# Testing in the Diagnosis and Management of Inflammatory Bowel Disease (IBD)



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## DESCRIPTION

Inflammatory bowel disease (IBD) is a chronic inflammatory condition. IBD is suggested by the presence of one or more of a variety of signs and symptoms that can be gastrointestinal (GI) (e.g., abdominal pain, bloody diarrhea, perianal fistulae), systemic (e.g., weight loss, fatigue, growth failure in children), or extraintestinal (e.g., characteristic rashes, uveitis, arthritis) in nature. Patients may present with or develop a range of severity of symptoms in the disease course, including life-threatening illness.

Noninvasive diagnosis of inflammatory intestinal diseases is difficult because the clinical manifestation of intestinal disorders are relatively non-specific. Endoscopy with histology is the gold standard for diagnosing bowel inflammation. Limitations of this approach are that it is invasive, with an associated risk of adverse events, and not well tolerated by

some patients. Low specificity and clinical sensitivity of numerous tests to evaluate symptoms, diagnose, and manage intestinal disease have failed to change clinical use of testing. Noninvasive tests to detect markers of intestinal inflammation have been studied for diagnosis and management of inflammatory bowel disease and will be discussed in this evidence review.

IBD is a *structural disease*. That means there is underlying physical damage that causing symptoms. Doctors can see chronic inflammation or ulcers when they examine the gut with an x-ray, endoscopy, surgery, or biopsy. Irritable Bowel Syndrome (IBS), on the other hand, is called a *functional disease*. Someone with this type of disease will have a constellation of symptoms, but tests won't show any physical explanation for those problems. In many cases, particularly if other symptoms hint at IBD, additional tests will be completed to find out whether there's any bleeding or inflammation in the digestive tract. The distinction of IBD from IBS will drive the level of specialty providers involvement, and ongoing follow up necessary to manage the condition.

There are two main forms of IBD; Crohn's disease (CD) and ulcerative colitis (UC). These conditions overlap in clinical and pathologic characteristics but have distinct features. Typical symptoms of episodes/exacerbations are diarrhea, defecation urgency, and sometimes rectal bleeding and abdominal pain. Crohn's disease can involve the entire gastrointestinal (GI) tract and is characterized by transmural inflammation. Ulcerative colitis involves inflammation limited to the mucosal layer of the colon, almost always involving the rectum.

In some cases, the clinical manifestations of IBD can be non-specific and suggestive of other disorders, including infectious colitis, colon cancer, and functional bowel disorders, including irritable bowel syndrome (IBS).

**Diagnosis**

Diagnosing IBD is associated with well-defined management changes. A typical diagnostic approach to IBD includes stool testing for enteric pathogens, blood tests (complete blood count, inflammatory markers) to differentiate etiologies and evaluate disease severity, as well as small bowel imaging and endoscopy (upper GI, colonoscopy) with biopsies.

There is a need for simple, accurate, noninvasive tests to detect intestinal inflammation. Potential noninvasive markers of inflammation fall into several categories, including serologic and fecal. Serologic markers such as C-reactive protein and anti-neutrophil cytoplasmic antibodies tend to have low sensitivity and specificity for intestinal inflammation because they are affected by inflammation outside the GI tract. Fecal markers, in contrast, have the potential to be more specific to the diagnosis of GI tract disorders, because their levels are not elevated in extra-digestive processes. Fecal leukocyte testing has been used to evaluate whether there is intestinal mucosal inflammation. The level of fecal leukocytes can be determined by the microscopic examination of fecal specimens; however, leukocytes are unstable and must be evaluated

promptly by skilled personnel. There is interest in identifying stable proteins in stool specimens, which may be representative of the presence of leukocytes, rather than evaluating leukocyte levels directly.

**Fecal Calprotectin**
Calprotectin is a protein that could be used as a marker of inflammation. It is a calcium- and zinc-binding protein that accounts for approximately 60% of the neutrophil's cytoplasmic proteins. It is released from neutrophils during activation or apoptosis/necrosis and has a role in regulating inflammatory processes. In addition to potentially higher sensitivity and specificity than serologic markers, another advantage of calprotectin as a marker is that it has been shown to be stable in feces at room temperature for up to one week, leaving enough time for patients to collect samples at home and send them to a laboratory for testing. In contrast, lactoferrin, another potential fecal marker of intestinal inflammation, is stable at room temperature for about two days.

Fecal calprotectin testing has been used to differentiate between organic (e.g., inflammation) and functional (no visible problem in the GI tract like IBS) disease. Some consider fecal calprotectin to be a marker of neutrophilic intestinal inflammation rather than a marker of organic disease and believe it has utility to distinguish between IBD and non-IBD. In practice, the test might be suitable for selecting patients with IBD symptoms for endoscopy (i.e., deciding which patients do not require endoscopy). Fecal calprotectin testing has also been proposed to evaluate the response to IBD treatment and for predicting relapse. If found to be sufficiently accurate, results of calprotectin testing could be used to change treatment, such as adjusting medication levels. Guideline-based treatments of IBD include oral and rectal salicylates, glucocorticoids, immunomodulators (e.g., methotrexate), and multiple biologic therapies (e.g., infliximab), depending on disease severity.

Fecal calprotectin is increasingly used to differentiate IBD from IBS when symptoms are overlapping. This is especially useful in pediatrics, where specific symptomology is at times hard to extract. If the test finds a large amount of calprotectin present in the stool, it is more likely that the patient has inflammatory bowel disease (IBD), while if the test comes back with low or normal levels of calprotectin, it points more toward irritable bowel syndrome (IBS). The other recommended use for fecal calprotectin is ongoing monitoring. Currently, the gold standard for monitoring patients with IBD continues to be endoscopy. Fecal calprotectin is frequently thought of as a noninvasive predictive marker of mucosal healing for patients with inflammatory bowel disease (IBD). Studies proving that calprotectin alone can replace invasive monitoring have failed to conclude fecal calprotectin testing can alone drive effective treatment changes. Other potential uses of calprotectin are to evaluate response to specific treatments for patients with IBD and as a marker of relapse in the asymptomatic individual.

Utilizing fecal calprotectin as a marker of inflammation may have potential disadvantages to include, but not limited to, levels may increase after the use of non-steroidal anti-inflammatory drugs, levels may change with age, and bleeding may cause

an elevated fecal calprotectin level. Moreover, there is uncertainty about the optimal cutoff to use to distinguish between inflammatory bowel disease and non-inflammatory disease. This cutoff value to drive treatment changes has been modified continuously in an attempt to increase testing sensitivity and specificity.

**Fecal Lactoferrin**

(2018) Abraham reports fecal lactoferrin is an iron-binding protein found inside neutrophils. The amount of lactoferrin released by neutrophils has been shown to correlate with the severity of inflammation in the gastrointestinal (GI) tract. Lactoferrin is stable in feces for several days at room temperature, and even longer if the stool is refrigerated. Fecal lactoferrin can be tested using commercial enzyme-linked immunosorbent assays to provide quantitative or qualitative results. Fecal lactoferrin testing can help physicians for the differentiation of inflammatory bowel disease (IBD) from irritable bowel syndrome (IBS), the initial evaluation of IBD severity and correlation to endoscopic findings, the monitoring of IBD activity, and potentially the prediction of IBD relapse.

Fecal lactoferrin testing is very useful when a patient presents with nonspecific GI symptoms, such as abdominal pain and diarrhea, especially without evidence of alarm symptoms of weight loss or GI bleeding. These non-specific symptoms could be due to a functional etiology, such as IBS, or from IBD or GI infections. If the patient's fecal lactoferrin level is undetectable, low, or normal, the symptoms are not likely to be related to inflammation or infection and are more likely to be functional. On the other hand, a high fecal lactoferrin level should prompt an evaluation for either IBD (Crohn's disease or ulcerative colitis) or infectious etiologies through stool panel testing, colonoscopy, or both. With low fecal lactoferrin levels, the need for further workup can be reduced or avoided, and health care costs in the long run can potentially be lowered.

Fecal lactoferrin testing can be quite useful for the primary care physician, as the testing can help determine how urgently a patient with GI symptoms should be referred to a gastroenterologist. For example, in the setting of elevated fecal lactoferrin with acute symptoms, GI infections should always be ruled out, but for chronic symptoms, referral to a gastroenterologist should be warranted.

A fecal lactoferrin baseline cutoff level less than 7.25 μg/g indicates lack of intestinal inflammation and, for a patient with GI symptoms, suggests a functional cause (e.g., IBS). When the level is far above this cutoff, the need for further evaluation is clear. However, when a patient has borderline results just above this level, the physician's discretion should be used to determine whether further testing is warranted, or if this level should be rechecked at a later time for improvement. In patients with fibrostenotic disease, where there may not be active inflammation, fecal lactoferrin levels may be low despite clinical symptoms. As with any laboratory testing, this tool should be used as an adjunct to the patient's full clinical picture to make management decisions.

**NOD2/CARD15 Genotyping**
Medline Plus reports, the NOD2 gene (previously known as CARD15) provides instructions for making a protein that plays an important role in immune system function. The NOD2 protein is active in some types of immune system cells (including monocytes, macrophages, and dendritic cells), which help protect the body against foreign invaders such as bacteria and viruses. The protein is also active in several types of epithelial cells, including Paneth cells, which are found in the lining of the intestine. These cells help defend the intestinal wall against bacterial infection.

The NOD2 protein has several critical functions in defending the body against foreign invaders. The protein is involved in recognizing certain bacteria and stimulating the immune system to respond appropriately. When triggered by specific substances produced by bacteria, the NOD2 protein turns on (activates) a protein complex called nuclear factor-kappa-B. This protein complex regulates the activity of multiple genes, including genes that control immune responses and inflammatory reactions. An inflammatory reaction occurs when the immune system sends signaling molecules and white blood cells to a site of injury or disease to fight microbial invaders and facilitate tissue repair.

The NOD2 protein also appears to play a role in a process called autophagy, which cells use to surround and destroy bacteria, viruses, and other harmful substances. In addition to protecting cells from infection, autophagy is used to recycle worn-out cell parts and break down certain proteins when they are no longer needed. This process is also involved in the self-destruction of cells (apoptosis).

**Serological and BioMarker Testing**
Serological testing and combined serological testing have been proposed to diagnose and assist in treatment planning for individuals with inflammatory bowel (IBD) (e.g., Crohn's disease (CD) and ulcerative colitis (UC)). Serological testing involves obtaining a blood sample for analysis to determine the presence of antibodies which help identify individuals with IBD.

A test for the measurement of two biomarkers has been developed to reportedly aid in the diagnosis of diarrhea-predominant IBS. The test measures anticytolethal distending toxin B (CdtB) and antivinculin. CdtB is a toxin released by the four main bacteria known to cause gastroenteritis and vinculin is a protein released as a result of nerve and intestinal tissue damage. The test results may indicate the presence of IBS as opposed to IBD. Examples of these tests include, but may not be limited to, the IBSDetex, IBSchek and ibs-smart

**Treatment**
Guideline-based treatments of IBD include oral and rectal salicylates, glucocorticoids, immunomodulators (eg, methotrexate), and multiple biologic therapies (eg, infliximab), depending on disease severity.

**Clinical Context and Test Purpose**
In individuals who have suspected inflammatory bowel disease (IBD), the purpose of this testing is to inform the decision whether to proceed to endoscopy with biopsy to confirm a diagnosis of IBD, either ulcerative colitis (UC) or Crohn's disease.

Irritable bowel syndrome (IBS) and IBD can share common presenting symptoms such as diarrhea and abdominal pain. IBS is generally managed by antidiarrheal agents, diet, and lifestyle changes. IBD has a more serious prognosis. For example, Crohn's disease can result in a bowel obstruction or fistulas requiring surgical intervention. Ulcerative colitis has similar complications but is more localized.

In a patient whose symptoms have not responded to conservative management, endoscopy with biopsy would be required to confirm a diagnosis of IBD and inform treatment choice, which may include biologic disease-modifying agents. However, in a significant proportion of patients undergoing endoscopy with biopsy, IBD is not present. If this noninvasive testing can predict which patients are unlikely to have IBD, fewer patients would be subjected to endoscopy with biopsy.

Also, serological testing using biomarkers of irritable bowel syndrome (IBS) is to differentiate IBS from other digestive disorders such as IBD.

The following PICO was used to select literature to inform this review.

**Populations**
The relevant population of interest is individuals who present with signs and/or symptoms of digestive disorders and are suspected of having irritable bowel syndrome (IBD). Alternative causes of abdominal pain and diarrhea would have been ruled out and there would be no other indication for endoscopy such as rectal bleeding or risk factors (eg, age) for cancer.

**Interventions**
The testing being considered is the following:

- Testing which detects the process of inflammation in the intestines to assist in diagnosis and management of IBD (i.e., fecal calprotectin, fecal lactoferrin).
- Differentiating irritable bowel syndrome (IBS) from other digestive disorders (IBD) (i.e., Calprotectin Chemiluminescence ELISA test, Crohn's Prognostic, IBD sgi Diagnostic, IBSchek®, IBS-Smart™, PredictSURE IBD,) Prometheus© IBD Serology 7.

**Comparators**
The following practice is currently being used to make decisions about diagnosing IBD: the reference standard is endoscopy with biopsy. In clinical practice, other tests such as magnetic resonance imaging, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and complete hemogram are part of the evaluation for IBD.

Differentiating IBS from other digestive disorders is a complex task for clinicians. Symptom-based diagnosis is usually guided by the Rome IV criteria and is the most widely employed method in practice today. An important shortcoming of the Rome criteria is its lack of validation.

**Outcomes**
The outcome of this testing for IBD is to inform the decision of whether to proceed to endoscopy with biopsy.

The beneficial outcome of correctly being classified as low-risk for IBD is avoiding unnecessary invasive testing. The harmful outcome of incorrect classification as low-risk IBD is omission or deferral of a necessary biopsy, with a consequent delay of appropriate treatment.

The general outcomes of this testing for IBD are to identifying alternative methods of testing techniques for more definitive diagnosis.

**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

**Review of Evidence**

**Fecal Calprotectin**
(2019) Petryszyn et al. reported colonoscopy is the standard medical procedure to identify inflammatory bowel disease (IBD) in patients with gastrointestinal symptoms. Noninvasive measurement of fecal calprotectin concentration may replace colonoscopy in this indication. The study aimed to assess efficacy of fecal calprotectin as a diagnostic marker of IBD in patients with symptoms suggestive of such diagnosis. Meta-analysis of diagnostic accuracy studies was performed. Cochrane, EMBASE and MEDLINE databases were searched until December 2018. Inclusion criteria comprised experimental and observational studies, adults with gastrointestinal symptoms, calprotectin as index and colonoscopy as reference test, presence of data on/enabling the calculation of diagnostic accuracy parameters. For each study, sensitivity and specificity of fecal calprotectin were analyzed as bivariate data. Nineteen studies were identified. The total number of patients was 5032. Calculated pooled sensitivity and specificity were 0.882 [95% confidence interval (CI), 0.827-0.921] and 0.799 (95% CI, 0.693-0.875), respectively. Following fecal calprotectin incorporation in the diagnostic work-up of 100 people with suspected IBD, 18 non-IBD patients will have a colonoscopy performed and one patient with the disease will not be referred for this examination. Fecal calprotectin concentration measurement is a useful screening test to rule out IBD, at the same time reducing the need for colonoscopy by 66.7%.

(2018) Brooks et al. reported the differentiation between inflammatory bowel disease (IBD) and functional gut disorders, and the determination of mucosal disease activity in

established cases of IBD remain the cornerstones of disease diagnosis and management. Non-invasive, accurate biomarkers of gut inflammation are needed due to the variability of symptoms, the inaccuracies of currently available blood markers and the cost and invasive nature of endoscopy. Numerous biomarkers have been used and/or considered with some in current use. This article reviews the current evidence base around the indications for using biomarkers and their limitations, with a particular focus on fecal calprotectin.

- Fecal calprotectin, in both adults and children, has been shown to have high sensitivity and specificity for differentiating between IBD and functional gastrointestinal disorders. In this regard, National Institute of Health and Care Excellence (NICE) recommended its use in primary and secondary care in diarrhea (testing not indicated unless new gastrointestinal symptoms persist for at least 4 weeks) and in the presence of bloody diarrhea.
- Calprotectin is not appropriate in older patients (aged >45–50 years), where other diagnoses including colonic polyps/malignancy are more common. The age cut-off should be determined on the basis of local audit data. In patients with diarrhea only, a normal calprotectin does not rule out drug-induced diarrhea (e.g., metformin, proton-pump inhibitors), bile salt malabsorption or coeliac disease.
- Microscopic colitis may have raised calprotectin but to date there are few data and there is more likely to be overlap with normal or intermediate range.

Summary Recommendations

- Fecal calprotectin is a sensitive and specific noninvasive marker of gastrointestinal inflammation.
- It is recommended that stool sample for calprotectin is collected from the first bowel action of the day and kept for no longer than three days at room temperature.
- It is recommended that threshold values are determined on the basis of local audit data, and assay used.
- It is recommended that fecal calprotectin is used to discriminate between functional gastrointestinal symptoms and IBD in primary and secondary care in adults with recent-onset lower gastrointestinal symptoms, where cancer is not suspected and for whom specialist assessment is being considered. It should not be used in patients with acute diarrhea, bloody diarrhea or in older patients where the need to rule out polyps or cancer mandates colonoscopy anyway.
- It is suggested that fecal calprotectin measurement is useful in patients with IBD, in whom it is unclear whether symptoms are due to active inflammation, or other causes such as coexisting IBS or bile salt malabsorption.
- It is suggested that fecal calprotectin can be useful in decision-making regarding either stopping or increasing drug therapy for IBD. It is not recommended that fecal calprotectin is used routinely in the monitoring of all patients with IBD.

(2017) Heida et al. conducted a systematic review to determine the accuracy of fecal calprotectin monitoring in asymptomatic patients. Six studies met the review inclusion criteria and evaluated fecal calprotectin levels every 1 to 3 months. One-third of patients

had a relapse during the study period, although the definitions of relapse varied across studies. Five of the 6 studies used an upward trend of fecal calprotectin between 2 measurements as the threshold. Asymptomatic patients with IBD who had fecal calprotectin levels above the study's cutoff had a 53% to 83% probability of developing disease relapse within the next 2 to 3 months, while patients with normal fecal calprotectin levels had a 67% to 94% probability of remaining in remission in the next 2 to 3 months (Table 14). Calprotectin levels began to rise 2 to 3 months before clinical relapse. The investigators could not identify the best fecal calprotectin cutoff for monitoring purposes.

A prospective nonblinded controlled trial by Lasson et al. (2015) randomized patients with ulcerative colitis in remission at high-risk of relapse in a 3:2 ratio to medication dosing decisions based on fecal calprotectin levels or to usual care. The fecal calprotectin monitoring group was included in the systematic review by Heida et al. (2017) described above. Both groups submitted fecal samples at baseline and on a monthly basis. In the intervention group, a fecal calprotectin cutoff of 300 μg/g was used for escalating the 5-aminosalicylic acid dose to the maximally tolerable dose. The high dose was continued for 3 months and then reduced when fecal calprotectin levels fell below 200 μg/g. The primary outcome was the number of patients to relapse by 18 months. At 1 year, there was no significant difference in relapse rates between the 2 groups. For 10 of the 18 patients in the intervention group who had a relapse, fecal calprotectin levels did not rise above the 300 μg/g cutoff for medication dosage escalation. In the subgroup of patients who had levels of 300 μg/g or more, there was a significantly lower rate of relapse in the intervention group (28.6%) than in the control group (57.1%). Trial limitations included lack of blinding, exclusion of patients without intention-to-treat analysis, and insufficient power.

(2013) Yamamoto et al.  completed prospective study was to evaluate the significance of fecal calprotectin and lactoferrin for the prediction of ulcerative colitis (UC) relapse. Eighty UC patients in remission for ≥3 months on mesalamine as maintenance therapy were included. At entry, stool samples were collected for the measurement of calprotectin and lactoferrin. All patients were followed up for the following 12 months. To identify predictive factors for relapse, time-dependent analyses using the Kaplan-Meier graphs and Cox's proportional hazard model were applied.

During the 12 months, 21 patients relapsed. Mean calprotectin and lactoferrin levels were significantly higher in patients with relapse than those in remission (calprotectin-173.7 vs 135.5 μg/g, P = 0.02; lactoferrin-165.1 vs 130.7 μg/g, P = 0.03). A cutoff value of 170 μg/g for calprotectin had a sensitivity of 76 % and a specificity of 76 % to predict relapse, while a cutoff value of 140 μg/g for lactoferrin had a sensitivity of 67 % and a specificity of 68 %. In a multivariate analysis, calprotectin (≥170 μg/g) was a predictor of relapse (hazard ratio, 7.23; P = 0.002). None of the following parameters were significantly associated with relapse: age, gender, duration of UC, number of UC episode, severity of the previous episode, extent of UC, extraintestinal manifestation, and lactoferrin level.

Fecal calprotectin showed a higher sensitivity and specificity than fecal lactoferrin for predicting UC relapse. Fecal calprotectin level appeared to be a significant predictor of relapse in patients with quiescent UC on mesalamine as maintenance therapy.

(2013) Waugh et al. published a systematic review as part of the U.K. Health Technology Assessment program. Investigators included 28 studies using fecal calprotectin tests to evaluate inflammation of the lower intestine in newly presenting patients. Studies using fecal calprotectin tests to monitor disease progression or response to treatment were excluded. Endoscopy with histology was the preferred reference standard, although some studies included used imaging or clinical follow-up. Studies were pooled when there was a minimum of 4 using the same calprotectin cutoff. A pooled analysis of 5 studies using fecal calprotectin detected by enzyme-linked immunosorvent assay to differentiate between IBD and IBS in adults at a cutoff of 50 µg/g was performed (Table 1). One study was rated as low-risk of bias and 3 studies had at least 3 domains with high or unclear risk of bias. The pooled studies had a combined sensitivity of 93% and a combined specificity of 94% to predict the presence of inflammatory disease on biopsy (1 study evaluated the absence of inflammatory disease). Table 2 summarizes clinical validity results and Tables 3 and 4 present individual study characteristics and results, with Table 4 presented in the order of increasing prevalence of IBD. Out of 100 cases with a prevalence of 20%,[4,] 76 invasive tests would be avoided with 1 case of IBD missed. At a prevalence of 68%,[5,] 35 invasive tests would be avoided with 5 cases missed.

**Characteristics of Studies at a Threshold of 50 µg/g**

| 11-Item QUADAS Quality Assessment | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| No. of Studies Rated as High or Unclear Risk of Bias | | | | | | | | |
| **Study** | **Studies Included** | **Study Populations Included** | **Study Designs Included** | **Study Reference Standards Included** | **No Domains** | **1-2 Domains** | **>2 Domains** | **Domains With >3 Studies at High-Risk of Bias** |
| Waugh et al (2013) | 5 studies | Adults newly presenting with IBD or IBS referred by general practitioners | Diagnostic accuracy of FC to detect inflammation of the lower intestine | Most used endoscopy with biopsy | 1 | 1 | 3 | Blinding of reference standard |

| 11-Item QUADAS Quality Assessment | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Waugh et al (2013) | 6 studies | Adults and children newly referred with IBD or non-IBD | Diagnostic accuracy of FC to detect inflammation of the lower intestine | -Most used endoscopy with biopsy<br>-Some studies in children used clinical follow-up | 0 | 5 | 1 | Blinding of reference standard |

FC: fecal calprotectin; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome.

**Clinical Validity Study Results at a Threshold of 50 µg/g**

| Study | Scenario (N) | Sensitivity (95% CI), % | Specificity (95% CI), % | PPV Range, % | NPV Range, % | Disease Prevalence Range (95% CI), % |
|---|---|---|---|---|---|---|
| Waugh et al (2013) | To detect IBD in adults with IBS or IBD (5 studies, n=596 patients) | 93 (83 to 97) | 94 (73 to 99) | 24 to 100 | 73 to 100 | 10.9 to 69.0 (5.8 to 77.3) |
| Waugh et al (2013) | To detect IBD in children and adults with IBD or non-IBD (6 studies, n=516 patients) | 99 (95 to 100) | 74 (59 to 86) | 62 to 96 | 93 to 100 | 21.4 to 61.1 (13.2 to 72.5) |

CI: confidence interval; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; NPV: negative predictive value; PPV: positive predictive value.

**Characteristics of Diagnostic Accuracy Studies (Inflammatory Bowel Disease versus Irritable Bowel Syndrome) in Adults with a Cutoff of 50 µg/g**

| Study | Study Population | Setting | Reference Standard | No. of Domains[a] at High or Unclear Risk of Bias |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| Basumani et al. (2012) | New referrals with diarrhea ≥4 wk to rule out IBD | District General Hospital, England | Histology | 4 |
| Otten et al. (2008) | Consecutive patients were referred with lower abdominal symptoms to the endoscopy unit. Excluded 25 patients with polyps or CRC. | Endoscopy unit, The Netherlands | Colonoscopy and biopsy | 2 |
| Li et al (2006) | Outpatients and inpatients with IBS or IBD, healthy controls; patients followed up after polyp removal with no recurrence. Excluded 60 patients with CRC. | Hospital, Peking | Colonoscopy with biopsy in IBD group | 6 |
| Schoepfer et al. (2008) | Outpatients and inpatients with IBS or IBD. Excluded patients with CRC. | Gastroenterology Department, University Hospital, Switzerland | Colonoscopy including terminal ileum and biopsies | 0 |
| El-Badry et al. (2010) | GI symptoms for at least 6 mo, and endoscopy necessary to exclude organic pathology. Excluded patients with CRC, diverticulitis, and polyps. | Internal Medicine Department, Egypt | Colonoscopy into ileum with biopsies | 3 |

CRC: colorectal cancer; GI: gastrointestinal; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome.
[a] QUADAS ratings.

**Results of Diagnostic Accuracy Studies (Inflammatory Bowel Disease versus Irritable Bowel Syndrome) in Adults with a Cutoff of 50 µg/g Stratified by Increasing Prevalence**

| Study | N | Prevalence (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) | PLR (95% CI) | NLR (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Basumani et al (2012) | 110 | 10.91 (5.77 to 18.28) | 1.00 (0.74 to 1.00) | 0.60 (0.50 to 0.70) | 0.24 (0.13 to 0.37) | 1.00 (0.94 to 1.00) | 2.51 (1.97 to 3.21) | 0 |

| Study | N | Prevalence (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) | PLR (95% CI) | NLR (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Otten et al (2008 | 114 | 20.18 (13.24 to 28.72) | 0.96 (0.78 to 1.00) | 0.87 (0.78 to 0.93) | 0.65 (0.47 to 0.81) | 0.99 (0.93 to 1.00) | 7.25 (4.25 to 12.38) | 0.05 (0.01 to 0.34) |
| Li et al (2006) | 120 | 50.00 (40.74 to 59.26) | 0.93 (0.84 to 0.98) | 0.95 (0.86 to 0.99) | 0.95 (0.86 to 0.99) | 0.93 (0.84 to 0.98) | 18.67 (6.18 to 56.63) | 0.07 (0.03 to 0.18) |
| Schoepfer et al (2008) | 94 | 68.09 (57.67 to 77.33) | 0.83 (0.71 to 0.91) | 1.00 (0.88 to 1.00) | 1.00 (0.93 to 1.00) | 0.73 (0.57 to 0.86) | NR | 0.17 (0.10 to 0.29) |
| El-Badry et al (2010) | 29 | 68.97 (49.17 to 84.72) | 0.85 (0.62 to 0.97) | 1.00 (0.66 to 1.00) | 1.00 (0.81 to 1.00) | 0.75 (0.43 to 0.95) | NR | 0.15 (0.05 to 0.43) |

CI: confidence interval; NLR: negative likelihood ratio; NPV: negative predictive value; NR: not reported; PLR: positive likelihood ratio; PPV: positive predictive value.

Six studies using fecal calprotectin with an enzyme-linked immunosorvent assay to differentiate between IBD and non-IBD in children and adults were pooled. Five of the studies included only children, most of whom had been referred to pediatric gastroenterologists. The children had undergone fecal calprotectin testing prior to endoscopy with biopsy or were followed clinically. No studies were at low-risk of bias and 5 studies had 1 to 2 domains with high or unclear risk of bias, as evaluated on the QUADAS quality assessment. The highest risk of bias was for blinding of the reference standard. The combined sensitivity was 99%, with a lower combined specificity (74%) to detect the absence of inflammatory disease on biopsy. Modeling indicated that the use of fecal calprotectin in children would result in fewer children undergoing an unnecessary invasive test (ie, endoscopy with biopsy). Out of 100 cases, at a prevalence of 36%,[9,] 47 invasive tests would be avoided with 1 case of IBD missed. At a prevalence of 51%,[10,] 36 invasive tests would be avoided with 1 case of IBS missed. Individual study characteristics and results, presented in the order of the increasing prevalence of IBD.

**Characteristics of Diagnostic Accuracy Studies (Inflammatory Bowel Disease versus Non-Inflammatory Bowel Disease) in Children and Adults with a Cutoff of 50 µg/g**

| Study | Study Population | Setting | Reference Standard | No. of Domains[a] at High or |
|---|---|---|---|---|

| | | | | Unclear Risk of Bias |
|---|---|---|---|---|
| Damms and Bischoff et al. (2008) | Patients ages >18 y referred for colonoscopy for GI disorders or CRC screening | Gastroenterology departments at 3 hospitals and 3 outpatient clinics in Germany | Colonoscopy: for CRC screening medical check-up | 2 |
| Van de Vijver et al. (2012) | Children ages 6 to 18 y referred for further investigation of high suspicion of IBD from pediatrician's global assessment, physical examination, and blood results | Pediatric outpatient clinics at 6 general hospitals and 1 tertiary care hospital in the North Netherlands Paediatric IBD Consortium | 68 patients had endoscopy; others had follow-up for at least 6 mo to confirm a diagnosis of IBS | 1 |
| Henderson et al. (2012) | All children who had a fecal calprotectin measurement as part of initial diagnostic workup before endoscopy | Pediatric gastroenterology department at a children's hospital in U.K. | • IBD patients: standard clinical, histologic, and radiologic findings<br>• Non-IBD (control) patients: upper and lower endoscopy | 2 |
| Sidler et al. (2008) | Children ages 2 to 18 y referred for further investigation of GI symptoms (chronic diarrhea, bloody stools, abdominal pain) suggestive of an OBD | Pediatric gastroenterology outpatient clinic at children's hospital in Australia | • Upper GI endoscopy and complete ileocolonoscopy with biopsy | 1 |

| | | | | |
|---|---|---|---|---|
| Tomas et al (2007) | Patients referred for further investigation of GI symptoms (intense abdominal pain, chronic diarrhea, weight loss, rectal bleeding) | Pediatric gastroenterology unit of university hospital in Spain | • Clinical criteria, laboratory, image, and endoscopic test results | 6 |
| Fagerberg et al (2005) | Children ages 6 to 17 y with GI symptoms and blood tests suggestive of inflammation who were scheduled for colonoscopy to rule out IBD | Pediatric gastroenterology departments at hospitals in Sweden | Complete ileocolonoscopy with biopsy | 1 |

CRC: colorectal cancer; GI: gastrointestinal; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; OBD; organic bowel disease.

[a] QUADAS ratings.

**Results of Diagnostic Accuracy Studies (Inflammatory Bowel Disease versus Non-Inflammatory Bowel Disease) in Children and Adults with a Cutoff of 50 µg/g Stratified by Increasing Prevalence**

| Study | N | Prevalence (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) | PLR (95% CI) | NLR (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Damms et al. (2008) | 84 | 21.43 (13.22 to 31.74) | 1.00 (0.81 to 1.00) | 0.79 (0.67 to 0.88) | 0.79 (0.60 to 0.88) | 1.00 (0.93 to 1.00) | 4.71 (2.96 to 7.50) | 0 |
| Van de Vijver et al. (2012) | 117 | 35.9 (27.24 to 45.29) | 1.00 (0.92 to 1.00) | 0.73 (0.62 to 0.83) | 0.68 (0.55 to 0.79) | 1.00 (0.94 to 1.00) | 3.8 (2.6 to 5.5) | 0 |
| Henderson et al. (2012) | 190 | 47.89 (40.61 to 55.25) | 0.98 (0.92 to 1.00) | 0.44 (0.34 to 0.55) | 0.62 (0.53 to 0.70) | 0.96 (0.85 to 0.99) | 1.8 (0.15 to 2.1) | 0.05 (0.01 to 0.20) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Sidler et al. (2008) | 61 | 50.82 (37.70 to 63.86) | 1.00 (0.89 to 1.00) | 0.67 (0.47 to 0.83) | 0.76 (0.60 to 0.88) | 1.00 (0.83 to 1.00) | 3.00 (1.81 to 4.98) | 0 |
| Tomas et al. (2007) | 28 | 53.57 (33.87 to 72.49) | 1.00 (0.78 to 1.00) | 0.92 (0.64 to 1.00) | 0.94 (0.70 to 1.00) | 1.00 (0.74 to 1.00) | 13.00 (1.98 to 85.46) | 0 |
| Fagerberg et al. (2005) | 36 | 61.11 (43.46 to 76.86) | 0.95 (0.77 to 1.00) | 0.93 (0.66 to 1.00) | 0.96 (0.77 to 1.00) | 0.93 (0.66 to 1.00) | 13.36 (2.02 to 88.54) | 0.05 (0.01 to 0.33) |

CI: confidence interval; NLR: negative likelihood ratio; NPV: negative predictive value; PLR: positive likelihood ratio; PPV: positive predictive value.

**Clinically Useful**

A test is clinically useful if the results inform management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

**Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).
No RCTs were identified that assessed the use of fecal calprotectin testing to diagnose suspected IBD.

**Chain of Evidence**

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.
Indirect evidence supports the clinical usefulness of fecal calprotectin in patients with suspected IBD for whom endoscopy is being considered. The evidence on clinical validity (sensitivity, specificity, negative predictive value [NPV]) permits inference on clinical usefulness as a result of avoidance of endoscopy with biopsy in patients who are unlikely to have an inflammatory disease.

**Section Summary: Suspected Inflammatory Bowel Disease**

The pooling of 6 studies in adults and children (n=1100) with IBD or non-IBD showed an NPV of 93% to 100%. Together, these results would suggest that fecal calprotectin testing at a threshold of 50 μg/g can identify patients who are unlikely to have the IBD and can forgo a more invasive test (endoscopy with biopsy). In another more recent meta-analysis involving 19 studies, investigators determined that incorporating a fecal calprotectin test into the regular diagnostic work-up would reduce the need for colonoscopy by 66.7%.

**Fecal Calprotectin Testing in the Home Environment (e.g., IBDoc)**
(2021) Ostlund et al. completed a randomized controlled trial on patients with inflammatory bowel disease. Patients were randomized to IBD-Home + standard care (n = 84) or standard care alone (n = 74). Intervention with IBD-Home included IBDoc® FC test kits and a digital application used for answering symptom questionnaires (Abbvie/Telia). They were instructed to use these on demand during a 12-month period. Data was collected retrospectively from medical records. Patients who completed the intervention were phoned and asked to answer a survey about the experience of IBD-Home. The compliance to IBD-Home was low (29%). Women were more compliant compared with men (43% vs 17%, $p < .001$). A significantly higher proportion of patients in the IBD-Home group increased their medical treatment during the study period in comparison to control subjects (33% vs 15% $p = .007$) and there was an association between an increase in treatment and compliance to IBD home (multivariate odds ratio 3.22; 95th confidence interval 1.04 - 9.95). Overall patients reported a positive experience with slight technical difficulties. The authors concluded as IBD increases worldwide new monitoring strategies are of great importance. Telemedicine and self-monitoring for IBD have proven themselves safe and feasible with several positive effects. Unlike other studies, our study shows that compliance to the IBD-Home model was associated with increased medical treatment and on the short basis with more contacts with health services. The overall low compliance, especially among men, highlights the importance of having optimal strategies when introducing new self-monitoring models. As there is currently limited knowledge about IBD self-monitoring with home-based FC tests more studies are needed to properly determine the optimal implementation of the technology in IBD care, as well as cost effectiveness. The authors also acknowledged the following limitations. most patients had an established care for IBD and if only patients at onset had been include the compliance rate and effect of the intervention could had been different. In addition, the IBD-Home group only received an instruction manual (written and video information) for the test kits and no initial training at our clinic. This could have had a negative effect on compliance to the model. However, at the IBD-Home web site there is clear written and video instruction how to use the fecal test and the digital application and most of the compliers reported that the digital application and HBFCT test were easy to use. The duration of the study was only one twelve months long and this could also have had effect on compliance. Perhaps, using a longer study period more patients might had started and had become more used to the IBD-Home model. Lastly, apart from changes in medical treatment we were not able to compare disease activity between the groups. A reason for this was that there was too much missing data on disease activity for the control persons and non-compliers.

(2018) Moore et al. completed a study noting fecal calprotectin (FC) is a stool biomarker that has been shown to be sensitive and specific for mucosal inflammation in patients with inflammatory bowel disease (IBD). The test is limited by the requirement for patients to collect and return stool samples. A home-based FC test may improve test adherence. The aim of this study is to evaluate the usability of the IBDoc, a home-based FC measuring test, and to determine the accuracy of results compared with traditional lab-based ELISA values. Patients were prospectively enrolled from three tertiary sites

across Canada between May and August 2017. Patients completed a questionnaire establishing ease-of-use of the IBDoc. Patients completed a FC measurement using the IBDoc, and results were compared with an ELISA-determined FC measurement on the same stool sample. Sixty-one participants were enrolled in the study (29 CD, 32 UC). Seventy-nine percent of patients (48 of 61) agreed that the IBDoc was easy to use, with 85% (52 of 61) of patients strongly agreeing that they were willing use the home kit in the future. The IBDoc and ELISA measurement comparison showed an 88% agreement across all values. There were no false positives or negatives using qualitative comparison. A limitation of this study includes the number of incomplete IBDoc kits. Ten patients' IBDoc results were not used in the statistical analysis because two results were invalid, three results were excluded because of the use of nonsupported smartphones, and five results were excluded for other reasons. Increased individual patient experience with the IBDoc will help reduce this failure rate, and smartphones that do not support the CapApp must be identified earlier. Among the patients who completed the IBDoc at the clinical site and were therefore observed, the most challenging part of the IBDoc was loading the sample onto the cassette correctly. This is likely to be the most common technical barrier for patients to complete this test. The study results are encouraging as the IBDoc is acceptable to patients and correlates extremely well with laboratory values. There is still a small group of patients that were unable to complete the test, but with errors, that could be corrected on a subsequent attempt. This study further strengthens the evidence of accuracy of the IBDoc, a home-based FC monitoring kit, and demonstrates that this technology is acceptable to patients to use. It may therefore enable clinicians to more easily adopt a treat-to-target approach, improve long-term outcomes and patients' quality of life with IBD in Canada. Further studies are needed to determine whether patients adopt the device for use beyond the clinical trial setting and to assess its impact on patient care for IBD as part of the evolving remote monitoring of IBD patients. They acknowledged there is a population bias towards those that have access to a smartphone which is a requirement to access this technology. Smartphone access is increasing but may be limited among those with a lower socioeconomic status. This study does not provide any long-term data on the adherence of patients to a home-based FC monitoring strategy as part of an individualized, proactive management plan

**Fecal Lactoferrin**

(2016) Wang et al. completed a review on the clinical utility of fecal lactoferrin in determining infectious etiology of diarrhea All patients with a test order for FL (LEUKO EZ VUE, TECHLAB) at a tertiary care institution in 2015 were eligible for inclusion (n = 4917). Repeat tests (408), unresulted tests (5), or patients without at least 1 enteric pathogen (EP) stool test ordered within 7 days of their FL test (246) were excluded. Demographic, comorbid, and encounter-level data were retrospectively collected. The EPs were classified as "inflammatory" or "non-inflammatory" based on prior literature. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of FL for EPs were determined. A total of 4273 patients with FL test results met criteria for study inclusion. Tests to detect inflammatory EPs performed in this cohort included 3488 bacterial stool cultures, 3486 Shiga toxin enzyme immunoassays (EIAs), 3198 Campylobacter EIAs, and 3497 Clostridium difficile toxin gene polymerase chain

reaction (PCR) assays. Tests performed for non-inflammatory EPs included 1324 Cryptosporidium EIA, 1324 Giardia EIA, 1325 ova and parasite exams, and 7 norovirus PCR tests. A total of 2537 FL tests (59%) were positive, and those patients were more likely to be older, male, and inpatients. Overall, FL was 81% sensitive and 43% specific for inflammatory EPs, but 55% sensitive and 42% specific for non-inflammatory EPs. The PPVs for inflammatory and non-inflammatory EPs were 16% and 1%, respectively; the NPVs were 95% and 99%, respectively. Fecal lactoferrin sensitivity for individual inflammatory EPs ranged from 76% for C difficile to 100% for Shigella sp. Fecal lactoferrin sensitivity for non-inflammatory EPs ranged from 11% for ova and parasites detected by microscopy to 100% for norovirus. The authors concluded the majority of FL tests ordered were positive and performed in conjunction with specific EP tests. Although FL was more sensitive for inflammatory than non-inflammatory pathogens, poor specificity and PPV limit the clinical utility of the test.

(2015) Li et al. reported on the clinical significance of fecal lactoferrin and multiplex polymerase chain reaction in patients with acute diarrhea. Clinical parameters and laboratory findings, including fecal leukocytes, fecal lactoferrin, stool cultures and stool multiplex PCR for bacteria and viruses, were evaluated prospectively for patients who were hospitalized due to acute diarrhea. A total of 54 patients were included (male, 23; median age, 42.5 years). Fecal leukocytes and fecal lactoferrin were positive in 33 (61.1%) and 14 (25.4%) patients, respectively. Among the 31 patients who were available for fecal pathogen evaluation, fecal multiplex PCR detected bacterial pathogens in 21 patients, whereas conventional stool cultures were positive in only one patient (67.7% vs 3.2%, p=0.000). Positive fecal lactoferrin was associated with presence of moderate to severe dehydration and detection of bacterial pathogens by multiplex PCR (21.4% vs 2.5%, p=0.049; 100% vs 56.5%, p=0.032, respectively) The authors concluded fecal lactoferrin is a useful marker for more severe dehydration and bacterial etiology in patients with acute diarrhea. Fecal multiplex PCR can detect more causative organisms than conventional stool cultures in patients with acute diarrhea but noted there may be some limitations to the present study. First, a relatively small number of patients were enrolled in the study. Secondly, the possibility of “innocent bystanders” among pathogens detected by multiplex PCR exists since a certain amount of infectious dose is required for the onset of an illness.

(2015) Wang et al. completed a systematic review using meta-analysis to assess the diagnostic accuracy of fecal lactoferrin (FL) in patients with inflammatory bowel disease (IBD). Methods: We performed a literature review and systematically searched the Medline and EMBASE databases for eligible studies. The quality of the included studies was assessed using the QUADAS tool. The sensitivity, specificity, and other diagnostic indexes of FL were pooled using a random-effects model. Results: Seven studies, involving 1816 patients, met the inclusion criteria. In all studies, the pooled FL sensitivity and pooled specificity were 0.82 (95% confidence interval [CI]: 0.72, 0.89) and 0.95 (95% CI: 0.88, 0.98), respectively. The positive and negative likelihood ratios were 16.63 and 0.18, respectively. The area under the summary receiver-operating characteristic curve (SROC) was 0.95 (95% CI: 0.93, 0.97), and the diagnostic odds ratio was 90.04

(95% CI: 37.01, 219.02). The pooled FL sensitivity and specificity for Crohn's disease (CD) diagnosis (sensitivity =75%, specificity =100%) was not as good as it was for ulcerative colitis (UC) diagnosis (sensitivity =82%, specificity =100%).

**Fecal Lacotferring: Pediatrics**

(2019) Park et al. completed a study on the clinical significance on the inflammatory biomarkers in acute pediatric diarrhea with clinical parameters including fever, bacterial and viral etiology based on stool culture and multiplex polymerase chain reaction, and nine biomarkers including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and leukocytes in blood and calprotectin, lactoferrin, myeloperoxidase, polymorphonuclear elastase, leukocytes, and occult blood in feces were evaluated in children who were hospitalized due to acute diarrhea without underlying disease. A total of 62 patients were included. Among these patients, 33 had fever, 18 showed bacterial infections, and 40 patients were infected with 43 viruses. Of all the biomarkers, CRP was significantly correlated with fever ($p<0.001$). CRP, ESR, calprotectin, lactoferrin, myeloperoxidase, fecal leukocytes, and occult blood were significantly associated with infection with bacterial pathogens ($p<0.001$, $p=0.04$, $p=0.03$, $p=0.003$, $p=0.02$, $p=0.03$, $p=0.002$, respectively). The combination of CRP and fecal lactoferrin at their best cut-off values (13.7 mg/L and 22.8 μg/mL, respectively) yielded a sensitivity of 72.2%, and a specificity of 95.5% for bacterial etiology compared with their individual use. The authors concluded blood CRP is a useful diagnostic marker for both fever and bacterial etiology in acute pediatric diarrhea. The combination of CRP and fecal lactoferrin yields better diagnostic capability for bacterial etiology than their use alone for acute diarrhea in children without underlying gastrointestinal disease.

(2011) Chen et al. explored the value of fecal lactoferrin in predicting and monitoring the clinical severity of infectious diarrhea. Patients with acute infectious diarrhea ranging from 3 mo to 10 years in age were enrolled, and one to three stool samples from each subject were collected. Certain parameters, including white blood cells /differential count, C-reactive protein, fecal mucus, fecal pus cells, duration of fever, vomiting, diarrhea and severity (indicated by Clark and Vesikari scores), were recorded and analyzed. Fecal lactoferrin was determined by enzyme-linked immunosorbent assay and compared in different pathogen and disease activity. Generalized estimating equations (GEE) were also used for analysis. Data included 226 evaluations for 117 individuals across three different time points. Fecal lactoferrin was higher in patients with Salmonella (11.17 μg/g ± 2.73 μg/g) or Campylobacter (10.32 μg/g ± 2.94 μg/g) infections and lower in patients with rotavirus (2.82 μg/g ± 1.27 μg/g) or norovirus (3.16 μg/g ± 1.18 μg/g) infections. Concentrations of fecal lactoferrin were significantly elevated in patients with severe (11.32 μg/g ± 3.29 μg/g) or moderate (3.77 μg/g ± 2.08 μg/g) disease activity compared with subjects with mild (1.51 μg/g ± 1.36 μg/g) disease activity ($P < 0.05$). GEE analysis suggests that this marker could be used to monitor the severity and course of gastrointestinal infections and may provide information for disease management. This study found that fecal lactoferrin is higher in patients with Salmonella infection or Campylobacter infections but lower in patients with rotavirus infection or norovirus infections. Fecal lactoferrin increased during bacterial infection and with

greater disease severity and may be a good marker for predicting and monitoring intestinal inflammation in children with infectious diarrhea.

**Section Summary: Fecal Lactoferrin**
In conclusion, despite the limitations the results indicate that FL is an inexpensive, simple, stable, and useful screening marker with high specificity and modest sensitivity for differentiating between IBD and functional disorders, appearing to have greater ability to evaluate UC rather than CD. The fecal lactoferrin methods are the first line of techniques that allow non-invasive assessment of IBD. In summary, FL will never fully replace colonoscopy and radiology, which are necessary to obtain tissue samples and investigate the complications of IBD. However, in a society where patient satisfaction, risk minimization, cost reduction, and hospitalization avoidance are a priority, these non-invasive, inexpensive, reproducible, and clinically significant measurements are likely to have a greater role in our future diagnostic and therapeutic pathways. In order to decrease the misdiagnosis rate, the FL could be used in conjunction with other parameters (FC or blood inflammatory markers) to determine the subset of patients who have active disease or who may require a step up in therapy.

**mRNA, Gene Expression Profiling Panel Testing (e.g., PredictSURE IBD)**
**mRNA (e.g., PredictSURE)**
(2019) Biasci et al. reported they have previously described a prognostic transcriptional signature in CD8 T cells that separates patients with IBD into two phenotypically distinct subgroups, termed IBD1 and IBD2. Here they sought to develop a blood-based test that could identify these subgroups without cell separation, and thus be suitable for clinical use in Crohn's disease (CD) and ulcerative colitis (UC). Design Patients with active IBD were recruited before treatment. Transcriptomic analyses were performed on purified CD8 T cells and/or whole blood. Phenotype data were collected prospectively. IBD1/IBD2 patient subgroups were identified by consensus clustering of CD8 T cell transcriptomes. In a training cohort, machine learning was used to identify groups of genes ('classifiers') whose differential expression in whole blood recreated the IBD1/IBD2 subgroups. Genes from the best classifiers were quantitative (q)PCR 21ptimized, and further machine learning was used to identify the optimal qPCR classifier, which was locked down for further testing. Independent validation was sought in separate cohorts of patients with CD (n=66) and UC (n=57). Results in both validation cohorts, 17-gene qPCRbased classifier stratified patients into two distinct subgroups. Irrespective of the underlying diagnosis, IBDhi patients (analogous to the poor prognosis IBD1 subgroup) experienced significantly more aggressive disease than IBDlo patients (analogous to IBD2), with earlier need for treatment escalation (hazard ratio=2.65 (CD), 3.12 (UC)) and more escalations over time (for multiple escalations within 18 months: sensitivity=72.7% (CD), 100% (UC); negative predictive value=90.9% (CD), 100% (UC)).

There are several limitations of this work. First, the study was non-interventional, and all patients were assessed and treated at the discretion of their gastroenterologists in accordance with national and international guidelines, rather than following a formal

protocol. This, however, represents real-world practice and is the setting in which the test will ultimately be used. Second, because patients were recruited before induction therapy, they do not yet know how the biomarker would perform if treatment had already been started. Nonetheless, if induction therapy was underway, the biomarker could still be used if/when patients next re-flare, since the CD8 T cell signature is readily detectable during active disease. Clarifying the effect of concomitant therapy is the subject of ongoing work. Third, while the performance characteristics of this assay meet the requirements of a useful prognostic biomarker, we have not yet conducted an interventional study to confirm that stratifying therapy using this biomarker would improve clinical outcomes. For this reason, we have concurrently designed a biomarker-stratified trial to test whether this assay can deliver personalized therapy from diagnosis. This trial (Predicting outcomes for Crohn's Disease using a molecular biomarker; www.crohnsprofiletrial.com) is currently recruiting in the UK and represents one of the first biomarker-stratified trials in any inflammatory disease. It will assess the relative benefit of 'Top Down' therapy (anti-TNFα and an immunomodulator) over 'Accelerated Step-Up' therapy in IBDhi and IBDlo patients to determine whether the biomarker can accurately match patients to the most appropriate treatment for them, thereby improving outcomes by optimizing disease control and minimizing drug toxicity. This is the first validated prognostic biomarker that can predict prognosis in newly diagnosed patients with IBD and represents a step towards personalized therapy.

mRNA, gene expression profiling panel testing for the diagnosis and ongoing management of IBD is unproven at this time.

**Serum/Bio Markers**

(2020) Porter et al. reported there are currently, two coprimary end points are used by health authorities to determine the effectiveness of therapeutic interventions in patients with CD: symptomatic remission (PRO assessment) and endoscopic remission by ileocolonoscopy (ICS). It is universally accepted that there is a need for minimally invasive monitoring of IBD patient enrichment and stratification and efficacy of treatments. The CDBpC was formed with members from industry, academia, and nonprofit organizations, with support from the Helmsley Charitable Trust, to evaluate the CD minimally invasive biomarker landscape and determine which biomarkers were ready for regulatory qualification. This team identified the primary drug development need as minimally invasive, fluid-based biomarkers that could be measured serially during clinical trials to monitor patient response to therapies. The preconsortium work also identified 2 regulatory ready biomarkers for CD, FC, and CRP, for which clinical data are available to support the biomarker for a specific COU. Furthermore, a list of exploratory biomarkers of interest was also identified, and the team suggested including UC in future biomarker work. The ultimate purpose of the CDBpC was to plan for the launch of a larger consortium (IBD-RSC) dedicated to IBD biomarker regulatory qualification to ensure that these biomarkers are available to drug developers for a specific COU. The IBD-RSC will pursue exploratory IBD biomarkers through sharing of knowledge and data, generation and/or sharing of biological samples, and assay development for novel biomarkers to evaluate interest in regulatory endorsement of FC and CRP utilizing

existing data. Exploratory biomarkers of interest include inflammatory markers, and markers of microbiota dysfunction, and tissue injury and may be a combination of biomarkers or a biomarker panel covering different biological processes involved in the pathogenesis of IBD. Working together with IBD stakeholders, including regulators, and sharing data and information in the precompetitive space will be critical to developing new tools to support drug development and potentially patient care for patients with IBD.

(2018) Berinstein et al. evaluated 367 adults who had an SGI panel drawn between January 1, 2011, and December 31, 2015, at the University of Michigan Health System. Of the 367 patients evaluated, 64.3% were female with a mean age of 49.3 years. Mean follow-up duration was 622.8 days.

They found only 80.7% of patients had gastrointestinal symptoms at the time the test was obtained, with the others being obtained as work-up for IBD-associated conditions such as seronegative spondyloarthropathies, suppurative hidradenitis, or dermatological complaints. Only 61.6% of the ordering providers were gastroenterologists (GI), with rheumatologists representing the largest non-GI group at 24.5% (Fig. 1). The test was obtained as a screening test (before endoscopy) in 43.9% of cases, and despite having a negative result, 41.4% of these later underwent endoscopy. Forty-one percent of the patients who had an SGI panel ordered by a non-GI provider never underwent endoscopy (compared to 11.1% of patients who had the test ordered by a GI provider).
While the components of the SGI panel have demonstrated value in the prognostication of future disease severity or phenotype, we do not believe there is a role for this test as screening for IBD. Based on the results, it appears that non-gastroenterologists are increasingly using the test for this purpose. It does not appear that providers place a great deal of faith in the results, since almost half undergo an endoscopy even in the case of a negative test. In instances when the test was negative, further evaluation was deferred, possibly missing cases of IBD. In instances when the test was positive, the patient underwent an endoscopy regardless to confirm the test result. These tests are expensive, especially considering that an endoscopy will likely be performed to confirm the test. Our findings suggest that increased education is needed for both gastroenterologists and non-gastroenterologists regarding the appropriate use and timing of this test.

**NOD2/CARD15 Genotyping**
(2013) Kovacs and associates stated mannose-binding lectin (MBL) is a pattern-recognition molecule of the innate immune system and may be involved in the pathogenesis of IBD. These researchers evaluated the prevalence of MBL deficiency in a cohort of patients with pediatric-onset IBD and examined if it is associated with the clinical manifestations, serum antibody formation, or genetic factors. This prospective study included 159 pediatric patients (mean age of 14.0 years) with IBD (107 patients with CD and 52 patients with UC). Furthermore, 95 controls were investigated. Serum samples were determined for MBL by ELISA and for serologic markers (ASCA and pANCA) by indirect immunofluorescent assay. NOD2/CARD15 variants were tested by PCR/restriction fragment length polymorphism. The MBL serum concentration was significantly lower in IBD patients (both with CD and UC) compared to controls (IBD, p

= 0.007; CD, p = 0.04; UC, p = 0.004). Prevalence of low MBL level (less than 500 ng/ml) was significantly higher in both CD and UC groups compared to controls (p = 0.002 and p = 0.006). Furthermore, low MBL level was associated with isolated ileal involvement (p = 0.01) and MBL deficiency (less than 100 ng/ml) with male gender (p = 0.004) in patients with CD. The authors concluded these findings suggested low MBL associated with pediatric-onset IBD and ileal CD may be considered an additional marker of the IBD pathogenesis. These investigators failed to confirm any correlation between MBL deficiency and serum autoantibodies or NOD2/CARD15 variants

(2011) Adler et al. noted that CD is often purely inflammatory at presentation, but most patients develop strictures and fistulae over time (complicated disease). Many studies have suggested that nucleotide-binding oligomerization domain 2 (NOD2) mutations are associated with a varying but increased risk of complicated disease. An accurate and sufficiently powerful predictor of complicated disease could justify the early use of biological therapy in high-risk individuals. These researchers performed a systematic review and meta-analysis to obtain accurate estimates of the predictive power of the identified mutations (such as p.R702W, P.G908R, and p.Leu1007fsX1008) in NOD2 for the risk of complicated disease. An electronic search of MEDLINE, Embase, and Web of Science identified 917 relevant papers. Inclusion required specification of genetic mutations at the individual level and disease phenotypes by Vienna classification (inflammatory (B1), stricturing (B2), and fistulizing (B3)). A total of 49 studies met these criteria, which included 8,893 subjects, 2,897 of whom had NOD2 mutations. Studies were weighted by median disease duration. Studies not providing duration data were weighted at the level of the study with the shortest disease duration (3.9 years). The relative risk (RR) of the presence of any NOD2 mutant allele for complicated disease (B2 or B3) was 1.17 (95 % confidence interval (95 % CI): 1.10 to 1.24; p < 0.001). P.G908R was associated with an RR of complicated disease of 1.33 (95 % CI: 1.11 to 1.60; p = 0.002). NOD2 did not predict peri-anal disease (p = 0.4). The RR of surgery was 1.58 (95 % CI: 1.38 to 1.80; p < 0.001). There was substantial heterogeneity across all studies (I(2) = 66.7 %). On the basis of logistic regression of these data, the sensitivity of any mutation in predicting complicated disease was 36 % and specificity was 73 %, with the area under the receiver operating characteristic curve 0.56. The authors concluded that the presence of a single NOD2 mutation predicted an 8 % increase in the risk for complicated disease (B2 or B3), and a 41 % increase with 2 mutations. Surgery risk is increased by 58 % with any NOD2 mutation, whereas peri-anal disease was unchanged. The predictive power associated with a single NOD2 mutation is weak. The RR of any NOD2 mutations for complicated disease was only 17 % across 36 studies. However, the presence of two NOD2 mutations had 98 % specificity for complicated disease. These data provide insufficient evidence to support top-down therapy based solely on single NOD2 mutations but suggest that targeted early-intensive therapy for high-risk patients with two NOD2 mutations might be beneficial, if prospective trials can demonstrate changes in the natural history in this subset of patients.

NOD2/CARD15 genotyping for Crohn's Disease, as the analytical validity of NOD2 genotyping has not been identified. In addition, no data regarding the impact of NOD2 gene status on the health outcome of patients were identified.

**Summary of Evidence**
Assessment of a diagnostic technology typically focuses on three parameters: 1) its technical performance; 2) diagnostic performance (sensitivity, specificity, and positive and negative predictive value) in appropriate patients; and 3) demonstration that the diagnostic information can be used to improve patient outcomes (clinical utility).

Technical performance of a device is normally assessed with two types of studies, those that compare test measurements with a gold standard, and those that compare results taken with the same device on different occasions (test-retest).

Diagnostic performance is evaluated by the ability of a test to accurately diagnose a clinical condition in comparison with the gold standard. The sensitivity of a test on the ability to detect a disease when the condition is present (true positive), while specificity indicates the ability to detect patients who suspected of disease but who do not have the condition (true negative). Evaluation of diagnostic performance, therefore, requires independent assessment by the 2 methods in a population of patients who are suspected of disease but who do not all have the disease.

Evidence related to improvement of clinical outcomes with use of this testing assesses the data linking use of a test to changes in health outcomes (clinical utility). While in some cases, tests can be evaluated adequately using technical and diagnostic performance, when a test identifies a new or different group of patients with a disease randomized trials are needed to demonstrate impact of the test on net health outcomes.

In summary, numerous studies have evaluated the ability of fecal calprotectin and fecal lactoferrin testing to distinguish between patients with inflammatory bowel disease and non-inflammatory bowel disease, the FDA-approved indication for the fecal calprotectin and lactoferrin test. Generally, studies have shown that the fecal calprotectin and lactoferrin test is reasonably accurate for this purpose when used in an appropriate patient population; that is, patients with clinical suspicion of inflammatory bowel disease based on examination and history. Specifically, in the scenario where an endoscopy is planned and could possibly be avoided based on calprotectin testing results. The evidence is sufficient to determine that the technology results in an approvement in the net health outcomes.

Monitoring fecal calprotectin and fecal lactoferrin testing to distinguish between patients with inflammatory bowel disease and non-inflammatory bowel disease,

The American Gastroenterological Association Institute (AGA) recommends the following:

- In patients presenting with chronic diarrhea, the use of either fecal calprotectin or fecal lactoferrin to screen for IBD is suggested.
- Clinicians may consider serial calprotectin monitoring to facilitate anticipatory management.
- In those with mild symptoms, serial calprotectin monitoring at three to six months intervals may be appropriate to facilitate early recognition with treatment of impending disease flares.

The American College of Gastroenterology (ACG) recommends the following:

- There are studies exploring fecal lactoferrin, FC, and, more recently, fecal immunohistochemical tests of hemoglobin. In general, these fecal markers are better tools in UC than in CD, and the attractiveness of them is that they offer less invasive and less resource-intense ways to serially assess disease activity. The most data exist for fecal calprotectin.

Based on the current society guidelines from the American Gastroenterological Association Institute (AGA) and the American College of Gastroenterology (ACG) their recommendation includes the fecal calprotectin and fecal lactoferrin in the treatment management of UC and CD, the evidence is sufficient to determine that the technology results in an approvement in the net health outcomes.

The effectiveness of serological testing cannot be established by review of the available published literature or recommended by national guidelines. Currently the decreased diagnostic value and decreased sensitivity compared with conventional testing are factors that contribute to the use to diagnose inflammatory bowel disease, to distinguish ulcerative colitis from Crohn's disease, and for all other indications not being established. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

**Professional Guidelines and Position Statements**

**American College of Gastroenterology (ACG)**

(2019) The ACG released a Clinical Guideline: Ulcerative colitis in adults which stated:

- Fecal calprotectin (FC) can be used in patients with UC as a noninvasive marker of disease activity and to assess response to therapy and relapse.
- There are studies exploring fecal lactoferrin, FC, and, more recently, fecal immunohistochemical tests of hemoglobin. In general, these fecal markers are better tools in UC than in CD, and the attractiveness of them is that they offer less invasive and less resource-intense ways to serially assess disease activity. The most data exist for fecal calprotectin. (*Accessed October 2022*)

(2018) The ACG published guidelines on the management of Crohn’s disease in adults

- The College gave a strong recommendation based on a moderate level of evidence that fecal calprotectin is a helpful test that should be considered to differentiate the presence of IBD from IBS.
- A summary statement without a recommendation indicated that fecal calprotectin measurements may have an adjunctive role in monitoring disease activity.
- Genetic testing is not indicated to establish the diagnosis of Crohn's disease.
    - Certain genetic variants are associated with different phenotypic expressions in Crohn's disease, but testing remains a research tool at this time. (*Accessed October 2022*)

**American Gastroenterological Association Institute (AGA)**
(2019) the AGA published a Clinical Practice Guidelines on the Laboratory Evaluation of Functional Diarrhea and Diarrhea-Predominant Irritable Bowel Syndrome in Adults (IBS-D) states:

- In patients presenting with chronic diarrhea, the AGA suggests the use of either fecal calprotectin or fecal lactoferrin to screen for IBD. Conditional recommendation; low-quality evidence.
    - Comment: A threshold value of 50 mg/g for fecal calprotectin is recommended to optimize sensitivity for IBD. Threshold values in the range of 4.0–7.25 mg/g for fecal lactoferrin are recommended to optimize sensitivity.
- In patients presenting with chronic diarrhea, the AGA makes no recommendation for the use of currently available serologic tests for diagnosis of IBS. No recommendation; knowledge gap. (*Accessed October 2022*)

(2018) The AGA published guidance on functional gastrointestinal symptoms in patients with inflammatory bowel disease:

- A stepwise approach to rule-out ongoing inflammatory activity should be followed in IBD patients with persistent GI symptoms (measurement of fecal calprotectin, endoscopy with biopsy, cross-sectional imaging).
- In those patients with indeterminate fecal calprotectin levels and mild symptoms, clinicians may consider serial calprotectin monitoring to facilitate anticipatory management.
- In those with mild symptoms, serial calprotectin monitoring at three to six months intervals may be appropriate to facilitate early recognition with treatment of impending disease flares.
- If a flare is suspected, endoscopy with biopsies and/or dedicated imaging of the small bowel in CD patients should be considered. As previously mentioned, the potential for persistent histological and/or transmural inflammation even with endoscopic evidence of mucosal healing cannot go unnoticed. The role of histology and cross-sectional imaging as a therapeutic target requires further study, particularly as they may reflect inflammatory mechanisms driving refractory symptoms or leading to clinical relapse. (*Accessed October 2022*)

**The European Crohn's and Colitis Organization (ECCO) and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR)**

(2018) ECCO-ESGAR published a joint guideline for the diagnostic assessment in IBD which stated:

- …*genetic* and serological testing is not recommended for the routine diagnosis of CD or UC.
- Additionally in guidelines prepared jointly by ECCO and ESGAR they also state that patients whose UC responds to medical treatment should be assessed for mucosal healing with endoscopic examination or FC testing approximately 3 to 6 months after the start of therapy (*Accessed October 2022*)

**National Institute for Health and Care Excellence (NICE)**

(2019) **PredictSure-IBD for Inflammatory Bowel Disease Prognosis**

- The technology described in this briefing is PredictSure-IBD. It is used as a prognostic tool to identify patients who will go on to have severe, relapsing Crohn's disease and ulcerative colitis and who might benefit from early aggressive (biological) therapy. The innovative aspect is that it is designed to predict clinical prognosis when Crohn's disease or ulcerative colitis are diagnosed, using a combination of existing assays based on polymerase chain reaction technology.
- The intended place in therapy would be to help the gastroenterologist's choice of treatment for people who have been recently diagnosed with Crohn's disease or ulcerative colitis.
- The main points from the evidence summarized in this briefing are from 2 biochemical studies and 1 prospective cohort study with 248 adult patients in a UK NHS secondary care outpatient setting. They show that PredictSure-IBD can accurately show which patients are likely to have severe relapsing disease. Evidence suggests an improved disease response when treatment with tumor necrosis factor (TNF) inhibitors is started early.
- Key uncertainties around the evidence or technology are that the test has only been validated in biochemical studies.
- The cost of PredictSure-IBD is 1, 250 per unit (exclusive of VAT). The resource impact could be much lower than the current standard of care if starting anti-TNF therapy early leads to disease remission and prevents disease flare-ups, but this is uncertain because it depends on the positive predictive value of the test, which is not yet determined**.**

**Recommendations were provided in the faecal calprotectin diagnostic tests for inflammatory diseases of the bowel NICE guideline as follows:**

- (2013) Fecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS) in adults with recent onset lower gastrointestinal symptoms for whom specialist assessment is being considered, if:
    - cancer is not suspected, having considered the risk factors (for example, age)

    - appropriate quality assurance processes and locally agreed care pathways are in place for the testing
- Fecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of IBD or non-IBD (including IBS) in children with suspected IBD who have been referred for specialist assessment, if:
    - appropriate quality assurance processes and locally agreed care pathways are in place for the testing
- Several technologies that measure the level of calprotectin in stool samples (fecal calprotectin) were evaluated, including fully quantitative laboratory-based tests, fully quantitative rapid tests and semi-quantitative point-of-care tests. Fecal calprotectin is excreted in excess into the intestinal lumen during the inflammatory process and so can act as a marker for inflammatory diseases of the lower gastrointestinal tract. The tests are intended to help distinguish between inflammatory bowel diseases and non-inflammatory bowel diseases.

  In summary, reviews conducted recently (published in 2010 or later) and judged to be medium or high quality by the External Assessment Group concluded that fecal calprotectin testing is a useful tool. For example, the Centre for Evidence-based Purchasing (2010) review focusing on fecal calprotectin for distinguishing between IBS and IBD concluded that fecal calprotectin performs well in distinguishing organic bowel disease from functional bowel disease (organic disease includes IBD and functional disease includes IBS). Sensitivity and specificity were over 80% in most of these studies (at a 50 micrograms/g cut-off) and, when calculated, most positive and negative predictive values were 70–90%. (*Accessed October 2022*)

**Regulatory Status**
Below are some of the identified gastrointestinal tests which have been reviewed by the U.S. Food and Drug Administration (FDA) or the Clinical Laboratory Improvement Amendments (CLIA). (*Please note, this is not an all-inclusive list*)

- Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory developed tests must meet the general regulatory standards. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing.

| Test | Manufacturer | Description |
|---|---|---|
| **CalApp®** | BÜHLMANN | The CalApp® turns your smartphone into a test cassette reader and is reported directly to the patient's gastroenterologist. |
| **CalFast** | Eurospital | This is a point of care calprotectin test with results in as little as 20 minutes. |

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| **CalPrest® / CalPrest®NG** | Eurospital SpA | According to the FDA summary, CalPrest "is identical" to the PhiCal™ test "in that they are manufactured by Eurospital S.p.A. Trieste, Italy. Compared with CalPrest®, the "differences in CalPrest® NG include the name of the test on the labels, detection antibody, the use of a Horse-radish peroxidase /TMB conjugate/substrate system, the provided Stop solution, the concentration of calibrators and controls in the kit and the dynamic range of the assay." |
| **Calprotectin Chemiluminescence ELISA test** | ALPCO | According to ALPCO its new Calprotectin Chemi ELISA exhibits a clinical specificity of 95.1% and provides the lowest false positive rate of any currently cleared *calprotectin* test without sacrificing clinical sensitivity. In addition, the ALPCO Chemi Calprotectin ELISA is capable of quantifying calprotectin levels between 7.9 – 6,000 µg/g from the primary dilution. This range is 1.7 – 25 times broader than the predicate devices on the market. |
| **Crohn's Prognostic** | PROMETHEUS® | According to PROMETHEUS® Crohn's Prognostic combines serologic and genetic markers in an innovative blood test that quantifies a patient's individual probability of developing disease complications over time. Serologic markers include ASCA IgA, ASCA IgG and priority markers anti-CBir1, anti-I2, anti-OMPC, and DNAse sensitive pANCA. Genetic markers include NOD2 variants (SNPS 8, 12, 13). The objective information from Crohn's Prognostic may allow physicians to stratify patients, assist in optimizing management strategies and assist with risk/benefit healthcare provider/patient discussions. |
| **IBDoc®** | BÜHLMANN | According to the manufacturer, IBDoc™, is an easy-to-use tool for patients to perform the *calprotectin stool test* without leaving their *home.* After the collection of a stool sample with a novel stool extraction device, CALEX®, a measured amount of stool |

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| | | extract is applied onto a calprotectin test cassette and the result is read with the help of a smart phone application. The results are displayed in a traffic light code as well as fully quantitative values. The results are immediately sent via the internet and stored in a web-based patient file, accessible to the patient, the supervising clinician, and health care professionals. |
| **IBD sgi Diagnostic** | PROMETHEUS® | IBD sgi Diagnostic is a panel of 17 serologic (n=8), genetic (n=4), and inflammatory biomarkers (n=5). A proprietary algorithm produces an IBD score; results are reported as consistent with IBD (consistent with ulcerative colitis, consistent with CD, or inconclusive for UC vs CD) or not consistent with IBD. The test is intended for use in patients with clinical suspicion of IBD. |
| **IBSchek®** | Commonwealth Diagnostics International | According to the manufacturer, IBSchek® Capillary Kit is is a diagnostic blood test designed to help patients and physicians quickly diagnose diarrhea-predominant or mixed-symptom IBS (IBS-D/M). Symptoms of this chronic ailment often occur following an incident of acute gastroenteritis (food poisoning). IBSchek is available with direct patient access with results in just a few days. It was clinically validated in 2015 and revalidated internationally and is available in the USA. |
| **IBS-Smart™** | Gemelli Biotech | Gemelli Biotech reports ibs-smart measures the levels of two validated IBS biomarkers, anti-CdtB and anti-vinculin. These biomarkers are elevated in a majority of IBS patients with diarrheal symptoms and can diagnose diarrhea-predominant or mixed-type IBS (IBS-D or IBS-M). These biomarkers are not commonly elevated in patients with constipation-predominant IBS (IBS-C). Only a licensed physician can order ibs-smart and diagnose IBS. |

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|---|---|---|
| **PredictSURE IBD** | Predict Immune | Predict Immune reports, PredictSURE IBD is a prognostic blood test for adults (16 years and older) with either Crohn's disease or ulcerative colitis, including newly diagnosed patients. The test uses *RNA* from whole blood to generate gene expression data that stratifies patients into high- and low-risk sub-groups, which reflect the likelihood of them experiencing a frequently relapsing disease course.<br><br>*This is currently available in the UK and Europe but recruiting for patients under a U.S. Study.* |
| **PhiCal™** | Genova Diagnostics | PhiCal™ is indicated to aid in the diagnosis of inflammatory bowel disease and to differentiate IBD from irritable bowel syndrome (IBS) by using a quantitative ELISA test for measuring concentrations of fecal calprotectin in fecal stool; it is intended to be used in conjunction with other diagnostic testing and clinical considerations. |
| **Prometheus© IBD Serology 7** | PROMETHEUS® | The Prometheus© IBD Serology is a quantitative analysis of biomarkers for IBD prediction and differentiation. Prometheus© IBD Serology 7 is only offered at Prometheus©. This system uses a 2-step process to diagnose IBD and to differentiate between ulcerative colitis and Crohn's disease. The first step is a panel of 4 markers intended to maximize the sensitivity and negative predictive value of the test. Patients who test positive on the initial screen are further analyzed by a set of proprietary markers and enzyme reagents to distinguish between true positive results and artifacts of fixation. In this way, the Prometheus© system is intended to increase the specificity of the test compared to other laboratories. |

*Note: Multiple laboratory tests, some general and some proprietary, have been utilized for the diagnosis and ongoing management of irritable bowel disease. Many individual tests do not require FDA approval for laboratory practices.*

*Rapid fecal calprotectin tests that can be used in the home or physician's office are commercially available in Europe and Canada (e.g., Calprosmart, Calpro AS, Norway; Quantum Blue Calprotectin, Bühlmann Laboratories, Switzerland). Rapid tests have not been approved for use in the United States.*

# PRIOR APPROVAL

Not applicable.

# POLICY

**Fecal Calprotectin**

Fecal measurement of calprotectin may be considered **medically necessary** in **one of the following**:

- Establishing the diagnosis Crohn's Disease; **or**
- Establishing the diagnosis ulcerative colitis (UC); **or**
- To assess the response to therapy and/or relapse in Crohn's disease; **or**
- To assess the response to therapy and/or relapse in ulcerative colitis (UC)

Fecal measurement of calprotectin is considered **not medically necessary** including but not limited to the following:

- When the above criteria are not met
- Fecal calprotectin utilized in colorectal cancer screening

**Fecal Lactoferrin**

Fecal measurement of lactoferrin may be considered **medically necessary** in **one of the following**:

- Establishing the diagnosis Crohn's disease; **or**
- Establishing the diagnosis ulcerative colitis (UC); **or**
- To assess the response to therapy and/or relapse in Crohn's disease; **or**
- To assess the response to therapy and/or relapse in ulcerative colitis (UC)

Fecal measurement of lactoferrin is considered **not medically necessary** including but not limited to the following:

- When *not* used in decision making or diagnosis for Crohn's disease as indicated above
- When *not* used in decision making or diagnosis for ulcerative colitis (UC) as indicated above

**Investigational**

Tests for inflammatory bowel disease (IBD) including but not limited to the following are considered **investigational** because the evidence is insufficient in determining the net health outcomes:

- Crohn's Prognostic
- Fecal calprotectin testing in the home environment (e.g., IBDoc)

- Fecal lactoferrin testing including for the evaluation of infectious diarrhea and clostridium difficile infection
- IBD Sgi Diagnostic™
- IBSchek®
- IBS-Smart™
- mRNA (e.g., PredictSURE IBD)
- NOD2/ CARD15 genotyping/genetic testing
- Prometheus IBD Serology 7

# Policy Guidelines

- A fecal calprotectin level of less than 50 µg/g is suggestive of a low likelihood of inflammatory bowel disease.
- A fecal lactoferrin with a threshold value in the range of 4.0–7.25 mg/g is recommended to optimize sensitivity.

# PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 83993 Calprotectin, fecal
- 83630 Lactoferrin, fecal; qualitative
- 83631 Lactoferrin, fecal; quantitative
- 81479 Unlisted molecular pathology procedure (*May be utilized for Crohn's Prognostic, IBDoc, IBD Sgi Diagnostic, NOD2/ CARD15 genotyping/ genetic testing, Prometheus IBD Serology 7)*
- 0164U Gastroenterology (irritable bowel syndrome [IBS]), immunoassay for anti-CdtB and anti-vinculin antibodies, utilizing plasma, algorithm for elevated or not elevated qualitative results (*May be utilized for IBS-Smart*)
- 0176U Cytolethal distending toxin B (CdtB) and vinculin IgG antibodies by immunoassay (i.e., ELISA) (*May be utilized for IBSchek)*
- 0203U Autoimmune (inflammatory bowel disease), mRNA, gene expression profiling by quantitative RT-PCR, 17 genes (15 target and 2 reference genes), whole blood, reported as a continuous risk score and classification of inflammatory bowel disease aggressiveness (*May be utilized for mRNA (e.g., PredictSURE IBD*))

# SELECTED REFERENCES


- United States Food and Drug Administration (FDA). PhiCal 510(k) Substantial Equivalence Determination Decision Summary. Available at: http://www.accessdata.fda.gov/cdrh_docs/reviews/K050007.pdf
- van Rheenen PF, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis. BMJ 2010; 341:c3369.

- von Roon AC, Karamountzos L, Purkayastha S et al. Diagnostic precision of fecal calprotectin for inflammatory bowel disease and colorectal malignancy. Am J Gastroenterol 2007; 102(4):803-13.
- Otten CM, Kok L, Witteman BJ et al. Diagnostic performance of rapid tests for detection of fecal calprotectin and lactoferrin and their ability to discriminate inflammatory from irritable bowel syndrome. Clin Chem Lab Med 2008; 46(9):1275-80. PMID 18597588
- Schroder O, Naumann M, Shastri Y et al. Prospective evaluation of faecal neutrophil-derived proteins in identifying intestinal inflammation: combination of parameters does not improve diagnostic accuracy of calprotectin. Aliment Pharmacol Ther 2007; 26(7):1035-42.
- Sidler MA, Leach ST, Day AS. Fecal S100A12 and fecal calprotectin as noninvasive markers for inflammatory bowel disease in children. Inflamm Bowel Dis 2008; 14(3):359-66.
- Ashorn S, Honkanen T, Kolho KL et al. Fecal calprotectin levels and serological responses to microbial antigens among children and adolescents with inflammatory bowel disease. Imflamm Bowel Dis 2009; 15(2):199-205.
- Turner D, Leach ST, Mack D et al. Faecal calprotectin, lactoferrin, M2-pyruvate kinase and S100A12 in severe ulcerative colitis: a prospective multicentre comparison predicting outcomes and monitoring response. Gut 2010; 59(9):1207-12.
- Wagner M, Peterson CG, Ridefelt P et al. Fecal markers of inflammation used as surrogate markers for treatment outcome in relapsing inflammatory bowel disease. World J Gastroenterol 2008; 14(36):5584-9; discussion 88.
- Costa F, Mumolo MG, Ceccarelli L et al. Calprotectin is a stronger predictive marker of relapse in ulcerative colitis than in Crohn's disease. Gut 2005; 54(3):364-8.
- Gisbert JP, Bermejo F, Perez-Calle JL et al. Fecal calprotectin and lactoferrin for the prediction of inflammatory bowel disease relapse. Inflamm Bowel Dis 2009; 15(8):1190-8.
- Garcia-Sanchez V, Iglesias-Flores E, Gonzales R et al. Does fecal calprotectin predict relapse in patients with Crohn's disease and ulcerative colitis? J Crohns Colitis 2010; 4(2):144-52.
- Kallel L, Ayadi I, Matri S et al. Fecal calprotectin is a predictive marker of relapse in Crohn's disease involving the colon: a prospective study. Eur J Gastroenterol Hepatol 2010; 22(3):340-5.
- Orlando A, Modesto I, Castiglione F et al. The role of calprotectin in predicting endoscopic post-surgical recurrence in asymptomatic Crohn's disease: a comparison with ultrasound. Eur Rev Med Pharmacol Sci 2006; 10(1):17-22.
- Scarpa M, D'Inca R, Basso D et al. Fecal lactoferrin and calprotectin after ileocolonic resection for Crohn's disease. Dis Colon Rectum 2007; 50(6):861-9.
- Jellema P, van Tulder MW, van der Horst HE, et al. Inflammatory bowel disease: a systematic review on the value of diagnostic testing in primary care. Colorectal Dis. 2011 Mar;13(3):239-54.

- Laharie D, Mesli S, El Hajbi F, et al. Prediction of Crohn's disease relapse with faecal calprotectin in infliximab responders: a prospective study. Aliment Pharmacol Ther. 2011 Aug;34(4):462-9.
- Gastroenterol Hepatol. 2013 Feb 19. pii: S0210-5705(13)00004-6. doi: 10.1016/j.gastrohep.2012.10.008. [Epub ahead of print,]
- Mao, R., Xiao, Y.-l., Gao, X., Chen, B.-l., He, Y., Yang, L., Hu, P.-j. and Chen, M.-h. (2012), Fecal calprotectin in predicting relapse of inflammatory bowel diseases: A meta-analysis of prospective studies. Inflamm Bowel Dis, 18: 1894–1899. doi: 10.1002/ibd.22861
- Higuchi LM and Bousvaros A. Clinical features and diagnosis of inflammatory bowel disease in children and adolescents. Waltham, MA : Wolters Kluwer Health; 2013. Available at: http://www.uptodate.com.
- National Institute for Health and Care Excellence (NICE). Faecal calprotectin diagnosis tests for inflammatory diseases of the bowel. NICE diagnostics guidance 11. London, UK: NICE; 2013. Available at: http://www.nice.org.uk/nicemedia/live/14285/65337/65337.pdf.
- National Institute for Health and Care Excellence (NICE). Irritable bowel syndrome in adults: Diagnosis and management of irritable bowel syndrome in primary care. NICE clinical guideline 61. London, UK: NICE; Feb 2008, updated 2015. http://www.nice.org.uk/guidance/cg61/evidence/full-guidance-196701661
- Menees SB, Powell C, Kurlander J, et al. A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. Am J Gastroenterol. Mar 2015;110(3):444-454. PMID 25732419
- Henderson P, Anderson NH, Wilson DC. The diagnostic accuracy of fecal calprotectin during the investigation of suspected pediatric inflammatory bowel disease: a systematic review and meta-analysis. Am J Gastroenterol. May 2014;109(5):637-645. PMID 23670113
- Khoshbaten M, Pishahang P, Nouri M, et al. Diagnostic value of fecal calprotectin as a screening biomarker for gastrointestinal malignancies. Asian Pac J Cancer Prev. 2014;15(4):1667-70.
- Kennedy NA, Clark A, Walkden A, et al. Clinical utility and diagnostic accuracy of faecal calprotectin for IBD at first presentation to gastroenterology services in adults aged 16-50 years. J Crohns Colitis. Jan 2015;9(1):41-49.
- Gallo A, Gasbarrini A, Passaro G, Landolfi R, Montalto M (2014) Role of Fecal Calprotectin in Monitoring Response to Therapy in Inflammatory Bowel Diseases. J Clin Cell Immunol 5: 252. doi:10.4172/2155-9899.1000252
- Rex DK, Johnson DA, Anderson JC et al. American College of Gastroenterology guidelines for colorectal cancer screening 2008. Am J Gastroenterol 2009; 104:739 – 750; doi: 10.1038/ajg.2009.104; published online 24 February 2009.
- Thomson AI, Lees CW. Genetics of ulcerative colitis. Inflamm Bowel Dis. 2011;17(3):831-848. Zholudev A, Zurakowski D, Young W, et al. Serologic testing with ANCA, ASCA, and anti-OmpC in children and young adults with Crohn's disease and ulcerative colitis: Diagnostic value and correlation with disease phenotype. Am J Gastroenterol. 2004;99(11):2235-2241

- Carrera Silva EA, et al. T cell-derived protein S engages TAM receptor signaling in dendritic cells to control the magnitude of the immune response Immunity. 2013;30:160.
- Wright EK, Kamm MA, De Cruz P et al. Measurement of fecal calprotectin improves monitoring and detection of recurrence of Crohn's disease after surgery. Gastroenterology. 2015 May;148(5):938-947.
- World Gastroenterology Organisation (WGO). World Gastroenterology Organisation Global Guideline: irritable bowel syndrome: a global perspective. September 2016. Available at: http://www.worldgastroenterology.org/guidelines/global-guidelines/irritable-bowel-syndrome-ibs/irritable-bowel-syndrome-ibs-english.
- Qiu Y, Mao R, Chen BL et al. Fecal calprotectin for evaluating postoperative recurrence of Crohn's disease: a meta-analysis of prospective studies. Inflamm Bowel Dis. 2015 Feb;21(2):315-22.
- Menees SB, Powell C, Kurlander J1 et al. A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. Am J Gastroenterol. 2015 Mar;110(3):444-54
- Bressler B, Panaccioni R, Fedorak, RN et al. Clinicians guide to the use of fecal calprotectin to identify and monitor disease activity in inflammatory bowel disease. Canadian Journal of Gastroenterology and Hepatology. Oct 2015, Vol 29, Issue 7: 369-372
- Genova Diagnostics®. GI Effects® Comprehensive Profile - Stool. https://www.gdx.net/product/gi-effects-comprehensive-stool-test.
- Pietzak MM, Schofield TC, McGinniss MJ, et al. Stratifying risk for celiac disease in a large at-risk United States population by using HLA alleles. Clin Gastroenterol Hepatol. Sep 2009;7(9):966-971. PMID 19500688
- Lasson A, Ohman L, Stotzer PO, et al. Pharmacological intervention based on fecal calprotectin levels in patients with ulcerative colitis at high risk of a relapse: A prospective, randomized, controlled study. United European Gastroenterol J. Feb 2015;3(1):72-79. PMID 25653861
- Sandborn W, Binion D, Persley K, et al. AGA Institute Guidelines for the Identification, Assessment and Initial Medical Treatment in Crohn's Disease: Clinical Care Pathway. 2014; http://campaigns.gastro.org/algorithms/IBDCarePathway/index.html.
- Heida A, Park KT, van Rheenen PF. Clinical utility of fecal calprotectin monitoring in asymptomatic patients with inflammatory bowel disease: a systematic review and practical guide. Inflamm Bowel Dis. Jun 2017;23(6):894-902. PMID 28511198
- Wei SC, Tung CC, Weng MT, Wong JM. Experience of patients with inflammatory bowel disease in using a home fecal calprotectin test as an objective reported outcome for self-monitoring. Intest Res. 2018;16(4):546–553. doi:10.5217/ir.2018.00052
- Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. 2018 Apr;113(4):481-517.

- American Gastroenterological Association (AGA). IBD Care Pathway. https://www.ibd.care/care-navigator/aga-care-pathways.
- Kennedy NA, Clark A, Walkden A, et al. Clinical utility and diagnostic accuracy of faecal calprotectin for IBD at first presentation to gastroenterology services in adults aged 16-50 years. J Crohns Colitis. 2015;9(1):41–49. doi:10.1016/j.crohns.2014.07.005
- AGA Clinical Practice Guidelines on the Laboratory Evaluation of Functional Diarrhea and Diarrhea-Predominant Irritable Bowel Syndrome in Adults (IBS-D) Smalley W., Falck-Ytter C., Carrasco-Labra A., Wani S., Lytvyn L., Falck-Ytter Y. (2019) Gastroenterology, 157 (3) , pp. 851-854.
- Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE, et al. American College of Gastroenterology. Management of Crohn's disease in adults. Am J Gastroenterol. 2018 Apr;113(4):481- 517.
- Maaser C, Sturm A, Vavricka SR, , et al. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. J Crohns Colitis. 2019 Feb 1;13(2):144-164.
- Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol. 2019 Mar;114(3):384-413.
- Gastrointestinal Tract Infections. https://www.uib.cat/depart/dba/microbiologia/ADSenfcomI/material_archivos/infeccion%20gastrointestinal.pdf.
- Bintsis T. Foodborne pathogens. AIMS Microbiol. 2017; 3(3): 529-563. PMID 31294175
- Sattar SBA, Singh S. Bacterial Gastroenteritis. [Updated 2019 Mar 8]. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2019 Jan. https://www.ncbi.nlm.nih.gov/books/NBK513295/.
- Burden of Norovirus Illness in the U.S. Centers for Disease Control and Prevention. https://www.cdc.gov/norovirus/trends-outbreaks/burden-US.html. Last reviewed June 1, 2018.
- Centers for Medicare & Medicaid Coverage. Local Coverage Determination (LCD): Foodborne Gastrointestinal Panels Identified by Multiplex Nucleic Acid Amplification (NAATs) (L37709). CMS.gov. https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=37709&ver=13&Date=10%2f31%2f2019&DocID=L37709&bc=iAAAABAAAAAA&. Revised October 31, 2019.
- Beckmann C, Heininger U, Marti H, et al. Gastrointestinal pathogens detected by multiplex nucleic acid amplification testing in stools of pediatric patients and patients returning from the tropics. Infection. Dec 2014; 42(6): 961-70. PMID 25015433
- Borst A, Box AT, Fluit AC. False-positive results and contamination in nucleic acid amplification assays: suggestions for a prevent and destroy strategy. Eur J Clin Microbiol Infect Dis. Apr 2004; 23(4): 289-99. PMID 15015033
- Petryszyn P, Staniak A, Wolosianska A, et al. Faecal calprotectin as a diagnostic marker of inflammatory bowel disease in patients with gastrointestinal symptoms:

meta-analysis. Eur J Gastroenterol Hepatol. Nov 2019; 31(11): 1306-1312. PMID 31464777
- ALPCO. Now available: 510(k) cleared fecal calprotectin ELISA. October 29, 2019.https://www.alpco.com/now-available-510k-cleared-fecal-calprotectin-elisa.
- Colombel JF, Shin A, Gibson PR. AGA Clinical Practice Update on Functional Gastrointestinal Symptoms in Patients With Inflammatory Bowel Disease: Expert Review. Clin Gastroenterol Hepatol. Feb 2019; 17(3): 380-390.e1. PMID 30099108
- Smalley W, Falck-Ytter C, Carrasco-Labra A, et al. Spotlight: Laboratory Evaluation of Functional Diarrhea and Diarrhea-Predominant Irritable Bowel Syndrome in Adults (IBS-D). Gastroenterology. Sep 2019; 157(3): 858. PMID 31377275
- Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. Apr 2018; 113(4): 481-517. PMID 29610508
- Heida A, Park KT, van Rheenen PF. Clinical Utility of Fecal Calprotectin Monitoring in Asymptomatic Patients with Inflammatory Bowel Disease: A Systematic Review and Practical Guide. Inflamm Bowel Dis. Jun 2017; 23(6): 894-902. PMID 28511198
- Lasson A, Ohman L, Stotzer PO, et al. Pharmacological intervention based on fecal calprotectin levels in patients with ulcerative colitis at high risk of a relapse: A prospective, randomized, controlled study. United European Gastroenterol J. Feb 2015; 3(1): 72-9. PMID 2565386
- National Institute for Health and Care Excellence (NICE). Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel [DG11]. 2013; http://guidance.nice.org.uk/DG11
- Yamamoto, Takayuki et al. “Fecal calprotectin and lactoferrin as predictors of relapse in patients with quiescent ulcerative colitis during maintenance therapy.” International journal of colorectal disease vol. 29,4 (2014): 485-91. doi:10.1007/s00384-013-1817-3
- Wang, Yan et al. “Diagnostic accuracy of fecal lactoferrin for inflammatory bowel disease: a meta-analysis.” International journal of clinical and experimental pathology vol. 8,10 12319-32. 1 Oct. 2015
- Rubin, D.T., Ananthakrishnan, A.N., Siegel, C.A., ACG Clinical Guideline: Ulcerative Colitis in Adults Am J Gastroenterol 2019;114:384–413. https://doi.org/10.14309/ajg.0000000000000152; published online February 22, 2019
- Brookes MJ, Whitehead S, Gaya DR, et al. Frontline Gastroenterology 2018;9:87–91.
- BioFire Diagnostics 2021. The BioFire® FilmArray® Gastrointestinal (GI) Panel. https://www.biofiredx.com/products/the-filmarray-panels/filmarraygi/
- BÜHLMANN Laboratories AG. BÜHLMANN launches Home Testing Device for IBD Patients. February 19, 2014. https://www.buhlmannlabs.ch/wp-content/uploads/2015/06/2014-02-19-buehlmann-launches-ibdoc-for-ibd-home-testing-3-.pdf Accessed October 2021

- Moore A.C., Huang V.W., Bourdages R., MD, et al. IBDoc Canadian User Performance Evaluation, Inflammatory Bowel Diseases, Volume 25, Issue 6, June 2019, Pages 1107–1114, https://doi.org/10.1093/ibd/izy357 https://academic.oup.com/ibdjournal/article/25/6/1107/5235633
- Prometheus Laboratories. Prometheus Crohn's Prognostic. Evaluate the probability of disease progression in a Crohn's disease patient by providing a personal serogenetic profile. https://www.prometheuslabs.com/disease-tests/crohns-prognostic/
- Porter A.C., Aubrecht J., Birch C., et al. Biomarkers of Crohn's Disease to Support the Development of New Therapeutic Interventions, Inflammatory Bowel Diseases, Volume 26, Issue 10, October 2020, Pages 1498–1508, https://doi.org/10.1093/ibd/izaa215. https://academic.oup.com/ibdjournal/article/26/10/1498/5896885?login=true
- Adler J, Rangwalla SC, Dwamena BA, Higgins PD. The prognostic power of the NOD2 genotype for complicated Crohn's disease: A meta-analysis. Am J Gastroenterol. 2011;106(4):699-712.52.
- Kovacs M, Papp M, Lakatos PL, et al. Low mannose-binding lectin (MBL) is associated with paediatric inflammatory bowel diseases and ileal involvement in patients with Crohn disease. J Crohns Colitis. 2013;7(2):134-141.
- Berinstein, Jeffrey A et al. "The IBD SGI Diagnostic Test Is Frequently Used by Non-gastroenterologists to Screen for Inflammatory Bowel Disease." Inflammatory bowel diseases vol. 24,5 (2018): e18. doi:10.1093/ibd/izy140
- Predict Immune. What is PredictSURE IBD™?. https://www.predictimmune.com/for-clinicians/. Accessed October 2021.
- National Institute for Health and Care Excellence (NICE). PredictSure-IBD for inflammatory bowel disease prognosis. March 25, 2019. Available at https://www.nice.org.uk/advice/mib178/resources/predictsureibd-for-inflammatory-bowel-disease-prognosis-pdf-2285963644281541
- Biasci D, Lee JC, Noor NM, et al. Gut Epub ahead of print: [please include Day Month Year]. doi:10.1136/ gutjnl-2019-318343. Available at https://www.predictimmune.com/wp-content/uploads/2020/09/Biasci-et-al-A-blood-based-prognostic-biomarker-in-IBD-Gut-2019.pdf
- Abraham, Bincy P. "Fecal Lactoferrin Testing." Gastroenterology & hepatology vol. 14,12 (2018): 713-716. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6383158/
- IBSchek® Capillary Collection Kit. Commonwealth Diagnostics International, Inc. The First Clinically Validated Blood Test for Irritable Bowel Syndrome with Predominant Diarrhea (IBS-D) and Mixed Symptoms (IBS-M). Accessed October 21, 2021. Available at https://commdx.com/ibschek-capillary-collection-kit/#:~:text=IBSchek%C2%AE%20Capillary%20Collection%20Kit%20%2D%20Commonwealth%20Diagnostics%20International
- Ibs smart. There's Now a Way to Diagnose IBS With a Simple Blood Test. Accessed October 21, 2021 Available at https://www.ibssmart.com/.

- MedlinePlus NOD2 gene nucleotide binding oligomerization domain containing 2. Normal Function. Accessed October 21, 2021. Available at https://medlineplus.gov/genetics/gene/nod2/#resources
- Hayes, Inc. Evidence Analysis Research. Fecal Calprotectin Assay for Monitoring Postoperative Recurrence of Crohn Disease. Hayes, Inc. Jun 27, 2022
- Hayes, Inc. Health Technology Assessment. Fecal Calprotectin Assay for Monitoring Disease Activity and Treatment Management of Ulcerative Colitis in Adults. Hayes, Inc. August 31, 2022.
- Hayes, Inc. Fecal Calprotectin for Predicting Clinical Relapse or Treatment Response in Adult Patients with Ulcerative Colitis. Health Technology Assessment. Hayes, Inc. September 1, 2022
- Hayes, Inc. Prometheus IBD sgi Diagnostic (Prometheus Laboratories Inc.). Molecular Test Assessment. Hayes, Inc. Nov 4, 2019.
- Bonis P.A., Lamont J.T., Friedman L.S. et al. Approach to the adult with chronic diarrhea in resource-abundant settings. Literature review current through: Aug 2022. Topic last updated: May 02, 2022. Available at: www.uptodate.com
- Gibson P., Talley N.J., Robson K.M., Approach to functional gastrointestinal symptoms in adults with inflammatory bowel disease. Literature review current through: Aug 2022. Topic last updated: Aug 24, 2022. Available at: www.uptodate.com
- Penner R.M., Tandon P., Kane S.V., et al. Management of Crohn disease after surgical resection. Literature review current through: Aug 2022. | This topic last updated: Jun 10, 2021. Available at: www.uptodate.com
- Waugh N, Cummins E, Royle P, et al. Faecal calprotectin testing for differentiating amongst inflammatory and non-inflammatory bowel diseases: systematic review and economic evaluation. Health Technol Assess. Nov 2013; 17(55): xv-xix, 1-211. PMID 24286461
- Schoepfer AM, Trummler M, Seeholzer P, et al. Discriminating IBD from IBS: comparison of the test performance of fecal markers, blood leukocytes, CRP, and IBD antibodies. Inflamm Bowel Dis. Jan 2008; 14(1): 32-9. PMID 17924558
- Basumani P, Bardhan K, Eyre R, et al. Faecal calprotectin: Rotherham experience (unpublished slide presentation). BSG Away; 2012 June 28.
- Li XG, Lu YM, Gu F, et al. [Fecal calprotectin in differential diagnosis of irritable bowel syndrome]. Beijing Da Xue Xue Bao Yi Xue Ban. Jun 18 2006; 38(3): 310-3. PMID 16778979
- El-Badry A, Sedrak H, Rashed L. Faecal calprotectin in differentiating between functional and organic bowel diseases. Arab J Gastroenterol. May 23 2010;11(2):70-73.
- Van de Vijver E, Schreuder AB, Cnossen WR, et al. Safely ruling out inflammatory bowel disease in children and teenagers without referral for endoscopy. Arch Dis Child. Dec 2012; 97(12): 1014-8. PMID 23019289
- Sidler MA, Leach ST, Day AS. Fecal S100A12 and fecal calprotectin as noninvasive markers for inflammatory bowel disease in children. Inflamm Bowel Dis. Mar 2008; 14(3): 359-66. PMID 18050298

- Damms A, Bischoff SC. Validation and clinical significance of a new calprotectin rapid test for the diagnosis of gastrointestinal diseases. Int J Colorectal Dis. Oct 2008; 23(10): 985-92. PMID 18629518
- Henderson P, Casey A, Lawrence SJ, et al. The diagnostic accuracy of fecal calprotectin during the investigation of suspected pediatric inflammatory bowel disease. Am J Gastroenterol. Jun 2012; 107(6): 941-9. PMID 22370604
- Bonnin Tomas A, Vila Vidal M, Rosell Camps A. [Fecal calprotectin as a biomarker to distinguish between organic and functional gastrointestinal disease]. Rev Esp Enferm Dig. Dec 2007; 99(12): 689-93. PMID 18290691
- Fagerberg UL, Loof L, Myrdal U, et al. Colorectal inflammation is well predicted by fecal calprotectin in children with gastrointestinal symptoms. J Pediatr Gastroenterol Nutr. Apr 2005; 40(4): 450-5. PMID 15795593
- Jorgensen LG, Fredholm L, Hyltoft Petersen P, et al. How accurate are clinical activity indices for scoring of disease activity in inflammatory bowel disease (IBD)?. Clin Chem Lab Med. 2005; 43(4): 403-11. PMID 15899657
- Mosli MH, Zou G, Garg SK, et al. C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis. Am J Gastroenterol. Jun 2015; 110(6): 802-19; quiz 820. PMID 25964225
- Ostlund I, Werner M, Karling P. Self-monitoring with home based fecal calprotectin is associated with increased medical treatment. A randomized controlled trial on patients with inflammatory bowel disease. Scand J Gastroenterol. Jan 2021; 56(1): 38-45. PMID 33284639
- Colombel JF, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. Lancet. Dec 23 2017; 390(10114): 2779-2789. PMID 29096949
- Heida A, Park KT, van Rheenen PF. Clinical Utility of Fecal Calprotectin Monitoring in Asymptomatic Patients with Inflammatory Bowel Disease: A Systematic Review and Practical Guide. Inflamm Bowel Dis. Jun 2017; 23(6): 894-902. PMID 28511198
- Ananthakrishnan AN, Nguyen GC, Bernstein CN. AGA Clinical Practice Update on Management of Inflammatory Bowel Disease in Elderly Patients: Expert Review. Gastroenterology. Jan 2021; 160(1): 445-451. PMID 33011177
- Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. Gastroenterology. Apr 2021; 160(5): 1570-1583. PMID 33359090
- National Institute Health Care Excellence (NICE). Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel. NICE website. October 2, 2013.
- Wang H., Deshpande A., Karichu J., et al., Clinical Utility of Fecal Lactoferrin in Determining Infectious Etiology of Diarrhea, *Open Forum Infectious Diseases*, Volume 3, Issue suppl1, December 2016, 210. https://doi.org/10.1093/ofid/ofw172.77

| POLICY HISTORY | | |
|---|---|---|
| **Date** | **Reason** | **Action** |
| October 2022 | Annual Review | Policy Renewal |
| October 2021 | Annual Review | Policy Revised |
| October 2020 | Annual Review | Policy Revised |
| June 2020 | Interim Review | Policy Revised |
| October 2019 | Annual Review | Policy Revised |
| October 2018 | Annual Review | Policy Revised |
| October 2017 | Annual Review | Policy Revised |
| October 2016 | Annual Review | Policy Revised |
| November 2015 | Annual Review | Policy Revised |
| December 2014 | Annual Review | Policy Renewed |
| February 2014 | Annual Review | Policy Renewed |
| March 2013 | Annual Review | Policy Renewed |
| March 2012 | Annual Review | Policy Renewed |
| April 2011 | Literature Review | New Policy |

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

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