Case Study Monograph

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Community Perspectives: Combining Serology, Genetics, and Inflammation Markers for the Diagnosis of IBD and Differentiation Between CD and UC

Introduction and Case Presenter

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Abstract

Diagnosis of inflammatory bowel disease (IBD) is complicated and is based on a combination of patient history and physical examination in association with laboratory, endoscopic, histologic, and radiographic investigations. Determination of the correct diagnosis is important for its implications in selecting treatment and in the timing and type of surgery that may be required. Information from testing incorporating serologic, genetic, and inflammatory markers can help to clarify the clinical picture. Measurement of biomarkers not only helps to differentiate a diagnosis of IBD versus non-IBD, it can also help to distinguish between ulcerative colitis and Crohn's disease in difficult cases. In this monograph, 5 cases illustrate how specialized testing can provide important information that can aid in diagnosis.

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Introduction

Douglas C. Wolf, MD

Inflammatory bowel disease (IBD)—including both Crohn's disease (CD) and ulcerative colitis (UC)—is a chronic condition that significantly affects patients' quality of life. Common symptoms include abdominal pain, diarrhea, rectal bleeding, and weight loss, as well as extraintestinal manifestations. IBD occurs relatively frequently in the United States, with this country having among the highest number of cases of IBD in the world.[1] There are 1–2 million patients with IBD in the United States.

The differential diagnosis of IBD is extensive, and differentiating between CD and UC can be difficult. Although a patient's clinical presentation may be suggestive of IBD, clinicians often must perform laboratory, radiologic, endoscopic, and histologic testing to confirm the diagnosis. While the complete pathogenesis of IBD remains unclear, data suggest that the disease results from a culmination of interactions between the immune system, enteric commensal bacteria, and genetic factors. Therefore, a biomarker-based diagnostic test has been developed that incorporates the measurement of multiple classes of markers to aid clinicians both in the separation of IBD versus non-IBD disease and in the distinction between CD and UC.

Various serologic markers have been studied in the literature, starting with antineutrophil cytoplasmic antibodies (ANCA) and anti–*Saccharomyces cerevisiae* antibodies (ASCA) in the 1990s. ANCA are autoantibodies directed against an unidentified component of the nuclear envelope within neutrophil granules. By indirect immunofluorescence, these antibodies have an atypical perinuclear stain (pANCA) and are DNase-sensitive. Higher levels of pANCA are associated more strongly with UC than with CD. In contrast, increased titers of ASCA—both immunoglobulin (Ig) A and IgG—are more strongly associated with CD.

Immune responses against the bacterial protein flagellin are also associated with IBD. One study found that 46% of CD patients who were ASCA-negative were positive for anti-CBir1 (flagellin) antibodies.[2] Two other antiflagellin markers, FlaX and A4-Fla2, demonstrated greater seropositivity in CD compared to irritable bowel syndrome (IBS), UC, and healthy controls. FlaX and A4-Fla2 were found in 59% and 57% of patients with CD, respectively; in 6% each of patients with UC; and in 0% and 2% of healthy controls, respectively.[3]

With the advances in genome-wide association studies, over 100 genes have been identified with associations in IBD, CD, and UC. Genetic variants do not cause disease on their own or discriminate between CD or UC themselves; however, together with serologic and inflammatory markers, genetics help in the separation of patients with IBD versus non-IBD. The rs10883365 variant of the NK2 transcription factor–related, locus 3 gene (*NKX2-3*) is expressed in small vessel endothelial cells and is associated with an increased susceptibility for development of CD.[4] A similar association was made between the *NKX2-3* gene and UC.[5] The epithelial barrier gene extracellular matrix protein 1 (*ECM1*) is expressed in the small and large intestines, where it interacts with the basement membrane and inhibits matrix metalloproteinase 9. *ECM1* was demonstrated to have an association with UC.[5] Defective bacterial handling has become one focus in the study of CD pathogenesis. *ATG16L1* (autophagy related 16-like 1 gene) has been associated with CD and acts as a housekeeping mechanism by which cells digest parts of their own cytoplasm for removal. Another gene, *STAT3* (signal transducer and activator of transcription 3), has been found to have an important role in various autoimmune disorders. Mutations in the *STAT3* gene have been reported as a biomarker for CD.

Not surprisingly, given the role of inflammation in the pathogenesis of IBD, inflammatory markers have also been found to be helpful in disease diagnosis. For example, circulating concentrations of the intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) are higher in patients with CD or UC compared to healthy controls.[6] Levels of vascular endothelial growth factor (VEGF) are also elevated in IBD patients, with higher levels correlating to increased disease activity.[7] Likewise, high levels of C-reactive protein (CRP) occur in both CD and UC, although the effect is greater in CD, and serum amyloid A (SAA), which is also released from the liver, is a marker of inflammation in both CD and UC.[8,9]

Together, these genetic, serologic, and inflammatory markers can be utilized as a useful adjunctive diagnostic tool to aid clinical practice.

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Prometheus IBD sgi Diagnostic Test Expediting Diagnosis and Work-Up for Crohn's Disease

Douglas C. Wolf, MD

Case 1

The mother of an 18-year-old male contacted me and requested that I see her son for a consultation. She was very concerned about his recent occurrence of loose stools and weight fluctuation. The mother was a patient of mine, as was the young man's sister; both mother and sister had been diagnosed with CD. I arranged an appointment with the patient for the following day.

The patient was a healthy-appearing young male in no discomfort. He stated that loose stools (up to 5 per day) had developed several months earlier but that they were not a problem. There was no history of rectal bleeding. He denied any history of abdominal pain. There was no nausea or vomiting. He stated that his weight had fluctuated by 5 lbs over the past year, based on whether he was exercising, but he was unconcerned about this fluctuation. He reported no extraintestinal manifestations. Physical examination revealed a pleasant, lean male in no distress. Abdominal examination revealed no tenderness. Perianal and rectal examinations were normal. Stool was hemoccult-negative.

Because of the family history of CD and because the patient would be leaving the country within 1 month to study in Spain, the mother asked me to do anything I could to clarify whether her son had CD. The mother had required surgery for CD and was receiving anti–tumor necrosis factor (anti-TNF) therapy; the patient's sister had also received anti-TNF therapy. I suggested that Prometheus testing be ordered.

The complete blood count (CBC), comprehensive metabolic profile, and erythrocyte sedimentation rate (ESR) were all normal. CRP was borderline-normal at 0.75 mg/dL (normal, <.80 mg/dL). Iron saturation and vitamin B_{12} level were normal. 25-OH vitamin D was borderline-low at 29 ng/mL (normal, 30–100 ng/mL). Stool testing was negative.

The Prometheus IBD sgi Diagnostic test was quite informative. Although the patient was double-ASCA negative, he was positive for anti-OmpC IgA (65.4 EU/mL), anti-CBir1 IgG (90.7 EU/mL), anti–A4-Fla2 IgG (65.0 EU/mL), and anti-FlaX IgG (>100.0 EU/mL; Table 1). IBD-specific pANCA was negative. Both *ECM1* and *NKX2-3* were heterozygous-positive. Among the

Table 1. Results of the Prometheus IBD sgi Diagnostic Test

Serology results		
Marker	**Result**	**Reference**
ASCA IgA	3.4 EU/mL	<8.5 EU/mL
ASCA IgG	10.9 EU/mL	<17.8 EU/mL
Anti-OmpC IgA	65.4 EU/mL	<10.9 EU/mL
Anti-CBir1 IgG	90.7 EU/mL	<78.4 EU/mL
Anti–A4-Fla2 IgG	65.0 EU/ml	<44.8 EU/ml
Anti-FlaX IgG	>100.0 EU/mL	<33.4 EU/mL
IBD-specific pANCA		
Autoantibody	<3.1 EU/mL	<19.8 EU/mL
IFA perinuclear pattern	ND	ND
DNAse sensitivity	ND	ND
Genetics results		
Marker	**Result**	**Reference**
ATG16L1 SNP (rs2241880)	No mutation detected	No mutation detected
ECM1 SNP (rs3737240)	Heterozygous C/T mutation detected	No mutation detected
NKX2-3 SNP (rs10883365)	Heterozygous A/G mutation detected	No mutation detected
STAT3 SNP (rs744166)	No mutation detected	Mutation detected
Inflammation results		
Marker	**Result**	**Reference**
ICAM-1	0.43 µg/mL	<0.54 µg/mL
VCAM-1	0.48 µg/mL	<0.68 µg/mL
VEGF	423 pg/mL	<345 pg/mL
CRP	10.8 mg/L	<13.2 mg/L
SAA	11.8 mg/L	<10.9 mg/L

ASCA=anti–*Saccharomyces cerevisiae* antibody; CBir1=flagellin; CRP=C-reactive protein; EU/mL=endotoxin units per milliliter; IBD=inflammatory bowel disease; ICAM-1=intercellular adhesion molecule 1; IFA=indirect fluorescent antibody assay; Ig=immunoglobulin; ND=not detected; OmpC=outer membrane protein C; pANCA=perinuclear antineutrophil cytoplasmic antibody; SAA=serum amyloid A; SNP=single nucleotide polymorphism; VCAM-1=vascular cell adhesion molecule 1; VEGF=vascular endothelial growth factor.

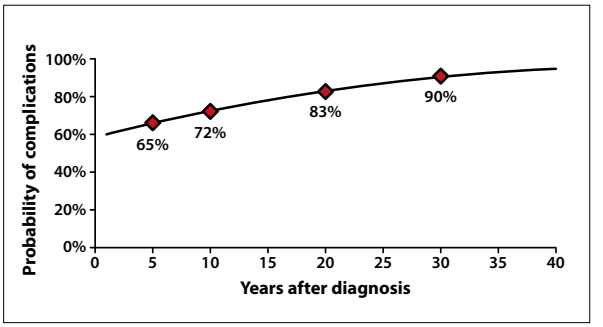

Figure 1. The Crohn's Prognostic test for this patient showed a 65% probability of complications at 5 years.

5 inflammation markers included in the Prometheus IBD sgi Diagnostic test, CRP was again normal, but VEGF was positive at 423 pg/mL, and SAA was elevated at 11.8 mg/L. The results of the 3 categories of the biomarkers produced a result with a pattern consistent with CD.

The Prometheus Crohn's Prognostic test was also obtained to assess *NOD2* status and risk of disease progression. This test revealed that the patient was positive for anti-I2 (1,595 EU/mL). He was negative for all *NOD2* mutations. The Crohn's Prognostic test analyzed the serologic marker expression and genetic information using a logistic regression algorithm to quantify the patient's likelihood of complications, and the probability of complications curve showed a risk of complications of 65% at 5 years (Figure 1).

Because of the family history of CD, multiple markers suggesting CD on the IBD sgi Diagnostic test, and a predicted 65% likelihood of aggressive CD over 5 years on the Crohn's Prognostic test, a proactive plan for evaluation, monitoring, and treatment was advised. Esophagogastroduodenoscopy (EGD) and biopsy, along with colonoscopy and biopsy, were performed. Upper endoscopy revealed no sign of upper gastrointestinal CD, but colonoscopy revealed pancolitis with a normal terminal ileum. There was inflammation throughout the colon but no erosions or ulcerations. Biopsies taken segmentally throughout the colon showed mild active colitis from the rectum to the cecum. No granulomas or other features were seen. Based on his symptoms and histology, the patient was started on mesalamine therapy.

Capsule endoscopy is being scheduled, and methotrexate is being considered, in part because of the mother's disease progression on immunomodulator (thiopurine) therapy. Careful and frequent monitoring will be needed to confirm response to therapy. Because of the biomarker profiles, family history, predictors of aggressive disease, and lack of standard surrogate markers of inflammation, a calprotectin test is being ordered, and annual colonoscopy is anticipated.

If the stool calprotectin level is elevated, this marker may be a useful alternative to periodic colonoscopy monitoring. If there is no improvement in diarrhea or weight gain within a 2–4-month period, escalation to immunomodulator therapy or, less likely, anti-TNF therapy will be reconsidered. If an increase of inflammatory markers and/or worsening of clinical symptoms occurs, such therapeutic escalation will be considered earlier.

Discussion

The Prometheus IBD sgi Diagnostic test was valuable in this patient's evaluation. While it is likely that colonoscopy would have been planned because of the family history and the patient's active, though low-grade, symptoms, the results of the Prometheus IBD sgi Diagnostic test made this step more pressing. The colonoscopy and biopsy findings appear to represent UC, but both the Prometheus IBD sgi Diagnostic test and the family history suggest that this case represents CD. It is relevant to note that, if a generic serology test had been ordered (rather than the Prometheus IBD sgi Diagnostic test), the results would have been negative (negative ASCA IgA/IgG). Additionally, although CBC, ESR, and CRP testing were normal, the Prometheus IBD sgi Diagnostic test inflammation results were positive in 2 of 5 assays. The IBD sgi Diagnostic test positivity, the suggestion that there may be a 65% probability of complications in 5 years with the Crohn's Prognostic test, and the patient's family history make it necessary to monitor for prompt response to mesalamine therapy. If mesalamine does not lead to improvement, then therapeutic escalation will be initiated.

32-Year-Old Frequent Traveler with Rectal Bleeding and a Change in Bowel Habits

Bincy P. Abraham, MD, MS

Case 2

A 32-year-old male with a job that requires frequent international travel presented due to a change in bowel habits following his most recent return to the United States. The patient reported loose stools occurring 3–5 times per day. The volume of each bowel movement varied, with some bowel movements producing only small amounts of stool. The patient also noticed the presence of bright red blood mixed in with most stools. He initially had mild upper abdominal cramping, which had recently improved, and his stools had become slightly more formed but still looser than his norm. The patient also reported passing a white non-moving item, which he described as looking "like a worm."

The patient denied having nocturnal symptoms, loss of appetite, weight loss, fever, or chills. He had occasional mouth sores (1–2) but no other significant symptoms over the past year. His medical history was positive for an anal fissure, but he was not currently taking any medications. He does not smoke but consumes up to 2 beers daily. He had a family history of skin cancer, and he believed that his great-grandfather died of colorectal cancer. He had no family members with IBD, celiac disease, or colonic polyps.

Upon physical examination, he appeared to be healthy, with a soft, nontender abdomen and normal bowel sounds. The patient's recent change in bowel habits was thought to be likely due to IBS resulting from an infection acquired while traveling. However, his rectal bleeding was an alarming symptom, especially given his prior history of an anal fissure. Further, his stool was found to be positive for leukocytes, which could indicate IBD.

As part of the differential diagnosis, several stool studies were ordered, including a stool culture, a *Clostridium difficile* test, and an examination for ova and parasites. A full blood work-up was also ordered, including celiac disease serology, a CBC, a comprehensive metabolic panel, and measurement of thyroid-stimulating hormone, ESR, and CRP. All of these tests were normal. A colonoscopy was then performed, which showed a diffuse area of mildly erythematous mucosa located in the rectum and a fissure located

in the anal canal. His terminal ileum appeared normal. Pathology showed crypt distortion and chronic inflammatory changes consistent with IBD in the rectum. Finally, a Prometheus IBD sgi Diagnostic test was ordered (Table 2). Results of this test confirmed a diagnosis of UC, with mildly elevated levels of ASCA IgA antibodies (14.5 EU/mL) and elevated pANCA autoantibodies (44.5 EU/mL). Two genetic mutations were detected: heterozygous *ATG16L1* and heterozygous *NKX2-3*.

Based on the patient's symptoms, test results, and the observation of mild inflammation on colonoscopy, the patient was diagnosed with mild-to-moderate UC. Treatment with mesalamine was initiated. Upon follow-up examination approximately 2 weeks later, the patient stated that he was asymptomatic with normally formed bowel movements and no further gastrointestinal bleeding. He denied any recurrence of abdominal pain. Physical examination showed improvement in the anal fissure and was otherwise normal. The plan is to continue mesalamine therapy and obtain a capsule endoscopy to rule out any small bowel disease.

Discussion

In this young patient who presented after international travel with acute onset of gastrointestinal symptoms, an infectious etiology was the initial concern. However, with initial stool studies ruling out common infections and with slightly improved symptoms, postinfectious IBS could also be considered as a diagnosis. However, the persistence of rectal bleeding prompted concern about IBD. In this case, the patient had a history of an anal fissure in the absence of other gastrointestinal symptoms. On the one hand, anal fissures can occur without IBD, and one could presume that the patient's gastrointestinal symptoms persisted due to postinfectious IBS, with the rectal bleeding being due to the anal fissure. On the other hand, the fissure could prompt a concern for IBD presenting as perianal disease.

In this case, the Prometheus IBD sgi Diagnostic test supported a diagnosis of UC, which fits with the patient's current presentation. In cases such as this one—where the patient's presentation, test results, and history lead to many questions and few answers—the IBD sgi Diagnostic test can help to provide some additional clarity.

Table 2. Results of the Prometheus IBD sgi Diagnostic Test

Serology results		
Marker	**Result**	**Reference**
ASCA IgA	14.5 EU/mL	<8.5 EU/mL
ASCA IgG	12.8 EU/mL	<17.8 EU/mL
Anti-OmpC IgA	<3.1 EU/mL	<10.9 EU/mL
Anti-CBir1 IgG	17.9 EU/mL	<78.4 EU/mL
Anti–A4-Fla2 IgG	7.0 EU/mL	<44.8 EU/mL
Anti-FlaX IgG	6.1 EU/mL	<33.4 EU/mL
IBD-specific pANCA		
Autoantibody	44.5 EU/mL	<19.8 EU/mL
IFA perinuclear pattern	ND	ND
DNAse sensitivity	ND	ND
Genetics results		
Marker	**Result**	**Reference**
ATG16L1 SNP (rs2241880)	Heterozygous A/G mutation detected	No mutation detected
ECM1 SNP (rs3737240)	No mutation detected	No mutation detected
NKX2-3 SNP (rs10883365)	Heterozygous A/G mutation detected	No mutation detected
STAT3 SNP (rs744166)	No mutation detected	Mutation detected
Inflammation results		
Marker	**Result**	**Reference**
ICAM-1	0.32 µg/mL	<0.54 µg/mL
VCAM-1	0.52 µg/mL	<0.68 µg/mL
VEGF	219 pg/mL	<345 pg/mL
CRP	0.6 mg/L	<13.2 mg/L
SAA	1.7 mg/L	<10.9 mg/L

ASCA=anti–*Saccharomyces cerevisiae* antibody; CBir1=flagellin; CRP=C-reactive protein; EU/mL=endotoxin units per milliliter; IBD=inflammatory bowel disease; ICAM-1=intercellular adhesion molecule 1; IFA=indirect fluorescent antibody assay; Ig=immunoglobulin; ND=not detected; OmpC=outer membrane protein C; pANCA=perinuclear antineutrophil cytoplasmic antibody; SAA=serum amyloid A; SNP=single nucleotide polymorphism; VCAM-1=vascular cell adhesion molecule 1; VEGF=vascular endothelial growth factor.

31-Year-Old Male with Frequent Bleeding and Portal Vein Thrombosis

Anita Afzali, MD, MPH, Christopher Carlson, MD, Scott D. Lee, MD, and Chelle Wheat, MPH

Case 3

The patient is a 31-year-old male maintenance supervisor who was diagnosed with UC at age 26 years. This diagnosis was based on a presentation of frequent bloody diarrhea, abdominal cramping, and a colonoscopy that showed active chronic colitis. His past medications included sulfasalazine, mesalamine, and prednisone; however, these medications did not provide adequate symptom control and caused the patient financial stress, so he chose to discontinue them. Instead, he has relied upon occasional hydrocortisone suppositories. He admits to social drinking and occasional marijuana use but does not smoke cigarettes. He currently lives alone and has no nearby family. His family history is negative for any malignancies or IBD, but his sister was previously diagnosed with IBS.

Over a 2-year period, the patient routinely experienced hematochezia (250 mL of bright red blood per rectum), as well as severe anemia requiring blood transfusions. A year ago, he desired surgical intervention, as he wanted to be cured of his UC, despite his treating gastroenterologist's recommendation to continue medical management instead of resorting to surgical intervention. During the first of a 3-stage surgery for a planned ileoanal anastomosis, he underwent a subtotal colectomy with the rectum and distal 25 cm of the sigmoid colon left in situ. During this procedure, chronic active colitis was identified in 2 separate areas: the distal and proximal colon. The presence of 2 separate disease foci was attributed to treatment effect and was not thought to indicate skipped lesions.

Continued bleeding after this surgical resection caused the patient to return to his surgeon, who then performed a rigid proctosigmoidoscopy. The surgeon's overall impression based on this examination was that the patient's lower gastrointestinal bleeding was due to ulcerative proctitis. At this visit, the patient was found to have significant anemia (hemoglobin level of 4 g/dL), and 5 units of packed red blood cells were administered.

Three days later, the patient began to experience epigastric abdominal pain that he described as sharp, cramping, and constant; this pain did not radiate and was not related to food ingestion. Other symptoms included anorexia, nausea, vomiting, increased abdominal girth, and night sweats. He had no changes in his ileostomy output.

A few days later, the patient presented to the emergency room, where a computed tomography (CT) scan revealed ascites and a new, acute, large portal vein thrombosis. Approximately 70% stenosis was present in the celiac artery. After being admitted to the hospital, the patient's pain improved with analgesics, and he was able to tolerate oral intake. The patient was started on anticoagulation therapy to reduce the risk of portal vein thrombosis. He was also treated with rectal mesalamine enemas, as he was having ongoing rectal bleeding.

During his hospital stay, the patient underwent a flexible sigmoidoscopy that revealed serpiginous and shallow ulcerations located diffusely throughout the colon. These ulcerations were more prominent in the proximal area and were associated with mucosal granularity, nodularity, and the presence of pseudopolyps. Although a copious amount of dark red blood was present throughout the colon, no focal source of the bleeding was found. There was no evidence of perianal disease. Further, an ileoscopy revealed no evidence of ileal disease. An EGD showed erosions, and histology revealed nonspecific inflammation of the upper gastrointestinal tract.

Biopsies taken during the sigmoidoscopy showed active chronic colitis with ulceration and fibrinopurulent exudate, cryptitis, and crypt abscesses. Overall, these observations were largely consistent with UC, although finding a considerable segment with no significant inflammation between 2 substantial segments of active ulceration was noted to be unusual for UC. Further, the pathologist observed evidence of at least focal penetration of exudate through the muscularis mucosae in some of the ulceration sites, suggesting a fissuring process. Following these endoscopic procedures and a pathology review, it was felt that the patient might actually have CD rather than UC, and the patient was started on prednisone therapy.

The gastroenterologist discussed the endoscopy findings with the patient and suggested that, instead of completing his proctocolectomy, he should begin biologic therapy to control his flare. The patient was hesitant to commit to biologic therapy because of cost considerations. He was discharged without starting biologic therapy, and follow-up visits were scheduled with his outpatient gastroenterologist and primary care provider. The patient's

surgeon agreed with the recommendation to postpone continuation of the proctocolectomy, especially in light of the new diagnosis of portal vein thrombosis.

Over the next month, the patient continued to experience 3–7 episodes of hematochezia daily, and he required 3 separate blood transfusions. During this time, the patient was started on infliximab therapy, which was initiated at a dose of 5 mg/kg at Weeks 0, 2, and 6. Maintenance therapy was scheduled every 8 weeks thereafter. The patient also began concurrent therapy with methotrexate.

At a follow-up visit nearly 2 months later, the patient reported feeling much better overall. He had not recently experienced any abdominal pain and had enough energy to resume golfing. He also reported that his blood loss per rectum had decreased to 2–3 times per day. His blood work-up showed steady improvement in several markers, including hematocrit, CRP level, ESR, and serum albumin level. A follow-up CT scan showed that his portal vein thrombosis had improved but was still present. A follow-up flexible sigmoidoscopy revealed continued severe inflammation in the colon, despite induction therapy with infliximab. Because the patient showed signs of continued active disease, the infliximab maintenance dose was increased to 10 mg/kg every 6 weeks.

Another flexible sigmoidoscopy was performed after the patient had received a total of 9 months of IBD treatment; this examination revealed continued active inflammation that was minimally responsive to therapy. At this time, the necessity of surgical treatment was discussed with the patient, and he was referred to an IBD clinic for a second opinion to clarify his diagnosis. After review of his history and disease course, there was a high suspicion that the patient had CD rather than UC, and it was recommended that the planned ileoanal anastomosis be postponed until the diagnosis could be further clarified, given the high risk of recurrence and the risk of complications if he indeed had CD rather than UC. The patient underwent repeat ileoscopy and upper endoscopy with biopsies, and a Prometheus IBD sgi Diagnostic test was ordered to try to clarify whether he had CD. The results of this test showed a very elevated CBir1 level and a highly elevated pANCA autoantibody level (>100.0 EU/mL; Table 3). These findings, along with the other clinical findings, suggested that the diagnosis of CD was more likely than UC. The referring IBD clinic suggested to the patient and the primary gastroenterologist that the patient would be best served by not proceeding with the planned surgery; instead, it was suggested that the best course of action would be to try to achieve remission of the patient's colonic inflammation and then proceed with an ileorectal anastomosis.

Table 3. Results of the Prometheus IBD sgi Diagnostic Test

Serology results		
Marker	**Result**	**Reference**
ASCA IgA	<3.1 EU/mL	<8.5 EU/mL
ASCA IgG	6.6 EU/mL	<17.8 EU/mL
Anti-OmpC IgA	<3.1 EU/mL	<10.9 EU/mL
Anti-CBir1 IgG	41.6 EU/mL	<78.4 EU/mL
Anti–A4-Fla2 IgG	4.2 EU/mL	<44.8 EU/mL
Anti-FlaX IgG	5.5 EU/mL	<33.4 EU/mL
IBD-specific pANCA		
Autoantibody	>100.0 EU/mL	<19.8 EU/mL
IFA perinuclear pattern	Detected	ND
DNAse sensitivity	DNAse-sensitive	ND
Genetics results		
Marker	**Result**	**Reference**
ATG16L1 SNP (rs2241880)	Homozygous G/G mutation detected	No mutation detected
ECM1 SNP (rs3737240)	Heterozygous C/T mutation detected	No mutation detected
NKX2-3 SNP (rs10883365)	Heterozygous A/G mutation detected	No mutation detected
STAT3 SNP (rs744166)	No mutation detected	Mutation detected
Inflammation results		
Marker	**Result**	**Reference**
ICAM-1	0.45 µg/mL	<0.54 µg/mL
VCAM-1	1.05 µg/mL	<0.68 µg/mL
VEGF	392 pg/mL	<345 pg/mL
CRP	1.6 mg/L	<13.2 mg/L
SAA	1.5 mg/L	<10.9 mg/L

ASCA=anti–*Saccharomyces cerevisiae* antibody; CBir1=flagellin; CRP=C-reactive protein; EU/mL=endotoxin units per milliliter; IBD=inflammatory bowel disease; ICAM-1=intercellular adhesion molecule 1; IFA=indirect fluorescent antibody assay; Ig=immunoglobulin; ND=not detected; OmpC=outer membrane protein C; pANCA=perinuclear antineutrophil cytoplasmic antibody; SAA=serum amyloid A; SNP=single nucleotide polymorphism; VCAM-1=vascular cell adhesion molecule 1; VEGF=vascular endothelial growth factor.

Discussion

This patient is a 31-year-old male with a diagnosis of indeterminate colitis who has failed a number of different medical treatment regimens and underwent a subtotal colectomy with an end ileostomy and a Hartmann pouch. Subsequent

to this operation, he developed a portal vein thrombosis, and he now remains on chronic anticoagulation therapy. Despite his current medical regimen, which consists of infliximab and methotrexate therapy, he continues to have severe active symptoms including abdominal pain, diarrhea, and rectal bleeding. He has elected to pursue surgical treatment and has been evaluated by our surgical colleagues for a complete proctectomy with an ileal J-pouch and a diverting loop ileostomy. This interesting case poses several points for discussion.

First, the Prometheus IBD sgi Diagnostic test demonstrated an elevated CBir1 level and a very high pANCA level. The sgi algorithm interpreted this pattern as being consistent with IBD but inconclusive for CD versus UC; however, given the patient's clinical history and the previously published literature showing that IBD patients with this profile have a high likelihood of Crohn's colitis, we felt it was highly likely that the patient had CD rather than UC. Therefore, there is concern about a high risk of severe disease recurrence postoperatively.

Second, repeat ileoscopy was performed, and histology was normal, with no evidence of ileal disease. An upper endoscopy was also performed, and biopsies of the duodenum were found to be normal. Biopsies of the stomach revealed evidence of chronic gastropathy. There was no evidence of *Helicobacter pylori* infection, and the patient was not taking any medications that would account for chronic gastritis. Does this finding suggest upper gastrointestinal CD involvement? These findings, along with the patient's original diagnosis, illustrate how an IBD sgi Diagnostic test result can provide additional information that helps both to resolve the diagnostic challenges of indeterminate colitis and to guide subsequent therapeutic decisions.

Finally, this was a unique and challenging case because the patient has elected to pursue a surgical option, despite the concern about underlying CD and the high risk for disease recurrence. He understands that, even with removal of the remainder of his colon, he has an elevated probability of requiring medical therapy to control any recurrence of inflammation in the future. In addition, he was counseled that he is at high risk for complications if he indeed develops recurrent active disease.

Young Adult Patient with Abdominal Pain and an Enterocutaneous Fistula

Ronen Arai, MD

Case 4

The patient is a 23-year-old Ashkenazi Jewish male who had just started a high-pressure accounting job. He had never smoked, admitted to social drinking, appeared relatively healthy, and weighed 147 lbs. Two years prior to presentation, he had received treatment for hemorrhoids with slight rectal bleeding; his CRP level was elevated at that time. The remainder of the patient's history was nonsignificant, with the exception of 1–2 years of isotretinoin treatment for acne at age 13 years. His family history was positive for several gastrointestinal disorders; his uncle had been diagnosed with CD at age 16 years, and his grandfather had UC and colorectal cancer.

The patient initially presented to the emergency room complaining of abdominal pain. He reported that he had started to experience left and right lower abdominal pain approximately 1 month previously; this pain had then progressed to include the periumbilical area. In the week prior to his presentation to the emergency room, he began experiencing more severe pain in the right lower abdominal quadrant, and he also noticed a slight nonpurulent drainage from his umbilical area.

The patient was admitted to the hospital, at which time further testing was performed. A CT scan revealed thickening of the ileum and an enterocutaneous fistula, and a colonoscopy showed active ileocecal disease. Ileal and colonic biopsies showed acute, nonspecific inflammation. The combination of these findings led to a presumptive diagnosis of ileal CD.

The hospital's consulting gastroenterologist ordered an IBD sgi Diagnostic test and a Crohn's Prognostic test in order to confirm this clinical suspicion. This physician also broached the possibility of initiating biologic therapy

with the patient and his family, but they felt slightly overwhelmed by the sudden diagnosis and were reluctant to commit to such treatment at that time. Instead, budesonide and a course of antibiotics (amoxicillin/clavulanic acid and metronidazole) were prescribed. The patient was discharged after 4 days.

After being discharged from the hospital, the patient sought a second opinion at the DigestiveCARE of North Broward IBD Center. During this office visit, no systemic abnormalities were noted, and the patient's blood pressure and pulse rate were normal. On physical examination, the patient experienced mild periumbilical tenderness. The periumbilical area appeared slightly red, but no drainage was observed. Fullness of the right abdomen consistent with a thickened bowel loop was noted, but there was no rebound upon palpation. Based on this examination and a review of the medical records, the diagnosis of ileocecal CD with enterocutaneous fistulizing disease was confirmed. Magnetic resonance enterography was recommended to determine the extent of small bowel disease and inflammation.

At the time of the patient's second office visit, the results of both Prometheus tests had been received and were included in the patient's chart. The IBD sgi Diagnostic test showed a biomarker pattern consistent with CD (Table 4). ASCA IgA antibody and ASCA IgG antibody levels were extremely high (>100.0 EU/mL and 74.4 EU/mL, respectively). In addition, the inflammatory markers CRP and SAA were both elevated (28.2 mg/L and >181.6 mg/L, respectively). The Crohn's Prognostic test reported a single mutation in the *NOD2/CARD15* gene. According to this test, the patient's probability of developing complications was very high: 95% at 5 years, 97% at 10 years, 98% at 20 years, and 99% at 30 years (Figure 2). These test results were reviewed with the patient and his parents.

Given that the patient had already developed an enterocutaneous fistula, the need for aggressive top-down therapy was stressed during a discussion about the various treatment strategies for CD. Further, the patient was informed about the possible need for surgical resection if his condition failed to respond to medical therapy. As a male under 30 years of age, the patient is in the group with the highest relative risk (albeit a low absolute risk) for developing hepatosplenic T-cell lymphoma if treated with combined biologic and immunomodulatory therapy; after a long discussion of the benefits and risks of both single-agent biologic therapy and combination therapy, the patient and his family elected not to pursue combination therapy.

After learning about the implications of his test results and potential treatment strategies, the patient felt more comfortable with the decision to initiate top-down treatment with a biologic agent. Because he had just started a new job, the patient chose the flexibility of at-home self-injection with adalimumab as opposed to infliximab infusions. This treatment request was submitted to his insurance company for approval. The patient was also referred to his primary care physician for an influenza vaccination.

Prior to initiation of adalimumab, the patient had initially responded to antibiotic treatment with a resolution of fistula drainage, but the drainage began to recur soon after the antibiotics were stopped. A second round of antibiotic therapy was then prescribed. At a subsequent follow-up visit, the patient had lost 8 lbs but was tolerating a low-residue diet. Examination of the abdominal area revealed mild periumbilical tenderness with minimal clear drainage and continued fullness in the right abdomen. The patient reported that his insurance company had approved the use of adalimumab, and he was scheduled to begin therapy that week.

At his most recent follow-up visit, the patient reported that his 27-year-old sister had also recently received a diagnosis of CD. The patient had completed approximately 8 weeks of adalimumab therapy and was no longer taking antibiotics or budesonide. He was feeling well, had regained 5 lbs, and his CRP level had dropped from 4 mg/dL at diagnosis to an undetectable level. There had been no further fistula drainage in the prior 4 weeks.

Discussion

This case demonstrates a very dramatic presentation of CD with a fistulizing phenotype at initial presentation. Although the finding of an enterocutaneous fistula manifesting as periumbilical drainage is not common at initial diagnosis of CD, several other factors supported the diagnosis in this case. The patient's Ashkenazi Jewish heritage, his family history of IBD, the imaging (CT scan) results, and the colonoscopy findings all supported a diagnosis of CD. In addition, the symptomatic hemorrhoidal disease 2 years earlier suggested a prior presentation of perianal disease. Despite these factors, there was no single diagnostic test that "ruled-in" CD. As is often the case, the pathologic evaluation of biopsy specimens was not diagnostic.

The Prometheus IBD sgi Diagnostic test provided more objective information and aided in confirming the clinical suspicion of CD. The elevated ASCA IgA and IgG levels have very high sensitivity and specificity in this clinical situation.[1-3] In addition, the high levels of inflammatory markers (CRP and SAA) provided support to the concept that this patient's disease course could be modified with early aggressive intervention to treat the underlying inflammatory component of the disease.

In addition to providing additional diagnostic information to clinicians, the results of the Prometheus IBD sgi Diagnostic test can also help the patient and his family to feel comfortable with the diagnosis, especially in cases where no single diagnostic test is confirmatory on its

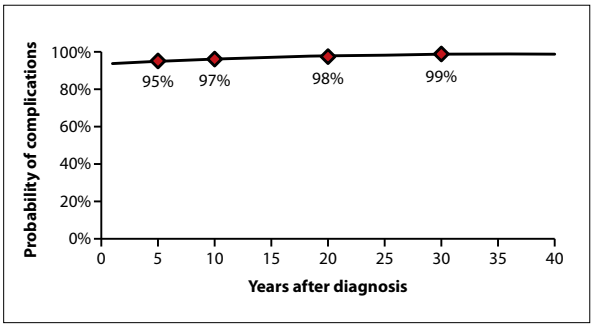

Figure 2. The Crohn's Prognostic test for this patient showed a very high risk of complications.

own. This benefit was especially true in the present case. Indeed, such confirmation is often helpful in acute cases, as a rapid diagnostic work-up can lead to the patient and the family experiencing feelings of anxiety and confusion.

Making the diagnosis was just the start in managing this complicated patient who was presenting for the first time with CD. Based on the location and extent of disease and the knowledge that early-onset fistulizing disease in such a young patient is likely to lead to more progressive disease, the need for aggressive (top-down) therapy was predictable. However, it was important to ensure that the patient and his family understood the severity of the disease and the rationale for aggressive therapy. The Crohn's Prognostic test was critically helpful in this regard, as it quantified the risk of disease complications going forward. While clinicians often try to explain risk in general and subjective terms, patients and families appreciate seeing an objective risk assessment. In addition, the knowledge of the mutated *NOD2* gene in this specific case led to a discussion of the future risk of fibrostenotic disease associated with this gene mutation and further highlighted the importance of using early aggressive therapy to change the predicted natural history of the disease.[4]

In this case, the joint decision regarding disease-altering therapy was made at the conclusion of the second consultation with the patient and his family, after a careful review of all the evidence, including the imaging studies, colonoscopy report, laboratory results, and Prometheus IBD sgi Diagnostic and Crohn's Prognostic test results. The patient and his family appreciated the patient's relatively high risk for future disease complications and the possible need for surgery; thus, they were able to make an informed decision regarding the appropriate therapy. The clinical data supporting early combined biologic and immunomodulator therapy as compared to single-agent biologic or immunomodulator therapy were discussed with the patient and his family.[5] This discussion also included the risks of these therapies, specifically focusing on infectious and neoplastic (lymphoma) risks.

Table 4. Results of the Prometheus IBD sgi Diagnostic Test

Serology results		
Marker	**Result**	**Reference**
ASCA IgA	>100.0 EU/mL	<8.5 EU/mL
ASCA IgG	74.4 EU/mL	<17.8 EU/mL
Anti-OmpC IgA	<3.1 EU/mL	<10.9 EU/mL
Anti-CBir1 IgG	19.7 EU/mL	<78.4 EU/mL
Anti–A4-Fla2 IgG	23.9 EU/mL	<44.8 EU/mL
Anti-FlaX IgG	29.8 EU/mL	<33.4 EU/mL
IBD-specific pANCA		
Autoantibody	11.7 EU/mL	<19.8 EU/mL
IFA perinuclear pattern	ND	ND
DNAse sensitivity	ND	ND
Genetics results		
Marker	**Result**	**Reference**
ATG16L1 SNP (rs2241880)	Homozygous G/G mutation detected	No mutation detected
ECM1 SNP (rs3737240)	Heterozygous C/T mutation detected	No mutation detected
NKX2-3 SNP (rs10883365)	Heterozygous A/G mutation detected	No mutation detected
STAT3 SNP (rs744166)	Mutation detected	Mutation detected
Inflammation results		
Marker	**Result**	**Reference**
ICAM-1	0.39 µg/mL	<0.54 µg/mL
VCAM-1	0.55 µg/mL	<0.68 µg/mL
VEGF	182 pg/mL	<345 pg/mL
CRP	28.2 mg/L	<13.2 mg/L
SAA	>181.6 mg/L	<10.9 mg/L

ASCA=anti–*Saccharomyces cerevisiae* antibody; CBir1=flagellin; CRP=C-reactive protein; EU/mL=endotoxin units per milliliter; IBD=inflammatory bowel disease; ICAM-1=intercellular adhesion molecule 1; IFA=indirect fluorescent antibody assay; Ig=immunoglobulin; ND=not detected; OmpC=outer membrane protein C; pANCA=perinuclear antineutrophil cytoplasmic antibody; SAA=serum amyloid A; SNP=single nucleotide polymorphism; VCAM-1=vascular cell adhesion molecule 1; VEGF=vascular endothelial growth factor.

Although the benefit of combined therapy was clear, the patient opted for single-agent biologic therapy (adalimumab) due to his increased relative risk for hepatosplenic T-cell lymphoma.[6] Critical in this discussion was the knowledge, emphasized by the Crohn's Prognostic test results, that a lack of response to therapy would likely lead

to surgery in the future. The patient and his family understood the ramifications of the therapeutic decision and were ready to move forward and deal with the future of his disease. Such cases of personalized medicine, made possible by the use of disease-specific confirmatory and prognostic information, exemplify the future of IBD therapy.

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Female Patient with Bloody Stools, Anemia, and Abdominal Pain

Paul D. Allegretti, DO

Case 5

A 27-year-old female was referred from her primary care physician after presenting with hematochezia. She reported having bright red rectal bleeding for 4 days, as well as intermittent urgent and loose bowel movements. Both symptoms were new for her, and she was extremely concerned regarding their appearance. The primary care physician had initially given the patient a diagnosis of IBS and prescribed dicyclomine; at the time of the referral, the patient was not yet sure if she was responding to this treatment. She reported no constipation, abdominal pain, nausea, vomiting, or dysphagia; her weight had been stable. The patient's history was significant only for hypothyroidism, and she had no family history of gastrointestinal malignancies.

After discussing a possible diagnosis of IBS with the patient, she remained very concerned about her bleeding symptoms and opted to undergo a colonoscopy to rule out a neoplasm. No definitive source of the bleeding was identified on colonoscopy, although large hemorrhoids were noted. Biopsies taken during the colonoscopy were unrevealing. A subsequent small bowel follow-through showed the small bowel to be normal. A subsequent capsule endoscopy showed gastric erosions, multiple distal erosions, and the presence of blood in the distal small bowel. Two weeks later, the patient reported abdominal pain; radiographs of the abdomen showed that she had retained the capsule, possibly due to a narrowing of the terminal ileum.

The patient's blood test results now revealed that she was anemic, with a hemoglobin level of 5.1 mg/dL. Iron supplements were prescribed, and her hemoglobin level rose to 10.5 mg/dL within approximately 3 weeks. Due to her continued anemia, the findings on capsule endoscopy, and continued bowel symptoms, an EGD and colonoscopy with deep intubation of the jejunum and distal ileum were recommended. This colonoscopy revealed a stricture in the distal ileum that was dilated to 16.5 mm. Lodged pills and a retained capsule were noted proximal to this area; the retained capsule and pills were removed. Biopsy samples taken during the colonoscopy showed acute ileitis, ulceration, and hemorrhage. A CT scan performed the same day showed 5 calcifications, each measuring approximately 1.5 cm, which were located in the distal small bowel proximal to a small bowel stricture. Given the patient's symptoms and the finding of a small intestinal stricture, the diagnosis was possibly Crohn's ileitis.

At a follow-up visit 2 weeks later, the patient reported more rectal bleeding over the prior 2 days; this bleeding had changed from bright red in color to maroon. She also reported having 9 loose stools over this 2-day period, including a rare nocturnal bowel movement. At this time, the patient was taking dicyclomine for her symptoms, with some relief, but no other medications. The night before this visit, she had a fever of 100.4ºF with fatigue and nausea, and she had had intermittent anorexia. At this visit, the patient was given a prescription for budesonide (9 mg daily) and ondansetron (as needed).

At a follow-up visit 1 month later, the patient reported that her stool frequency had decreased to 1–2 bowel movements per day, her stools were more solid in appearance, and she had not observed any bright red blood or melena. Aside from occasional mild abdominal discomfort, she had no other gastrointestinal symptoms. Her hemoglobin level was holding steady at approximately 10.6 mg/dL.

A Prometheus IBD sgi Diagnostic test was ordered to confirm a possible diagnosis of CD (Table 5). The patient displayed multiple irregularities in the serology panel, including elevated levels of ASCA IgA antibody (12.1 EU/mL), ASCA IgG antibody (18.1 EU/mL), anti-CBir1 IgG antibody (>100.0 EU/mL), anti–A4-Fla2 IgG antibody (60.8 EU/mL), and anti-FlaX IgG antibody (52.7 EU/mL). She also had mutations in 3 of the 4 genetic markers included in this test. Although her CRP level was within the normal range, several other markers of inflammation were elevated, including ICAM-1 (1.10 µg/mL), VEGF (423 pg/mL), and SAA (13.9 mg/L).

Overall, the findings of the IBD panel were consistent with a diagnosis of CD; these findings were discussed with the patient. Based on these results, it was recommended that infliximab therapy should be initiated if her condition worsened. The patient was also counseled to obtain hepatitis B viral serology and tuberculosis testing.

Two months later, the patient presented to the emergency room after experiencing 2 fainting episodes at home. She reported rectal bleeding for 4 days prior to this presentation, and trace blood was noted upon rectal examination. Because her hemoglobin level and vital signs were stable, she was discharged with a recommendation for a gastroenterology follow-up. At this follow-up visit, she reported intermittent and frequent rectal bleeding with her bowel movements, which had increased to approximately 4–5 times daily and alternated between loose and formed stools. She also reported intermittent pain in her lower left abdominal quadrant; this pain was not associated with any aggravating factors. Her hemoglobin level remained stable at 10.4 mg/dL. She had initially responded to budesonide but stated that she had never felt completely well from a gastrointestinal standpoint. The patient's hepatitis B virus and tuberculosis tests were negative, so she began infliximab therapy at a dose of 5 mg/kg on Weeks 0, 2, and 6, with ongoing therapy every 8 weeks thereafter. She is stable and doing reasonably well at the present time.

Table 5. Results of the Prometheus IBD sgi Diagnostic Test

Serology results		
Marker	**Result**	**Reference**
ASCA IgA	12.1 EU/mL	<8.5 EU/mL
ASCA IgG	18.1 EU/mL	<17.8 EU/mL
Anti-OmpC IgA	<3.1 EU/mL	<10.9 EU/mL
Anti-CBir1 IgG	>100.0 EU/mL	<78.4 EU/mL
Anti–A4-Fla2 IgG	60.8 EU/mL	<44.8 EU/mL
Anti-FlaX IgG	52.7 EU/mL	<33.4 EU/mL
IBD-specific pANCA		
Autoantibody	19.1 EU/mL	<19.8 EU/mL
IFA perinuclear pattern	ND	ND
DNAse sensitivity	ND	ND
Genetics results		
Marker	**Result**	**Reference**
ATG16L1 SNP (rs2241880)	Heterozygous A/G mutation detected	No mutation detected
ECM1 SNP (rs3737240)	No mutation detected	No mutation detected
NKX2-3 SNP (rs10883365)	Heterozygous A/G mutation detected	No mutation detected
STAT3 SNP (rs744166)	Mutation detected	Mutation detected
Inflammation results		
Marker	**Result**	**Reference**
ICAM-1	1.10 µg/mL	<0.54 µg/mL
VCAM-1	0.58 µg/mL	<0.68 µg/mL
VEGF	423 pg/mL	<345 pg/mL
CRP	4.2 mg/L	<13.2 mg/L
SAA	13.9 mg/L	<10.9 mg/L

ASCA=anti–*Saccharomyces cerevisiae* antibody; CBir1=flagellin; CRP=C-reactive protein; EU/mL=endotoxin units per milliliter; IBD=inflammatory bowel disease; ICAM-1=intercellular adhesion molecule 1; IFA=indirect fluorescent antibody assay; Ig=immunoglobulin; ND=not detected; OmpC=outer membrane protein C; pANCA=perinuclear antineutrophil cytoplasmic antibody; SAA=serum amyloid A; SNP=single nucleotide polymorphism; VCAM-1=vascular cell adhesion molecule 1; VEGF=vascular endothelial growth factor.

Discussion

This case was particularly challenging in terms of obtaining the correct diagnosis. Despite multiple initial tests, including a colonoscopy and small bowel series, the diagnosis remained unclear. The patient was labeled with IBS, but her symptoms remained out of proportion to this entity. After the capsule endoscopy, I became concerned that this case did not represent typical IBS.

The follow-up enteroscopy and colonoscopy were quite remarkable. The finding of an ileal stricture just distal to the retained capsule definitely shifted my thinking toward IBD. However, I lacked definitive evidence. Strictures of the distal small bowel do not necessarily mean that the patient has CD. I decided to give the patient a trial of budesonide, and her reasonably good response further suggested IBD. Her condition had become more stable, but I was unsure of what to do in regard to therapy moving forward. In addition, the patient desired more definitive evidence of CD.

Thus, the IBD sgi panel was ordered, which confirmed my suspicions. I then felt much more comfortable moving forward. I discussed possible therapeutic options with the patient, including early biologic therapy given the stricturing nature of her disease on presentation. The patient desired some time to think about her options. Ultimately, she developed another flare 2 months later. Based on all of the previous findings and armed with strong serologic evidence, I chose to treat her with biologic therapy alone. Presently, she is doing well with no recent flare-ups on therapy.

CD can present in a myriad of ways and can affect the gastrointestinal tract from mouth to anus. Diagnosis can be quite challenging, despite all of the technology and tests available to a physician. Thus, physicians would like as much diagnostic information as possible before deciding on a particular therapy.

This information also aids in the discussion of therapy with an apprehensive and rightfully concerned patient. Serologic testing helps to detail the immunology and genetics of a particular patient, and patients seem much more comfortable knowing that their genetics point in a particular direction. Physicians also can use this information, in concert with endoscopic and imaging studies, to feel much more confident in using biologic therapy early in the course of treatment, now that they have further confirmation of the diagnosis. The serologic studies helped confirm my suspicions and allowed the patient to be as well informed as possible about her disease.

Serologic testing has also been helpful in my practice in diagnosing indeterminate IBD cases and ruling out IBD in other cases. Imaging studies and endoscopy are excellent tests, but serologic testing can provide other pieces of data for the clinician. As readers can see in this case, not all presentations are "classic," and clinicians therefore welcome any relevant and reliable data to aid in diagnosis and therapy.


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