GASTROENTEROLOGY & HEPATOLOGY™
The Independent Peer-Reviewed Journal

January 2009 www.clinicaladvances.com Volume 5, Issue 1, Supplement 1

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Diagnostic Challenges in the Management of Irritable Bowel Syndrome

A Case Study Compendium

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Supported through an educational grant from Prometheus Laboratories.

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Introduction

In the United States, irritable bowel syndrome (IBS) accounts for over 2.5 million physician office visits yearly. This, despite the fact that only somewhere between 10% and 30% of affected patients seek treatment.[1] A wide variety of symptomatic manifestations and a complex and ill-defined etiology make the definite diagnosis of IBS a continued challenge, impeding both physician and patient recognition of the disease state and contributing to overall patient dissatisfaction with conventional management strategies.[2]

As defined by Manning and associates in 1978, IBS was characterized as a functional gastrointestinal disorder with a collection of four hallmark symptoms (distension, relief of pain with bowel movement, looser bowel movements, and more frequent bowel movements with the onset of pain) and a demonstrated absence of organic gastrointestinal disease.[3] This led to the prevailing concept of IBS as a "diagnosis of exclusion" and as a "symptom collection" with no identifiable pathophysiology. With ongoing research and the continued refinement of the Rome criteria from 1990 to 2006, a complex pathophysiologic mechanism has begun to emerge, along with a more specific diagnostic approach that defines IBS as a well characterized disease, rather than a catch-all for symptoms of no known origin.[4,5]

Despite these advances, physicians continue to have difficulty with the application of the Rome criteria in clinical practice. In a 2004 assessment of general practitioners in the United Kingdom, 80% of physicians had no knowledge of the validated IBS criteria and only 4% had actually utilized them in practice. Although the majority of gastroenterologists in the same study were aware of the Rome criteria, the authors concluded that "if rigidly applied in the clinical situation [the Rome II guidelines] would lead to much diagnostic uncertainty."[6] Other recently proposed mechanisms for IBS, such as small-intestinal bacterial overgrowth (SIBO),[7] as well as the accompanying breath tests to detect SIBO, have proven controversial and not particularly sensitive for diagnostic purposes.[8,9]

Current theories of IBS pathophysiology describe a complex combination of psychosocial factors, abnormal motility and secretion, and visceral hypersensitivity contributing to dysregulation of the brain-gut axis.[5] Given this complex etiology and the wide variety of symptomatic manifestations, clinical diagnosis will continue to provide significant challenges and it seems unlikely that any one genetic or serum marker will be uncovered to indicate a definitive disease mechanism.

Table 1. Positive and Negative Predictive Values of the PROMETHEUS® IBS Diagnostic Based on Pretest Probability

Pretest Probability	15%	25%	50%	75%	85%
PPV	48%	61%	81%	94%	95%
NPV	93%	85%	64%	38%	23%

Sensitivity 50%; Specificity 88%.

The PROMETHEUS® IBS Diagnostic was developed to measure a variety of serum markers, examining their individual levels as well as levels in relation to one another, in a manner that predicts the manifestation of IBS and is highly specific for a positive diagnosis (Table 1). This design, which emphasizes the confirmation of a positive diagnosis, offers an alternative approach to other serum tests that rule out organic disease without testing for the presence of IBS.

The initial design of the IBS diagnostic has application as a tool for determining basic IBS diagnosis. With further research of the markers used, as well as refinement of the sophisticated pattern-recognition algorithm that interprets test results, the utility of the diagnostic will continue to expand. Ultimately, the IBS diagnostic may have possible applications in the determination of IBS subtype, research of IBS pathophysiology, and individualization of treatment. It is hoped that as the application for the IBS diagnostic grows, it will play a role in earlier diagnosis of IBS as well as obviating the need for other, unnecessary, testing.

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Two IBS Patients With Diagnostic and Treatment Challenges

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Patient 1: Diarrhea-Predominant IBS

A female, 24-year-old, first year graduate student presents with a 7-month history of lower abdominal pain and irregular, unpredictable bowel movements. She complains of pain followed by loose watery stools. These episodes occur mainly in the morning, but may occur after lunch as well. The first stool of each movement is of normal consistency, but they become more watery with each passage. Her symptoms are worse after eating, particularly when eating out at restaurants. She spends an inordinate amount of time in bathrooms, which causes her to be overly concerned about their location when in public places, due to frequent urgency and an episode of incontinence. There is no blood in the stool or on the toilet tissue. She has trouble sleeping and reports nocturnal pain, which is relieved by a bowel movement.

She is otherwise healthy, her appetite is good and her weight has been stable. She had similar symptoms in her freshman year as an undergraduate, but it was attributed to food poisoning and resolved when she returned home for summer vacation. Her school work is suffering and she complains about her inability to maintain a social life. She is very concerned as her symptoms are worsening and she is considering dropping out of graduate school.

Her physical examination is normal and symptoms are compatible with IBS. She is advised that symptoms can be helped through dietary and lifestyle modifications. The patient becomes agitated and states that "it is not in my head and something must be seriously wrong." She expresses a desire that "tests be done." Limited evaluation reveals normal CBC, ESR, thyroid function, and negative test for occult blood.

Diagnosis and Discussion

The patient's symptoms are consistent with Rome III criteria for diarrhea-predominant IBS and no alarm signs are noted. Current guidelines recommend criteria-based diagnosis and limited laboratory investigation including a CBC, ESR, and, in some cases, a thyroid function study and/or Celiac serology. Any patient over 50 years of age should also undergo complete colonoscopy.[1]

This patient's nighttime pain and diarrhea are of concern. Nocturnal symptoms are often associated with organic disease. However, many IBS patients have difficulty sleeping and may already be awake when symptoms occur. In taking a detailed history, patients should be asked specifically if they are awakened from sleep by the symptoms or if they are already awake when symptoms occur.

A subset of patients (15%)[2-4] may have onset of IBS after an intestinal infection, but in this patient, pain and diarrhea may have been exacerbated by a stressful first year in college and relieved by returning home.[5-6]

All laboratory tests return normal and, although she is somewhat reassured, the patient remains concerned that she may have colitis. A subsequent sigmoidoscopy and mucosal biopsy are normal. Upon follow-up and discussion of possible treatments, the patient asks "if all my tests are normal, how can you be so sure that I have irritable bowel syndrome?" At this point the IBS diagnostic serology (Prometheus) is ordered, with a pattern consistent with IBS. The patient is now more reassured about the lack of organic disease and is satisfied with the IBS diagnosis.

Although helpful in this case at this point in time, it may have been more useful to administer the IBS diagnostic earlier in the evaluation. The patient may have been more confident with the diagnosis knowing the test was positive, and more accepting of the negative results of other tests eliminating other disease states. It is important to explain at the outset that a patient's symptoms fit the criteria for IBS, with a brief explanation of the pathophysiology causing symptoms, followed by an explanation of the fact that other disorders may mimic IBS and a few basic tests should be run to ensure a lack of alarm signals or "red flags." When the routine tests are negative, but the IBS diagnostic is consistent with irritable bowel, the patient is more likely to be reassured and more confident in their diagnosis. This will result in a patient

more willing to commence treatment and forego extensive, expensive evaluation, which will be negative and unrewarding.

Treatment and Follow-up

The patient was instructed to commence a high-fiber, low-fat diet and to add a fiber supplement to bulk the stool and help regulate intracolonic pressure. An anticholinergic is prescribed before meals and as needed for severe cramps. Although a recent meta-analysis of multiple studies showed no significant benefit from anticholinergics available in the United States, they are still widely used, although not US Food and Drug Administration-approved for IBS.[7] The patient was scheduled to return in 4 weeks for follow-up.

Patient 2: Constipation-Predominant IBS

A 45-year-old, African-American male, employed as a nurse, presents with complaints of abdominal pain and bloating. He reports a 20-year history of difficulty moving his bowels, beginning in nursing school, but the problem has worsened over the preceding 6 months.

His abdominal pain is mostly in the left lower quadrant without radiation, but cannot be well characterized. He states that "it just feels uncomfortable." The pain increases in intensity after 2–3 days without a bowel movement and is relieved by a bowel movement. The stool tends to be hard and lumpy and difficult to pass. Although he has hard stool, he is often required to return to the toilet several times with progressively looser and more watery stools. He never experiences a feeling of complete evacuation. He complains additionally of diarrhea, 1–2 days monthly.

He frequently works night shifts and uses laxatives to clear his bowels so that work will not be interrupted. He uses a variety of over-the-counter products and notes that he does not abuse them. He also notes the use of organic, natural laxatives only. His appetite is good and his weight is stable. He has not seen any blood in the stool and a home testing kit was negative for occult blood.

Physical examination is normal, including a detailed rectal examination. Laboratory test results from his primary care physician, including complete blood count, erythrocyte sedimentation rate, and electrolytes are all normal. His primary care physician checked his thyroid function at his annual examination and he is euthyroid. The patient is scheduled for a colonoscopy.

Diagnosis and Discussion

Constipation is a common disorder and it is estimated that it affects 10–20% of the US population. However, only about 20% of constipated individuals seek the help of a physician, relying instead on available over-the-counter products.

A symptom-based approach, along with a thorough physical examination to eliminate red flags, allows for the diagnosis of IBS in this patient. Per the Rome III criteria, patients with constipation-predominant IBS may have straining, urgency, feelings of incomplete evacuation, and bloating. The presence of abdominal pain or discomfort differentiates constipation-predominant IBS from chronic idiopathic constipation. Other causes of constipation need to be considered in appropriate situations.

In the past, colonoscopic screening has been recommended to begin at age 50 in patients without risk factors. However, it has recently been suggested that screening begin earlier in African Americans, because of higher rates of aggressive colon cancer at an early age. Even though the patient has no alarm signs, a colonoscopy would be indicated.

Routine laboratory examinations were all normal, including stool occult blood. Colonoscopic examination revealed melanosis coli and sigmoid diverticulosis. These findings remain consistent with IBS, but suggest that previously used natural laxatives contain pigment agents such as anthracene compounds. They also suggest more frequent laxative use than the patient admits. The IBS diagnostic serology is administered at this point to clarify and validate the diagnosis for the physician and reassure the patient of no organic disease.

Treatment and Follow-up

The patient is instructed to begin a high-fiber, low-fat diet. He is started on fiber supplements and an osmotic laxative, polyethylene glycol (PEG), 17 grams in 8 ounces of water, once daily. The use of osmotic agents (PEG) in clinical practice has increased significantly in recent years, perhaps due to the increasing belief that bulking agents, primarily useful in mild constipation, are of no benefit in severe constipation. A return visit is scheduled in 4 weeks to evaluate therapy and adjust treatment, if necessary.

However, the patient calls in 2 weeks, complaining of worsened symptoms. He has stopped fiber due to increased bloating and reports that the osmotic laxative has not helped at all. At this point, the laxative dose is increased to twice daily.

The patient returns for his 4-week visit complaining of persistent symptoms. Increasing the osmotic laxative to twice daily has led to explosive episodes and occasional leakage. The patient is counseled on the difficulty of retraining a bowel with 20 years of abnormal motility and reassured that his symptoms are compatible with constipation-predominant IBS. Positive results of the IBS diagnostic are shared with him. He is encouraged to continue a healthy high-fiber diet (increasing the amount

of fiber gradually over several weeks), drink fluids, and get regular exercise. He is started on a chloride channel activator (lubiprostone 8 µg twice daily) to be taken with food.[8] He returns in 8 weeks and reports decreased bloating and more frequent bowel movements.

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A Patient With Constipation-Predominant IBS

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Examination

The patient is a 28-year-old nulliparous woman who presents with complaints of abdominal cramping, bloating, and constipation. She has had intermittent symptoms since adolescence but seeks care after seeing a television commercial that recommends discussing such symptoms with a doctor. She experiences intermittent left lower quadrant cramping several times per week. Her cramping improves with the passage of a bowel movement. She also reports bloating, which usually worsens after eating or if her bowel movements are less frequent and improves following a bowel movement. She reports experiencing a bowel movement once to twice per day. She often has to strain to pass stool and sometimes does not feel fully evacuated after a bowel movement. She states that her stools are often small and their consistency is often hard and lumpy. She denies the use of manual maneuvers, weight loss, rectal bleeding, melena, or a family history of colon cancer, inflammatory bowel disease, or celiac sprue. She has tried to increase the fiber in her diet but found that this worsened her problems with bloating and cramping. She has also tried a reduced-lactose diet and a 2-week trial with a probiotic-containing yogurt, without benefit. Pertinent medical history is unremarkable. She denies alcohol abuse or the use of tobacco or illegal drugs. She is taking a multivitamin supplement and an oral contraceptive medication.

Physical examination reveals a well developed female in no acute distress. Her weight is 125 pounds and blood pressure measures 115/85 mm Hg. General physical examination is normal. Abdominal examination reveals minimal left lower quadrant tenderness to deep palpation. Bowel sounds are normal and there is no organomegaly. Digital rectal examination reveals an intact anal wink, normal baseline sphincter tone, and a normal response to simulated defecation.

Discussion

Irritable bowel syndrome (IBS) can be confidently diagnosed using symptom-based criteria such as the Rome III criteria (Table 1), excluding red flags (bleeding, weight loss, nocturnal diarrhea, fever, family history of colorectal

Table 1. Rome III Diagnostic Criteria for Irritable Bowel Syndrome

Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with 2 or more of the following:

1. Improvement with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool

Diagnostic criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

Criteria for IBS Subtypes

- IBS with constipation (IBS-C)

1. Hard or lumpy stools for >25% of bowel movements
2. Loose (mushy) or watery stools for <25% of bowel movements

- IBS with diarrhea (IBS-D)

1. Loose (mushy) or watery stools for >25% of bowel movements
2. Hard or lumpy stools for <25% of bowel movements

- Mixed IBS (IBS-M)

1. Hard or lumpy stools >25% of bowel movements
2. Loose (mushy) or watery stools for >25% of bowel movements

- Unsubtyped IBS

1. Insufficient abnormality of stool pattern to meet criteria for IBS-C, IBS-D or IBS-M

Data from Longstreth et al.[1]

Table 2. Pretest Probability of Organic Gastrointestinal Disease in Patients Meeting Symptom-Based Criteria for IBS

Organic GI Disease	IBS Patients (Pretest Probability)	General Population (Prevalence)
Colitis/IBD	0.51–0.98%	0.3–1.2%
Colorectal Cancer	0–0.51%	4–6%
Gastrointestinal Infection	0–1.7%	N/A
Thyroid Dysfunction	6%	5–9%
Lactose Malabsorption	22–26%	25%

Data from Cash et al.[5]

cancer, inflammatory bowel disease, or celiac disease), and performing a careful physical examination. IBS subgroups are predicated upon differences in stool consistency rather than stool frequency.[1,2] As the case illustrates, stool frequency is an unreliable surrogate for complaints of constipation. Studies suggest that such a strategy provides excellent specificity and positive predictive value for IBS.[3] Despite evidence to support this statement, most primary care physicians and gastroenterologists view IBS as a "diagnosis of exclusion."[4] Undoubtedly, this view is a byproduct of the broad differential diagnosis of IBS symptoms and the heterogeneous pathogenesis of IBS. Related to such concerns, primary care physicians and gastroenterologists often order a myriad of tests to consolidate the diagnosis of IBS.

When clinicians are deciding upon the need to order a diagnostic test, it is useful to consider the pretest probability of the disease in question. If the pretest probability of a particular disease is sufficiently small, then diagnostic testing directed at uncovering that improbable disease is unlikely to be either clinically useful or cost-effective. Second, clinicians should be aware of the performance characteristics (eg, sensitivity, specificity, positive and negative predictive value) of the diagnostic test under consideration.

The results of a diagnostic test should shift the clinician's estimate of pretest probability of a disease up or down, so that he or she may be reasonably assured that the disease being considered is either present or absent. In the case of IBS, since there are no consistently reproducible anatomic or biologic abnormalities, diagnostic tests are performed in order to exclude organic diseases that may present with similar symptoms, and in so doing, reassure both the clinician and the patient that the diagnosis of IBS is correct. Clinicians are most often concerned about colorectal cancer, inflammatory bowel disease, endocrine diseases, enteric infections, and malabsorptive diseases when faced with a patient with symptoms suggestive of IBS. Diagnostic tests to identify these conditions are the ones most commonly ordered in patients with IBS symptoms. We performed a systematic review to determine the pretest probabilities of such organic gastrointestinal diseases in patients with suspected IBS versus non-IBS controls (Table 2).[5] Based upon limited data, we found that the prevalence of most organic gastrointestinal diseases were not significantly different between patients with IBS symptoms and non-IBS controls. It is important to point out that the available data are derived from studies of variable methodologic quality and are restricted to patients without alarm features. As such, these data should not be generalized to patients with IBS symptoms and alarm features.

The American College of Gastroenterology (ACG) Functional Gastrointestinal Disorders Task Force published a clinical practice guideline on the management of IBS in 2002.[6] This guideline concluded that the *routine* performance of diagnostic tests to rule out other conditions in patients with typical IBS symptoms and no alarm features was not supported by the available literature. One possible exception to this statement related to celiac disease, which may be more prevalent in patients with IBS symptoms than in non-IBS controls. In a recent meta-analysis presented at the annual meeting of the ACG, Ford reported data from 6 studies (1,209 patients) and found that 4.3% (95% CI=1.7–8.0) of IBS patients had biopsy-proven celiac sprue. Data from 5 case control studies yielded an odds ratio of 4.34 (95% CI=1.78–10.6).[7] Based upon these results, many experts now recommend serologic screening for celiac disease in IBS patients with diarrhea or mixed bowel habits. Another issue worthy of discussion is lactose intolerance. It remains controversial whether lactose intolerance is more prevalent in IBS patients. However, even if the prevalence of lactose intolerance is similar in IBS patients compared to non-IBS controls, the clinical consequences of a disorder which leads to an increased osmotic load in the colon may not be the same for IBS patients, who often have abnormalities in motility and visceral sensation. As such, breath testing for lactose intolerance may be appropriate in selected IBS patients who do not improve or cannot comply with a reduced lactose diet. Many of these issues will be addressed in the update of the ACG monograph on IBS which is expected in the first quarter of 2009.

The presence of alarm features may identify a subgroup of patients with a greater pretest probability of organic disease. Most experts recommend a more aggressive diagnostic evaluation in such patients. Generally accepted "alarm features" include new onset of symptoms in patients older than 50 years, unexplained weight loss, gastrointestinal bleeding, progressive or unrelenting pain, nocturnal or large-volume diarrhea, and a family history of colon cancer, inflammatory bowel disease, or celiac sprue.[2]

If alarm features are not present and the patient fulfills symptom-based criteria, as was the case for our patient, a confident diagnosis of IBS can be offered and symptom-directed therapy should be initiated. A crucial aspect of this minimalistic approach is appropriate follow-up. If standard therapeutic interventions fail to improve the patient's IBS symptoms, a more detailed diagnostic evaluation can be pursued. Once made, clinicians should be reassured by the durability of the diagnosis of IBS over time. In two studies with 3–20 years of follow-up, less than 1% of IBS patient were diagnosed with an alternative organic disease that explained their gastrointestinal symptoms.[8,9]

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Diagnostic Process in a Case of Diarrhea-Predominant IBS

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A 44-year-old white woman presents with an 8-month history of recurrent abdominal pain associated with passage of loose stools. In addition, she reports the sensation of abdominal bloating following meals, increased flatulence, and improvement in abdominal pain with defecation. She has had a change in bowel habits from passage of one formed bowel movement daily to passage of multiple loose stools every day without a nocturnal component. She has no weight loss, nausea, vomiting, melena, or hematochezia. The patient reports having an older sister with celiac sprue, but denies any family history of gastrointestinal malignancy or inflammatory bowel disease. She denies any travel, recent antibiotic use, or excessive intake of chewing gum or sugar-substitute products. In an attempt to relieve her symptoms, the patient had tried over-the-counter bulking agents and avoidance of dairy products, with limited efficacy. Her physical examination is generally unremarkable including a normal digital rectal examination and negative fecal occult blood test. Laboratory evaluation reveals normal red blood cell indices, liver function tests, renal function, and erythrocyte sedimentation rate.

Diagnosis of a functional bowel disorder requires characteristic symptoms during the preceding three months with symptom onset at least six months before diagnosis.[1] According to current clinical guidelines, IBS can generally be diagnosed without additional testing beyond a careful history taking, a general physical examination, and routine laboratory studies (not including colonoscopy). In patients who have symptoms that meet the Rome criteria, who do not have warning signs including rectal bleeding, anemia, weight loss, fever, family history of colon cancer, onset of the first symptom after 50 years of age, or a major change in chronic symptoms, no additional testing is recommended.[2]

Despite the above recommendations, a variety of serious conditions can be present in those patients who meet Rome criteria and lack classic warning signs. These include celiac sprue and inflammatory bowel disease. In fact, the pretest probability of celiac disease in patients meeting symptom-based criteria for IBS has been found to be as much as 10 times higher than the prevalence of celiac disease in the general population[3] and new IBS guidelines recently published by the American College of Gastroenterology recommend performance of serologic testing for celiac disease in patients with symptoms of diarrhea-predominant or mixed-symptom IBS.[4]

A blood-based diagnostic test (Prometheus) was recently developed to aid in the identification of patients with IBS. This test uses 10 biomarkers derived from multiple pathophysiologic pathways thought to be associated with IBS. Included in the IBS panel is TTG—one of the major autoantigens in celiac disease, as well as anti-*Saccharomyces cerevisiae* antibody Immunoglobulin A (ASCA IgA) and Antineutrophil cytoplasmic antibody (ANCA), both of which have been associated with inflammatory bowel disease. The remaining 7 biomarkers include a variety of cytokines, chemokines, growth factors, and lipocalins. The overall accuracy of the IBS diagnostic is 70%, with a sensitivity of 50% and a specificity of 88%.

In the current case, an IBS diagnostic serology was obtained revealing a pattern consistent with IBS. The high positive predictive value of the test fully reinforced diagnosis. Although for most patients, fulfillment of Rome III criteria, with no alarm symptoms, adequately confirms the presence of IBS, in a subset of patients who cannot accurately define their symptoms, or who have a confounding medical history, the IBS diagnostic panel is a potentially useful tool. The patient was started on loperamide before meals and dicyclomine with moderate improvement in abdominal pain and frequency of bowel movements. If at the time of follow-up, symptoms continue to interfere with quality of life, the risks and benefits of a trial of alosetron will be discussed with the patient. The patient was pleased to have a definitive diagnosis and was relieved that her symptoms were not related to a more dangerous condition. Further, the appropriate treatment of IBS allowed her to return to her previous diet and activities.

IBS is a chronic condition and one of the most common syndromes seen by gastroenterologists and

primary care providers. In clinical practice, IBS is often diagnosed by the exclusion of more serious illnesses such as inflammatory bowel disease and celiac sprue. With the introduction of the new IBS diagnostic serology, it may be possible to achieve a greater degree of certainty regarding the diagnosis of IBS while minimizing the need for costly and invasive procedures. This panel, complimented by a thorough history and physical examination, can add to a gastroenterologist's armamentarium in making the diagnosis of IBS.

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Two Cases of Primary Care Referral for IBS

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Patient 1: IBS With Alternating Constipation and Diarrhea

The patient is a 31-year-old woman referred for a second opinion in gastroenterology due to a 5-year history of bloating, lower abdominal pain, and alternating symptoms of constipation and diarrhea. Symptoms of constipation usually last for several days and include infrequent, hard, pebble-like stools, with excessive straining and feelings of incomplete evacuation. The patient states that after passing hard stool there may be a small amount of bright red blood in the toilet bowl. This is typically followed by several days of urgent, loose, nonbloody bowel movements. The patient describes intermittent, crampy, diffuse abdominal pain that is worse during periods of constipation and for the 3–4 days preceding the onset of her menstrual cycle. Her pain is generally relieved after evacuating stool. At times she becomes so bloated and distended that she is unable to wear her normal clothes.

The patient has seen several physicians over the last several years and feels frustrated and discouraged due to conflicting advice and persisting symptoms, despite medical therapy. Her gynecologist theorized that all of her symptoms were due to endometriosis and recommended surgery and hysterectomy. Her first family physician told her that her symptoms were due to inflammatory bowel disease and another told her that her symptoms were due to celiac disease. Her local gastroenterologist told her that her symptoms were consistent with IBS but that she could not "rule out" chronic intestinal pseudo-obstruction. She states that she has used a variety of fiber supplements without relief (psyllium, methylcellulose, and polycarbophil), and all of these agents made her bloating worse. Trials of docusate sodium, polyethylene glycol-3350, milk of magnesia, and lactulose temporarily improved her symptoms of constipation but did not help her pain. Imodium and diphenoxylate-atropine helped her diarrhea but worsened her bloating and did not improve her pain. When asked what her goals for treatment were, given multiple visits to other physicians, the patient stated three: 1) she wanted a definitive diagnosis because she was confused by the conflicting information and advice; 2) she wanted to know if any further tests were required; 3) she wanted to avoid prescription medications but would consider "safer" alternative therapies.

Physical Examination

The patient is a talkative, well-nourished 31-year-old woman; slightly anxious, but in no apparent distress. Vitals signs are as follows: weight 124 lbs., heart rate 74 beats per minute, blood pressure 113/68 mm Hg, and respiratory rate, 14. Examination of the head, eyes, neck, mouth, heart and lungs is normal. The abdomen is flat, soft, and slightly distended. A well-healed scar was noted

in the right lower quadrant. Bowel sounds were present; no succussion splash or bruit were heard. No masses or enlarged organs were felt. A slight tenderness in the left lower quadrant over the sigmoid colon was noted with no stool felt in the colon. There was no evidence of rebound, guarding, or ascites. Rectal examination was normal. During simulated evacuation there was normal relaxation of the anal sphincter and puborectalis muscles. One month prior, the patient's primary care physician ordered a complete blood count (CBC), erythrocyte sedimentation rate (ESR), electrolytes, lipase, thyroid-stimulating hormone (TSH), beta-human chorion gonadotropin, serum transglutaminase antibody (TTG), and liver function tests, all of which were within normal limits.

Colonoscopy performed a year prior by a local gastroenterologist (to the terminal ileum) was normal with the exception of small internal hemorrhoids. Random biopsies of the right and left colon were normal. An upper gastrointestinal series with small bowel follow-through one year prior was also normal. Recent pelvic and transvaginal ultrasound were both normal.

Diagnosis and Treatment Plan

Our working diagnosis was of IBS with mixed symptoms of constipation and diarrhea, with comorbid conditions of migraine headaches, temporomandibular joint syndrome, interstitial cystitis, fibromyalgia, dyspareunia, and chronic fatigue syndrome. We informed the patient that she had IBS with mixed symptoms of constipation and diarrhea and reassured her of normal tests to date, particularly given the chronicity of symptoms. She was informed that it was quite common to have other symptoms and disorders associated with IBS, and in fact, the presence of these other symptoms (ie, interstitial cystitis, fibromyalgia) increased the likelihood that the diagnosis of IBS was correct. She was advised to avoid dairy and fructose for 10 days, in order to see what role these food substances played in symptom generation. She was also encouraged to continue eating a healthy diet but to decrease the amount of insoluble fiber and to focus on foods with predominantly soluble fiber. She was asked to use the bathroom routinely 30 minutes after breakfast to take advantage of the natural gastrocolic reflex, to start a regular exercise program, and to focus on ways to reduce stress in her life. She was given information on fibromyalgia and interstitial cystitis, and asked to monitor her urinary symptoms. Hypnotherapy was discussed as an alternative therapy and she said she would investigate that with her local provider. The risks and benefits of probiotics were discussed and she said she would consider using these after doing more research (she later decided to start daily *Bifidobacterium*).

She was told that she did not need any specialized tests at present and seemed reassured. However, her local internist called a week later and inquired about a new blood test to diagnose IBS. She said that she was not as confident with the diagnosis, and would like to order the IBS diagnostic panel (Prometheus). This was ordered, in addition to a serum IgA (which had not been ordered in the past). The test returned 2 weeks later, showing a "pattern consistent with IBS" and the repeat TTG in

Table 1. Baseline Characteristics: Patient 1

Allergies	Sulfa (rash)
Current Medications	Daily oral contraceptive, ibuprofen and imitrex as needed
Past Medical History	Migraine headaches, interstitial cystitis, fibromyalgia
Past Surgical History	Appendectomy–age 13; wisdom tooth extraction (4)–age 18
Social History	Single, no children, works full time at an art gallery
Habits	Occasional cigarettes (2–3 each weekend), social alcohol (1–2 glasses of wine each night)
Family History	Mother: history of chronic constipation. Father: celiac disease. Sister: history of IBS with constipation. Second sister and brother: healthy. No first degree family members have a history of inflammatory bowel disease or any type of gastrointestinal malignancy.
Review of Systems	Patient denies symptoms of reflux and dyspepsia. No history of ulcer. Weight stable for several years. No anemia, weight loss, fever, chills, vomiting. Her menstrual cycles are fairly painful and gastrointestinal symptoms seem to worsen before the onset of menses. She denies symptoms of depression and anxiety. She has urinary urgency and frequency on most days and repeated urine cultures have been normal. She describes a deep pelvic pain that is worse with intercourse. She has diffuse myalgias most days and has 1–2 migraine headaches each week. Her jaw frequently hurts. She feels "exhausted" most of the time, even after a good night's sleep.

the panel was negative. The patient and the referring provider seemed satisfied with the diagnosis of IBS and 2 months later, during telephone follow-up, the patient stated that her symptoms were 75% better and that she did not require any follow-up or medications.

Patient 2: Diarrhea-Predominant IBS

The patient is a 25-year-old, female graduate student referred for the evaluation of a 2-year history of diarrhea and abdominal pain. She states that during high school and college she would typically have one bowel movement daily. Towards the end of her collegiate career, she noted that she would often have a loose bowel movement every day, a novel development. Over the last 2 years, her bowel movements have become more frequent and on average she now has 3–4 loose, somewhat urgent bowel movements each day, which are never bloody. She describes lower abdominal "cramps and spasms," which predictably occur before having a bowel movement. These are always worse just before having a bowel movement, and are relieved after having a bowel movement. She frequently feels bloated and distended, and her friends have joked that she looks 4 months pregnant. Although she has always been lean, she had to buy new clothes with elastic waistbands because many of her clothes felt "tight" on the days she was bloated.

The patient initially believed herself lactose intolerant. She stopped all milk products for 2 days but this did not improve her symptoms. A friend advised her that she was not getting enough fiber in her diet; afterward, she became a strict vegetarian. This dietary change served only to worsen her bloating symptoms and increased her stool frequency to 4–5 loose stools per day. Another friend advised that she may have a pancreatic condition and suggested a trial of enzyme supplements—these did not help. After some library research, the patient theorized that her symptoms were due to a wheat allergy, and she eliminated all wheat products from her diet for 2 months. Again, her symptoms did not improve. Acetaminophen, aspirin, and a variety of over-the-counter anti-inflammatory agents did not help her lower abdominal pain. The patient consulted with her internist, who gave a diagnosis of probable IBS, but wanted to rule out celiac disease and inflammatory bowel disease. The internist ordered a CBC, ESR, TSH, and serum immunoglobulin A and TTG antibody levels to check for celiac disease. Serum lipase and liver function tests were also performed, and serum glucose and $HgbA_{1c}$ levels were checked in order to rule out diabetes. All of these tests returned normal. The internist prescribed fiber supplements twice daily and referred the patient for colonoscopy, which was grossly normal, including random biopsies of the terminal ileum and the right, transverse, and descending colon. The patient was placed on a routine dose of imodium and at 4–5 tablets per day, her bowel habits improved to 2 loose stools per day, although she still had significant bloating, distention, and lower abdominal cramps and spasms. A trial of diphenoxylate-atropine worked no better than imodium, and subsequent trials of dicyclomine, glycopyrrolate, amitriptyline, a probiotic (*Lactobacillus*), and hyoscyamine were not helpful. Due to persistent symptoms, an upper gastrointestinal series with small bowel follow-through was performed and was normal. Formal consultation was requested with our practice, due to "intractable" IBS symptoms with diarrhea.

Upon examination, patient was observed as a well-appearing, talkative young woman in no acute distress with a body mass index of 21.8, blood pressure of 116/72 mm Hg, and a respiratory rate of 14. Examination of the head, neck, chest, heart, and extremities was normal. Abdominal examination revealed mild distention. No stool was palpated in the colon. No succussion splash or bruits were heard. No rebound, guarding, or ascites were noted. Spleen tip was not palpated. The liver edge was smooth. Bowel sounds were present. Rectal examination revealed normal sphincter tone without evidence of masses or tenderness. No stool was present in the rectal vault.

Diagnosis and Treatment Plan

Although the patient was diagnosed with IBS and diarrhea by her primary care provider, there were several factors which called this diagnosis into question. The patient did not have any of the common comorbid disorders associated with IBS such as acid reflux, dyspepsia, interstitial cystitis, migraine headaches, or fibromyalgia. Although IBS does occur without the presence of other visceral or somatic disorders, these disorders are quite commonly seen in conjunction with IBS. Further, the patient had multiple dietary components that could potentially play a role in symptom generation, including dairy, caffeine, fructose, and excess fiber. Finally, the patient did not have any response to agents commonly used to treat IBS.

We advised the patient that her examination was reassuring and along with her history, presented no major warning signs. We further noted that, based on normal blood work and normal colonoscopy with biopsies, the absence of a family history, normal physical examination, and normal small bowel follow-through, inflammatory bowel disease could be ruled out. We discussed a new approach, utilizing an elimination diet to see what role food had in her symptom generation, rather than attempting another medication trial. The patient insisted that she was sure she had IBS and did not believe that foods

Table 2. Baseline Characteristics: Patient 2

Allergies	Latex (rash)
Current Medications	Oral contraceptive, acetaminophen as needed for headaches
Past Medical History	Occasional headaches
Past Surgical History	None
Social History	Single, no children, full-time graduate student
Habits	No tobacco, 3–4 glasses of wine per week
Family History	Mother alive at age 54 with reflux symptoms, sister with diagnosis of IBS and constipation, father alive and healthy at age 55. No first degree family member with any gastrointestinal malignancy, inflammatory bowel disease or celiac sprue.
Review of Systems	No symptoms of reflux or dyspepsia; no complaints of dysphagia; no prior history of ulcer, hepatitis, or pancreatitis; no symptoms of fibromyalgia, interstitial cystitis, TMJ syndrome, back pain, or dyspareunia. Patient denied any symptoms of anxiety or depression. High fiber diet–greater than 40 grams per day; daily dairy intake of milk, cheese, and ice cream; 4–5 cups of coffee per day along with iced tea; 1 liter of regular soda per day; occasional use of "energy" drinks.

were playing any role in her symptoms. She also stated that her internist had advised her of a new blood test to diagnose IBS and expressed an interest in having it done. As a compromise, she returned to her internist for the IBS diagnostic panel while also initiating an elimination diet, which had her restrict intake to water, white rice, and boiled chicken for one week.

She called back at the end of one week and said that her bloating had resolved, as had her cramps, and that she was now constipated. Over the next month we slowly added in small amounts of other foods including corn products, potato, lean turkey, egg whites, plain pasta, and lamb. She tolerated these well without any symptoms of gas, bloating, distention, or diarrhea. Over the next month, we added in small amounts of soluble fiber and wheat products without any return of her symptoms. The IBS diagnostic blood test returned, showing that the blood work was not consistent with IBS (of note, the repeat serum TTG in this panel was negative). The patient seemed reassured by the results of the elimination diet and blood work and slowly reintroduced small amounts of fiber into her diet without any return of symptoms, although she continued to refrain from dairy, caffeine, and excess fructose.

Commentary

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The diagnostic criteria for irritable bowel syndrome (IBS) have evolved considerably since the term was first coined as a catch-all designation for patients with functional gastrointestinal symptoms and no identifiable organic disease. It has been 30 years since Manning and associates established four specific symptoms to differentiate IBS from other organic disease. With the publication of the Rome I IBS criteria in 1992, the Rome II revised criteria in 1999 and further refinement with Rome III in 2006, symptomatology, disease behavior, and disease duration have been further codified to provide a more specific definition for IBS. Both exclusive and inclusive criteria now play a critical role in diagnosis of the condition, development of guidelines for treatment, and recommendations for continued follow-up of patients. These can be utilized to provide effective management strategies for patients.

Despite the progress of these consensus documents in defining a well-characterized clinical syndrome, the pathophysiology of IBS remains poorly understood, presenting an ongoing diagnostic and treatment challenge. Because IBS is a chronic condition with a variety of symptomatic manifestations that vary from patient to patient and even within a single patient over time, ambiguities and uncertainties can cloud physicians' treatment strategies, as well as patient attitudes toward their own illness and physician advice. The PROMETHEUS® IBS diagnostic represents an important step in reinforcing clinical diagnoses, exploring IBS pathophysiology, and allowing for a positive diagnostic approach.

Indications for the PROMETHEUS IBS Diagnostic

As the varying scenarios presented in the previous cases illustrate, the diagnosis of IBS is not made from a single initial examination. Consideration of the chronic symptom complex as defined by Rome II and Rome III, initial evaluation of the patient's symptomatology and history, and observation and follow-up all play a part. Additionally, the majority of physicians conduct a series of baseline tests to ensure that symptoms are not caused by other organic conditions, which may have similar presenting symptoms. Even with this information, there may be some points of query or contradictory signals that thwart a definite diagnosis. One of the important roles for the IBS diagnostic may be to add confidence and reinforcement. In the ongoing follow-up of IBS patients, the diagnostic panel could provide needed validation at any point when further confirmation is desired. Establishment of its role will be dependent on clinical studies.

Many patients will present with a symptom complex that closely matches IBS criteria, seemingly obviating the need for a diagnostic panel. However, with the initiation of treatment, some patients may not respond in the manner hoped. In these patients, where there are no alarm symptoms and initial diagnosis may have ruled out Celiac disease and inflammatory bowel disease (IBD), it might be hard to justify additional costly or invasive testing like computed tomography imaging or colonoscopy. At this juncture, physicians may wish for some further confirmatory data before continuing or altering their treatment strategy and the IBS diagnostic panel would provide a reasonable alternative.

Further, patients may be referred to a gastroenterology practice with a pre-existing diagnosis that the gastroenterologist feels requires refutation. Patients may have had a previous evaluation with some equivocal findings on colonic biopsy and been told that they have IBD. If current evaluation based on symptoms, history, and family history, calls into question the IBD diagnosis, the IBS diagnostic panel could play an appropriate role in correcting a diagnosis and steering an appropriate course of effective management. Other patients are referred to gastroenterologists with strong suspicion of IBS, based on their diagnostic work up, which may warrant confirmation before proceeding with treatment.

Finally, there is the scenario of patient questioning. Some patients do not feel comfortable with a diagnosis of IBS as they may have heard it referred to as a diagnosis of exclusion and not a "real" disease. If a physician feels confident of an IBS diagnosis, opposition from the patient can create obstacles to effective treatment. A positive IBS diagnostic result could provide an effective way to reassure the patient that the diagnosis is correct and to ensure their cooperation in an optimal management strategy.

All of these situations have in common an initial suspicion of IBS, with some contradictory piece of evidence that requires further investigation. Due to the validated,

high specificity of the IBS diagnostic, use of the test incurs a very low false positive rate, which is extremely important in the management of this disease. The high specificity contributes to a high positive predictive value (confidence in positive test results) when the pretest probability of IBS is 50% or greater. Positive test results are correct (true positive) at least 81% of the time. These scenarios with a high pretest probability of IBS are ideal for a tool like the IBS diagnostic that is highly specific in confirming a suspected diagnosis.

Development of the Current Diagnostic Panel

Most diagnostic studies are developed because a particular marker is found to be abnormally lowered or elevated in association with a particular disorder. For Celiac disease, antinuclear antibodies (ANA) or TTG are elevated as a result of disease pathophysiology and the resultant serologic screenings are relatively straightforward. Similarly, IBD markers like ASCA and ANCA indicate a predisposition to disease and are specifically associated with Crohn's versus ulcerative colitis in certain combinations.

No single biomarker has been identified for IBS diagnosis. The IBS serology panel is based on analysis of a large number of markers that were associated with the pathophysiologic pathways of IBS, but not necessarily with IBS directly. Through the application of a series of reviews, a collection of markers that showed differential expression in IBS versus non-IBS samples was compiled. All of these markers were then measured in the serum of population cohorts with and without confirmed IBS, and further algorithms were developed to determine the most likely sets of markers and marker profiles that could differentiate IBS from non-IBS patients, without the need for specific pathophysiologic evidence. A final set of 10 biomarkers was selected, based on the combined accuracy for differentiating IBS from non-IBS.

The IBS diagnostic panel does not employ typical cut-off analysis but rather an algorithm for pattern recognition that relates marker measures both to their own normal ranges and to levels of other markers in the panel. Thus, none of the markers, at any specific level, has an independent predictive value. It is only in relation to one another that they can be interpreted to determine a positive or negative IBS diagnosis.

This research methodology allowed for the evaluation of a vast number of markers simultaneously, rather than searching through the literature for a single marker to test in known cases. Thus, in the future, this method may become standard research practice, with the ability to uncover new markers for diagnosis and pathophysiologic research in a wide variety of diseases.

As research continues and interpretation of the IBS diagnostic panel is further refined, different recognizable patterns may emerge for different disease behaviors, just as they have in IBD. Diarrhea-predominant and constipation-predominant subtypes of IBS may have distinct profiles that will lead to further phenotypic description and useful research into pathophysiology of the syndrome. With these evolving study results, the role of the panel will likely evolve as well, gaining more prominence in the diagnostic algorithm and further formalizing our ability to positively diagnose IBS as a specific syndrome with a physiologic and biochemical basis.


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