of mood disorders and extraintestinal symptom reporting, in keeping with a referral population of patients with IBS. All patients were followed up successfully, with a mean follow-up per patient of 4.2 years

Table 1. Baseline Characteristics of Patients Meeting the Rome IV Criteria for IBS

	Met Rome IV criteria for IBS (N = 373)
Female, n (%)	286 (76.7)
Mean age (SD)	34.8 (14.0)
IBS subtype, n (%)	
Constipation	88 (23.6)
Diarrhea	129 (34.6)
Mixed bowel habits	143 (38.3)
Unclassified	9 (2.4)
Mean IBS-SSS score (SD)	343.4 (93.6)
IBS-SSS severity, n (%)	
Remission	0 (0)
Mild	20 (5.4)
Moderate	98 (26.3)
Severe	244 (65.4)
Mean HADS anxiety score (SD)	10.6 (4.9)
HADS anxiety, n (%)	
Normal	105 (28.2)
Borderline abnormal	73 (19.6)
Abnormal	184 (49.3)
Mean HADS depression score (SD)	7.2 (4.8)
HADS depression, n (%)	
Normal	204 (54.7)
Borderline abnormal	75 (20.1)
Abnormal	80 (21.4)
Mean PHQ-12 score (SD)	10.2 (4.4)
PHQ-12 severity high, n (%)	107 (28.7)

HADS, Hospital Anxiety and Depression Scale; IBS, irritable bowel syndrome; IBS-SSS, IBS Severity Scoring System; PHQ-12, Patient Health Questionnaire-12; SD, standard deviation.

(median, 4.3 years [range, 75 days to 6.3 years]) and a total follow-up among all patients of 1565 years.

Rates of Rereferral

In total, 62 (16.6%) patients were rereferred with gastrointestinal symptoms. Of these, 35 (56.5% [9.4% of total cohort]) were rereferred with IBS symptoms and 27 (43.5% [7.2% of total cohort]) with other gastrointestinal symptoms ([Table 2](#)). Of those rereferred with IBS, only 5 (14.3%) experienced a change in their IBS symptoms; the other 30 (85.7%) had similar symptoms to baseline. There was a trend toward those who were rereferred being older (39.1 years vs 34.0 years;

Table 2. Reason for Rereferral of Patients Meeting the Rome IV Criteria for IBS Who Were Rereferred With Other Gastrointestinal Symptoms

	Met Rome IV criteria for IBS and rereferred with other gastrointestinal symptoms (n = 27)
Rectal bleeding	5 (18.5)
Dysphagia/odynophagia	5 (18.5)
Abdominal pain without a change in bowel habit	4 (14.8)
Nausea and/or vomiting	3 (11.1)
Epigastric pain/dyspepsia	2 (7.4)
Gastroesophageal reflux	2 (7.4)
Weight loss	1 (3.7)
Perianal skin tags	1 (3.7)
Diarrhea and rectal bleeding	1 (3.7)
Anemia and rectal bleeding	1 (3.7)
Weight loss and abdominal pain	1 (3.7)
Right upper quadrant pain and vomiting	1 (3.7)

NOTE. Values are number (%).
IBS, irritable bowel syndrome.

$P = .020$) (Table 3), which persisted after logistic regression controlling for all baseline features (odds ratio per year, 1.02; 95% confidence interval, 1.00–1.04; $P = .029$) but no significant predictors of rereferral. There were no significant predictors of rereferral among only the 35 patients rereferred with IBS.

Rates of Reinvestigation

Of the 62 patients rereferred, 19 (30.6%) were not reinvestigated, and 43 (69.4% [11.5% of the total cohort]) underwent further testing. Twenty-one (60.0%) of 35 patients rereferred with IBS were reinvestigated versus 22 (81.5%) of 27 rereferred with other gastrointestinal symptoms ($P = .12$). Among the 311 patients who were not rereferred, 48 (15.4%) had further investigations as part of their ongoing episode of care after their initial contact with the IBS clinic. Colonoscopy and upper endoscopy were the commonest investigations requested, followed by 23-seleno-25-homo-tauro-cholic acid (SeHCAT) scan (Table 4). Among those rereferred, 14 patients had colonoscopy, 5 (35.7%) of whom underwent colonoscopy as part of their previous episode of care; 12 underwent upper endoscopy, 3 (25.0%) of whom had upper endoscopy as part of their initial care; and 6 abdominal computed tomography (CT), 2 (33.3%) of whom had previously had abdominal CT.

Rates of Missed Organic Gastrointestinal Disease

No patients who had investigations that had already been performed in the IBS clinic and were repeated subsequently were found to have organic gastrointestinal disease. There was only 1 potentially relevant organic gastrointestinal disease diagnosed subsequently among 21 patients reinvestigated for IBS. This was a case of chronic calcific pancreatitis detected on abdominal CT in a 53-year-old woman with IBS mixed type at study entry, rereferred with identical symptoms, who had a normal CT abdomen and CT colonography 22 months previously, and with no evidence of exocrine pancreatic insufficiency on fecal elastase (Table 5).

Among those reinvestigated for other symptoms, potentially relevant organic gastrointestinal diseases included 1 patient found to have IBD unclassified after colonoscopy for abdominal pain and fever, 1 patient with moderate BAD after SeHCAT scan for diarrhea and rectal bleeding, and 1 patient with small bowel obstruction believed to be secondary to nonsteroidal anti-inflammatory drugs after an abdominal CT for vomiting. The patient with IBD unclassified was a 45-year-old woman who presented with symptoms compatible with IBS with constipation at baseline and had not had a colonoscopy as part of the initial work-up, but had a normal colonoscopy and random colonic biopsies 4 years before the diagnosis of IBD unclassified. The patient with moderate BAD was a 38-year-old woman with IBS with diarrhea type symptoms at baseline with a normal colonoscopy performed during the initial episode of care, with the SeHCAT scan undertaken 2.5 years later. Finally, the patient with small bowel obstruction was a 60-year-old woman who met criteria for IBS mixed type at baseline who had routine blood studies, but had declined other investigations, during the initial management and underwent CT scanning 3 years later. Therefore, among the 43 patients reinvestigated, 4 (9.3%) had a potential missed organic gastrointestinal disease (Table 5).

A further 3 patients had other “incidental” organic gastrointestinal diseases, including acute pancreatitis in 1 patient rereferred with epigastric pain, gallstones in 1 patient with right upper quadrant pain and vomiting, and intra-abdominal adhesions diagnosed after laparoscopy for abdominal pain in 1 patient. Finally, among those who had further investigations as part of their ongoing first episode of care after initial contact with the IBS clinic, 2 patients had severe BAD after SeHCAT scanning (Table 5).

Discussion

This study has examined the durability of a diagnosis of IBS using a combination of limited investigations and the Rome IV criteria in 373 patients seen in a single secondary care clinic. During mean follow-up of 4 years

Table 3. Baseline Characteristics of Patients Meeting the Rome IV Criteria for IBS Rereferred Versus Those Not Rereferred

	Met Rome IV criteria for IBS and rereferred	Met Rome IV criteria for IBS and not rereferred	<i>P</i> value ^a
	(n = 62)	(n = 311)	
Female, n (%)	48 (77.4)	238 (76.5)	.88
Mean age (SD)	39.1 (16.0)	34.0 (13.4)	.020
IBS subtype, n (%)			
Constipation	14 (23.0)	74 (24.0)	
Diarrhea	19 (31.1)	110 (35.7)	
Mixed bowel habits	24 (39.3)	119 (38.6)	
Unclassified	4 (6.6)	5 (1.6)	.14
Mean IBS-SSS score (SD)	349.9 (103.3)	342.0 (91.6)	.58
IBS-SSS severity, n (%)			
Remission	0 (0)	0 (0)	
Mild	5 (8.2)	15 (5.0)	
Moderate	13 (21.3)	85 (28.2)	
Severe	43 (70.5)	201 (66.8)	.38
Mean HADS anxiety score (SD)	11.1 (5.6)	10.5 (4.8)	.46
HADS anxiety, n (%)			
Normal	19 (31.1)	86 (28.6)	
Borderline abnormal	9 (14.8)	64 (21.3)	
Abnormal	33 (54.1)	151 (50.2)	.51
Mean HADS depression score (SD)	8.4 (5.2)	6.9 (4.6)	.051
HADS depression, n (%)			
Normal	7 (20.6)	98 (29.9)	
Borderline abnormal	8 (23.5)	65 (19.8)	
Abnormal	19 (55.9)	165 (50.3)	.52
Mean PHQ-12 score (SD)	11.4 (4.5)	10.0 (4.3)	.022
PHQ-12 severity high, n (%)	24 (38.7)	83 (27.0)	.065

HADS, Hospital Anxiety and Depression Scale; IBS, irritable bowel syndrome; IBS-SSS, IBS Severity Scoring System; PHQ-12, Patient Health Questionnaire-12; SD, standard deviation.

^a*P* value for independent samples *t*-test for continuous data and Pearson chi-square for comparison of categorical data.

per patient, 1 in 6 patients were rereferred to the same center for another opinion. Of these, more than 50%, and almost 10% of the entire cohort, were rereferred because of ongoing IBS symptoms, with the remainder rereferred for other gastrointestinal symptoms. Among those rereferred with IBS, only 14% had experienced a fluctuation in their bowel habit, meaning the rest were rereferred with similar symptoms to those at their index appointment. Importantly, despite reinvestigation rates among those rereferred ranging from 60% for those with ongoing IBS to more than 80% with other gastrointestinal symptoms, 9% of those reinvestigated, and only 1% of the total cohort, were found to have an alternative organic diagnosis that may have explained their initial

consultation with IBS symptoms. Another 3 patients had incidental organic gastrointestinal disease detected, and 2 were found to have BAD after SeHCAT scanning performed as part of their ongoing first episode of care. No patients who had investigations performed previously that were repeated as part of their second referral were found to have an alternative diagnosis to IBS.

Strengths of this study include the large sample size, with more than 350 individuals referred to our clinic recruited and providing complete symptom data. We used a relatively standardized work-up, with all patients screened for celiac disease, a fecal calprotectin to exclude IBD, or a colonoscopy in those of appropriate age with diarrhea or a recent change in bowel habit. We also

Table 4. Investigations Requested in Patients Meeting the Rome IV Criteria for IBS Reinvestigated and Those With Other Investigations Requested as Part of Their Ongoing Episode of Care

	Met Rome IV criteria for IBS and reinvestigated for IBS (n = 21)	Met Rome IV criteria for IBS and reinvestigated for other gastrointestinal symptoms (n = 22)	Met Rome IV criteria for IBS and had further investigations as part of ongoing care (n = 48)
Colonoscopy	9 (42.9)	5 (22.7)	19 (39.6)
Upper endoscopy	5 (23.8)	7 (31.8)	8 (16.7)
SeHCAT	3 (14.3)	2 (9.1)	14 (29.2)
Abdominal CT	2 (9.5)	4 (18.2)	8 (16.7)
Flexible sigmoidoscopy	3 (14.3)	4 (19.0)	4 (8.3)
Abdominal US	2 (9.5)	5 (22.7)	1 (2.1)
CT colonography	3 (14.3)	3 (13.6)	0 (0)
Anorectal physiology	2 (9.5)	1 (4.5)	3 (6.3)
Small bowel MRI	1 (4.8)	0 (0)	2 (4.2)

NOTE. Values are number (%).

CT, computed tomography; IBS, irritable bowel syndrome; MRI, magnetic resonance imaging; SeHCAT, 23-seleno-25-homo-tauro-cholic acid; US, ultrasound.

performed SeHCAT scanning in many patients with diarrhea, to exclude BAD as a cause of symptoms. This is 1 of the largest studies to examine the durability of a diagnosis of IBS, and the first, to our knowledge, to use the Rome IV criteria to define IBS. This combined with the limited investigations is a pragmatic approach to diagnosing IBS, mirroring recommendations for clinical practice from national guidelines.^{5,6} Finally, the fact that the patients we recruited were secondary care referrals means the results are likely to be generalizable to clinicians consulting with individuals with IBS in usual clinical practice.

Weaknesses of the study include the fact that although we are the sole provider of care for all these patients through the UK NHS, we cannot exclude the

possibility that a small number of patients may have been seen in a private hospital subsequently. In addition, other patients may have moved during the period of longitudinal follow-up and now be under the care of another NHS hospital. There is also the possibility that other organic explanations for the initial presentation with symptoms compatible with IBS will come to light during extended follow-up, although given the average duration of follow-up per participant in this study was 4.2 years and the total duration of follow-up in patients was 1565 years, we suspect this is unlikely. Our use of a SeHCAT scan may mean the study results cannot be generalized to countries, such as the United States, where SeHCAT scanning is unavailable. However, there are alternative methods to diagnose BAD. Finally, among

Table 5. Organic Gastrointestinal Diseases Diagnosed in Patients Meeting the Rome IV Criteria for IBS Rereferred and Those With Other Investigations Requested as Part of Their Ongoing Episode of Care

	Met Rome IV criteria for IBS and reinvestigated for IBS (n = 21)	Met Rome IV criteria for IBS and reinvestigated for other gastrointestinal symptoms (n = 22)	Met Rome IV criteria for IBS and had further investigations as part of ongoing care (n = 48)
Potentially relevant organic gastrointestinal disease	1 (1 patient with chronic calcific pancreatitis but no evidence of exocrine pancreatic insufficiency)	3 (1 IBD unclassified, 1 moderate BAD, 1 small bowel obstruction caused by nonsteroidal anti-inflammatory drugs)	2 (2 severe BAD)
Other organic gastrointestinal disease	0	3 (1 acute pancreatitis, 1 gallstones, 1 intra-abdominal adhesions)	0
No organic gastrointestinal disease	20	16	46

BAD, bile acid diarrhea; IBS, irritable bowel syndrome.

those patients rereferred, almost one-third were not reinvestigated. We cannot, therefore, exclude the possibility that an organic gastrointestinal disease has been missed in these individuals.

Although previous validation studies and meta-analyses of prior iterations of the Rome criteria have demonstrated that they perform only modestly in diagnosing IBS,^{22,31-34} the Rome IV criteria outperformed the Rome III criteria in our recent validation study,²¹ because of their higher specificity, with a positive likelihood ratio for the diagnosis of IBS approaching 5. In a secondary or tertiary referral population with lower gastrointestinal symptoms where the prevalence of IBS is likely to be 50% or more, a positive likelihood ratio of this magnitude would be clinically useful, identifying IBS with a posttest probability of 83%. This longitudinal follow-up of the initial validation study adds further to the literature, demonstrating that making a diagnosis of IBS after a limited, but relatively standardized, diagnostic work-up in combination with the Rome IV criteria is safe and durable for most patients. Other than the patient rereferred with diarrhea and rectal bleeding found to have moderate BAD in this study, whether the initial symptoms compatible with IBS were attributable to some of the organic gastrointestinal diseases diagnosed after reinvestigation is debatable. Even in the patient with BAD, it is unclear whether bile acids entering the colon is part of the pathophysiology of IBS with diarrhea.³⁵ Given the duration of follow-up, and the fact that time is often used as a diagnostic test for more serious organic pathology, we suspect other missed organic gastrointestinal disease is unlikely. Repeating previously normal investigations seemed to be of particularly low utility, in terms of diagnostic yield.

In summary, this study to assess durability of a diagnosis of Rome IV IBS, with patients managed as per national guidance, demonstrates that even though 1 in 6 patients were rereferred, either with ongoing IBS or other gastrointestinal symptoms, and more than two-thirds of those rereferred were reinvestigated, only 1% were diagnosed with an organic gastrointestinal disease subsequently. Physicians should be aware that using an approach of limited investigations combined with the application of recommended diagnostic criteria is a safe strategy for managing IBS in secondary care and that the yield of further investigation in a patient in whom IBS has already been diagnosed using this approach is extremely low.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <https://doi.org/10.1016/j.cgh.2023.05.022>.

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- Conflicts of interest**
The authors disclose no conflicts.

Supplementary Methods

Initial Diagnostic Work-up

All patients had a complete blood count, C-reactive protein, and celiac serology checked, regardless of bowel habit. Fecal calprotectin was checked in patients aged <40 years with diarrhea, with colonoscopy if $\geq 100 \mu\text{g/g}$. Those aged ≥ 40 years with diarrhea or recent change in bowel habit also had colonoscopy. Random colonic biopsies are taken as standard in patients with diarrhea undergoing colonoscopy in our center. Colonoscopy was otherwise avoided but could be requested at the physician's discretion in those with atypical features, such as nocturnal symptoms. All patients with diarrhea were considered for SeHCAT scanning to exclude BAD. Given response to bile acid sequestrants is best in those with moderate to severe BAD,²⁷ only patients with a SeHCAT retention of <10% at 7 days were classed as having BAD.

In patients with constipation with symptoms suggestive of obstructive defecation, anorectal physiology was requested. Any other investigations (eg, fecal elastase or small bowel investigations) were at the discretion of the consulting doctor. We classified the following as organic gastrointestinal disease after investigation: celiac disease, Crohn's disease, ulcerative colitis, IBD unclassified, microscopic colitis, ischemic colitis, radiation enteritis, colorectal carcinoma, BAD, or exocrine pancreatic insufficiency (defined as fecal elastase <200 $\mu\text{g/g}$). Incidental diverticulosis, colorectal adenoma, hemorrhoids, or anal fissures were not considered as organic disease. Using these data, we classified patients according to presence or absence of organic gastrointestinal disease after investigation. All patients meeting Rome IV criteria for IBS, with no organic cause for their symptoms after the previously mentioned investigations, were defined as having Rome IV IBS and were the population of interest for follow-up in this study.

Supplementary Table 1. Investigations Requested in All 577 Patients Referred With Suspected IBS During Their Initial Diagnostic Work-up

Investigation	Total number of patients (N = 577)	Number with organic disease
Anorectal physiology studies	32 (5.5)	6 (18.8) ^a
Colonoscopy or CT pneumocolon	102 (17.7)	1 (1.0)
Elastase	18 (3.1)	3 (16.7)
Flexible sigmoidoscopy	24 (4.2)	0 (0)
SeHCAT scan ^b	99 (17.2)	14 (14.1) ^c

NOTE. All values are number (%).

CT, computed tomography; IBS, irritable bowel syndrome; SeHCAT, 23-seleno-25-homo-tauro-cholic acid.

^aAll patients were also believed to have IBS with constipation; the diagnosis was not revised in any individual.

^bOf the 395 patients meeting Rome IV criteria in the original study, 146 had IBS with diarrhea, therefore 67.8% of those with suspected IBS with diarrhea underwent SeHCAT scanning.

^cThere were also 4 patients with mild bile acid diarrhea (SeHCAT retention between 10.0% and 14.9%); including these individuals the proportion increases to 18.2%.