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Health Insurance for New Yorkers

Reimbursement Policy

Subject:	Laboratory Testing for the Diagnosis of Inflammatory Bowel Disease		
Policy Number:	PO-RE-058v5		
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I. Policy Description

Inflammatory bowel disease (IBD) is a class of inflammatory bowel disorders comprised of two major disorders: ulcerative colitis and Crohn's disease each with distinct pathologic and clinical characteristics.[1]

Ulcerative colitis (UC) is a chronic inflammatory condition characterized by relapsing and remitting episodes of inflammation limited to the mucosal layer of the colon[2] beginning at the rectum and may extend in a proximal and continuous fashion to involve other parts of the colon.[3]

Crohn's disease (CD) is characterized by patchy transmural inflammation (skip lesions) of the gastrointestinal tract resulting in sinus tracts, and ultimately micro-perforations and fistulae.[2] It may also lead to fibrosis, strictures and to obstructive clinical presentations that are not typically seen in ulcerative colitis.[4,5]

Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

1. Fecal calprotectin **or** fecal lactoferrin testing (see Note 1) **MEETS COVERAGE CRITERIA** for any of the following situations:
   a. For the differential diagnosis between non-inflammatory gastrointestinal disease (e.g., IBS) and inflammatory gastrointestinal disease (e.g., IBD).
   b. To monitor individuals with IBD (e.g., assess for response to therapy or relapse).

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

2. For all other situations not described above, fecal calprotectin and fecal lactoferrin testing **DOES NOT MEET COVERAGE CRITERIA.**
3. For the workup and monitoring of individuals with inflammatory bowel disease (IBD), the use of serologic markers (e.g., anti-neutrophil cytoplasmic antibody [ANCA]; perinuclear ANCA; anti-*Saccharomyces cerevisiae* antibody; antibody to Escherichia coli outer membrane porin C; anti-CBir1 flagellin antibody; antibody to *Pseudomonas fluorescens*-associated sequence I2; antichitobioside, antilaminaribioside, or antimannobioside antibodies; pyruvate kinase M2) **DOES NOT MEET COVERAGE CRITERIA**.
4. The use of multianalyte serum biomarker panels (with or without algorithmic analysis) that are designed to distinguish between IBD and non-IBD or that are designed to diagnose or monitor IBD (e.g. ibs-smart™, IBSchek®, PredictSURE IBD™ Test, Prometheus® testing) **DOES NOT MEET COVERAGE CRITERIA**.

NOTES:

Note 1: Fecal calprotectin is the preferred biomarker. If fecal calprotectin and fecal lactoferrin are ordered at the same time, only fecal calprotectin will be approved.

Scientific Background

Inflammatory bowel disease (IBD) includes several chronic, immune-mediated inflammatory gastrointestinal disorders, the most common being Crohn's disease and ulcerative colitis.[6] In contrast, irritable bowel syndrome (IBS), another gastrointestinal disorder, is a non-inflammatory condition. These disorders often share similar symptoms including abdominal discomfort, pain, bloating, and diarrhea.[7] An estimated two thirds of Americans have experienced these IBS and/or IBD symptoms.[8] Differentiating gastrointestinal tract symptoms due to IBS from those due to residual inflammation from IBD is challenging.[9,10] However, the detection of fecal calprotectin can be used to effectively distinguish between these conditions.[11]

The diagnoses of Crohn's disease (CD) and ulcerative colitis (UC) depend on a combination of clinical, laboratory, radiographic, endoscopic, and histological criteria. Differential diagnosis can be challenging but is highly important toward treatment and prognosis. Serological markers could be of value in differentiating CD from UC, in cases of indeterminate colitis, and in predicting the disease course of IBD.[1,3,4]

Investigations based on animal models have led to the current theory that chronic intestinal inflammation is the result of an aberrant immunologic response to commensal bacteria within the gut lumen.[12,13] Immune responses toward commensal enteric organisms have been investigated in CD and UC.[14,15] Patients with IBD can have a loss of tolerance to specific bacterial antigens and autoantigens. These distinct antibody response patterns may indicate unique pathophysiological mechanisms in the progression of this complicated disease and may underline the basis for the development of specific phenotypes.[16,17]

Numerous serological markers have been proposed as having utility in assessment of IBD patients. The most widely studied markers are the antineutrophil cytoplasmic antibodies (pANCA) and anti-

Saccharomyces cerevisiae antibodies (ASCA), particularly for diagnosing IBD and distinguishing CD from ulcerative colitis.[4,18] pANCA is thought to be an antibody corresponding to histone 1 whereas ASCA is an antibody against mannan from baker's yeast.[19] Although there have been promising results regarding the clinical validity of these antibodies,[20-22] its utility in indeterminate bowel disease is uncertain.[17,23] ASCA were present in 50 percent of patients with celiac disease and described in cystic fibrosis and intestinal tuberculosis, suggesting that they may reflect a nonspecific immune response in small bowel disease.[24,25]

Additional antibody tests under investigation include laminaribioside (ALCA), chitobioside (ACCA), CBir1 flagellin, OmpC, and I2. ALCA and ACCA are antiglycan antibodies whereas the CBir1 flagellin comes from an indigenous species of bacteria.[26,27] OmpC is an antibody to an outer membrane protein of *E. coli* and I2 is an antibody against the I2 component of *Pseudomonas fluorescens.*[19] The accuracy and predictive value of antibody tests is uncertain[28] and the prevalence of these antibodies in patients with a variety of inflammatory diseases affecting the gut has not been well-studied.

Additionally, bile acid deficiency--as indicated by serum 7α-hydroxy-4-cholesten-3-one (7C4) --has been documented in patients with irritable bowel syndrome (IBS).[29,30] This test has shown utility as an alternative test to measuring bile acids in stool,[31] but it is not recommended in the workup for IBD.

Another proposed biomarker for IBD is serum pyruvate kinase M2 (PKM2), which is "emerging" in IBD as a mediator of inflammatory processes. Almousa, et al. (2018) evaluated its association with IBD and its correlation with traditional IBD indices, BD disease type, and intestinal microbiota. The authors found that serum PKM2 levels were six times higher in IBD patients compared to healthy controls. However, no sensitivity to disease phenotype or localization of inflammation was observed. A positive correlation between PKM2 and *Bacteroidetes* was identified, as well as a negative correlation between PKM2 and *Actinobacteria*. The investigators concluded that their data "suggests PKM2 as a putative biomarker for IBD and the dysbiosis of microflora in CD," but noted that further validation was required.[32]

Genetic studies have identified over 200 distinct susceptibility loci for irritable bowel disease with a significant portion of these overlapping with Crohn's and ulcerative colitis.[33,34] Most of these are located within introns, which more likely modulate the expression of proteins, with each only conferring a slight increase in risk.[35] Altogether, the known loci only explain ~13% of variation in disease liability.[33] These results indicate that the genetic architecture of IBD represents that of multifactorial complex traits where a combination of multiple genes, along with the environment, lead to disease.[36] Given the low predictive value of individual genetic markers and high number of putative risk alleles, genetic testing does not currently offer much in terms of clinical utility.[36-39]

Laboratory evidence of inflammation is common in IBD. Fecal calprotectin, lactoferrin, ESR and CRP have each been correlated with disease activity,[40,41] but are not specific. Additional inflammatory markers including vascular endothelial growth factor, intercellular adhesion molecule, vascular adhesion molecule, and serum amyloid A offer no significant advantage.[37] Fecal calprotectin has been shown to be useful to help differentiate the presence of IBD from irritable bowel syndrome and in monitoring disease activity and response to treatment.[38] Inflammation and calprotectin testing are discussed in greater detail in AHS-G2155 and AHS-G2061, respectively.

Calprotectin is a small calcium- and zinc-binding protein. This protein is primarily detected in monocytes and macrophages. During active intestinal inflammation, neutrophils migrate to the mucosa, damaging the mucosal structure. This causes leakage of these neutrophils and therefore

calprotectin into the lumen and eventually the feces. Calprotectin is homogenously distributed in feces, is stable up to seven days at room temperature, and correlates well with the "gold standard" of the indium-labeled leukocyte test.[11]

Fecal calprotectin is now accepted as one of the most useful tools to assist with the clinical management of IBD, although the optimal cut-off laboratory value for both differentiating IBD from IBS and managing IBD may vary depending on clinical settings.[42-44] A value of 50 µg/g is quoted by most manufacturers of calprotectin kits.[45] In a young patient, a cutoff of 150 µg/g is recommended. As fecal calprotectin is increased in gastroenteritis associated with viral or bacterial infection, a value between 50 µg/g and 150 µg/g should always be repeated two to three weeks later.[11]

Fecal calprotectin is typically measured with polyclonal or monoclonal antibodies that detect various features on the protein structure; these tests may be quantitative or qualitive. Manufacturers of this type of test include Calpro and Bühlmann.[11]

Clinical Utility and Validity

Panels to improve the predictive value of IBD testing incorporating serologic, genetic, and inflammation markers have been created.[46] The clinical validity and utility of antibody tests and panels of combinations of serologic tests for the diagnosis of IBD and the disease course and severity are still uncertain.[28,47-50] For example, Prometheus Biosciences offers a series of tests intended for IBS. This series includes "IBDsgi Diagnostic," which evaluates 17 biomarkers (serological and genetic markers, intended to provide "diagnostic and prognostic clarity,"[51] "Crohn's Prognostic" (evaluates "proprietary serologic (anti-CBir1, anti-OMPC, DNAse sensitive pANCA) and genetic (NOD2 variants SNPs 8,12,13) markers"), and "Monitr" (evaluates 13 biomarkers to provide an "Endoscopic Healing Index Score" which represents endoscopic disease activity).[52] In February 2022, Prometheus announced the release of PredictrPK IFX, a test that helps healthcare providers with biologic dose optimization by using individualized pharmacokinetic modeling. According to the Prometheus site, "PredictrPK IFX combines serology markers, patient-specific variables, current dosing information, and a proprietary machine-learning algorithm to provide individualized actionable insights to optimize the dose and interval for inflammatory bowel disease (IBD) patients treated with infliximab (IFX) or IFX biosimilars."[53]

Fecal calprotectin is increasing in utilization for the evaluation of IBD.[54] Meta-analyses of fecal calprotectin by both von Roon, et al. (2007) and van Rheenen, et al. (2010) found an overall sensitivity and specificity for IBD of >90%. Waugh, et al. (2013) also completed a meta-analysis as part of the national Health Technology Assessment program which found a pooled sensitivity of 93% and specificity of 94% when distinguishing between IBS and IBD in adults with a fecal calprotectin cut-off of 50 µg/g.

Molander, et al. (2012) evaluated fecal calprotectin levels after induction therapy with TNFα antagonists to determine whether this treatment can help to predict the outcome of IBD patients during maintenance therapy. Sixty patients with IBD were treated with TNFα antagonists and had their fecal calprotectin measured. Fecal calprotectin was found to be normalized (≤100 µg/g) in 31 patients and elevated in 29 patients. After 12 months, 26 of the 31 patients with normal fecal calprotectin levels were in clinical remission whereas only 11 of the 29 with elevated fecal calprotectin were in remission. A cutoff concentration of 139 µg/g was found to have a sensitivity of 72% *and* specificity of 80% to predict a risk of clinically active disease after one year.[58]

Mitsuyama, et al. (2014) conducted a multicenter study to explore the possible diagnostic utility of antibodies to the CD peptide (ACP) in patients with CD. A total of 196 patients with CD, 210 with UC, 98 with other intestinal conditions, and 183 healthy controls were examined. In CD patients, ACP had a higher sensitivity and specificity (63.3% and 91.0%, respectively) than ASCA (47.4% and 90.4%, respectively). ACP was also found to be negatively associated with disease duration. The authors concluded that "ACP, a newly proposed serologic marker, was significantly associated with CD and was highly diagnostic. Further investigation is needed across multiple populations of patients and ethnic groups, and more importantly, in prospective studies."[59]

Kaul, et al. (2012) performed a meta-analysis/systemic review aimed to evaluate the diagnostic value, as well as the association of anti-glycan biomarkers with IBD susceptible gene variants, disease complications, and the need for surgery in IBD. A total of 23 studies were included consisting of 14 in the review and nine in the meta-analysis. They found that "individually, anti-Saccharomyces cerevisiae antibodies (ASCA) had the highest diagnostic odds ratio (DOR) for differentiating IBD from healthy (DOR 21.1), and CD from UC (DOR 10.2…)."[47] The authors concluded, "ASCA had the highest diagnostic value among individual anti-glycan markers. While anti-chitobioside carbohydrate antibody (ACCA) had the highest association with complications, ASCA and ACCA associated equally with the need for surgery."[47]

Schoepfer, et al. (2008) aimed to determine the accuracy of fecal markers, C-reactive protein (CRP), blood leukocytes, and antibody panels for discriminating IBD from IBS. Sixty-four patients with IBD, 30 patients with IBS, and 42 healthy controls were included within the study. They found that "Overall accuracy of tests for discriminating IBD from IBS: IBD-SCAN 90%, PhiCal Test 89%, LEUKO-TEST 78%, Hexagon-OBTI 74%, CRP 73%, blood leukocytes 63%, CD antibodies (ASCA+/pANCA- or ASCA+/pANCA+) 55%, UC antibodies (pANCA+/ASCA-) 49%. ASCA and pANCA had an accuracy of 78% for detecting CD and 75% for detecting UC, respectively. The overall accuracy of IBD-SCAN and PhiCal Test combined with ASCA/pANCA for discriminating IBD from IBS was 92% and 91%, respectively."[60]

Plevy, et al. (2013) validated a diagnostic panel incorporating 17 markers. The markers were as follows: "8 serological markers (ASCA-IgA, ASCA-IgG, ANCA, pANCA, OmpC, CBir1, A4-Fla2, and FlaX), 4 genetic markers (ATG16L1, NKX2-3, ECM1, and STAT3), and 5 inflammatory markers (CRP, SAA, ICAM-1, VCAM-1, and VEGF)." A total of 572 patients with CD, 328 with UC, 427 non-IBD controls, and 183 controls were assessed. These results were compared to another panel with serological markers only. The extended panel increased the IBD vs non-IBD discrimination area under the curve from 0.80 to 0.87 and the CD vs UC from 0.78 to 0.93. The authors concluded that "incorporating a combination of serological, genetic, and inflammation markers into a diagnostic algorithm improved the accuracy of identifying IBD and differentiating CD from UC versus using serological markers alone."[46]

Molander, et al. (2015) studied whether fecal calprotectin can predict relapse after stopping TNFα-blocking therapy in IBD patients in remission. Forty-nine patients were examined, of which 15 relapsed (34 in remission). Relapsing patients showed an elevated fecal calprotectin for a median of 94 days before relapsing. Normal fecal calprotectin levels were "highly predictive" of clinical and endoscopic remission. The authors suggested that fecal calprotectin may be used as "a surrogate marker for predicting and identifying patients requiring close follow-up in clinical practice."[61]

Biasci, et al. (2019) validated a 17-gene prognostic classifier. The classifier was intended to separate IBD patients into two subgroups of prognosis, IBDhi (poorer prognosis) and IBDlo. Two validation cohorts were used, one of CD (n=66) and one of UC (n=57). IBDhi (separated by the classifier) patients experienced both an "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)."[62]

Czub, et al. (2014) compared PKM2 to fecal calprotectin (FC) as markers for mucosal inflammation in IBD. A total of 121 patients (75 with UC, 46 with CD) were compared to 35 healthy controls. The authors found that, PKM2 was "inferior" to FC. The differences in the area under curve were as follows: 0.10 (FC above PKM2, IBD), 0.14 (UC), and 0.03 (IBD). PKM2 was also considered inferior to FC in differentiating patients from mild UC from healthy patients by an AUC of 0.23.[63]

Kovacs, et al. (2018) investigated "prognostic potential of classic and novel serologic antibodies regarding unfavorable disease course in a prospective ulcerative colitis (UC) patient cohort." They measured the auto-antibodies anti-neutrophil cytoplasmic (ANCA), anti-DNA-bound-lactoferrin (anti-LFS), anti-goblet cell (anti-GAB) and anti-pancreatic (pancreatic antibody (PAB): anti-CUZD1 and anti-GP2) and the anti-microbial antibodies anti-Saccharomyces cerevisiae (ASCA) IgG/IgA and anti-OMP Plus™ IgA. A total of 187 patients were included. The authors found a total of "73.6%, 62.4% and 11.2% of UC patients were positive for IgA/IgG type of atypical perinuclear-ANCA, anti-LFS and anti-GAB, respectively." Occurrences of PABs were 9.6%, ASCA IgA/IgG was 17.6%, and anti-OMP IgA was 19.8%. IgA type PABs were found to be more prevalent in patients with primary sclerosing cholangitis (37.5% vs. 4.7% for anti-CUZD1 and 12.5% vs. 0% for anti-GP2). IgA type ASCA was associated with a higher risk for requiring long-term immunosuppressant therapy. The authors found that none of the autoantibodies, either alone or in combination, were associated with the "risk of development of extensive disease or colectomy," although "multiple antibody positivity [≥3]" was associated with UC-related hospitalization. Overall, the authors concluded that "Even with low prevalence rates, present study gives further evidence to the role of certain antibodies as markers for distinct phenotype and disease outcome in UC. Considering the result of the multivariate analysis the novel antibodies investigated do not seem to be associated with poor clinical outcome in UC, only a classic antibody, IgA subtype ASCA remained an independent predictor of long-term immunosuppressive therapy."[64]

Tham, et al. (2018) showed that fecal calprotectin is an accurate surrogate marker of postoperative endoscopic recurrence of Crohn's disease. They evaluated the diagnostic sensitivity, specificity, and diagnostic odds ratio (DOR), and constructed summary receiver operating characteristic (SROC) curves in a meta-analysis of 54 studies; Nine studies were eligible for analysis. Diagnostic accuracy was calculated for fecal calprotectin values of 50, 100, 150 and 200 µg/g. A significant threshold effect was observed for all fecal calprotectin values. The optimal diagnostic accuracy was obtained for a fecal calprotectin value of 150 µg/g, with a pooled sensitivity of 70% [95% confidence interval (CI) 59-81%], specificity 69% (95% CI 61-77%), and DOR 5.92 (95% CI 2.61-12.17); the area under the SROC curve was 0.73.[65]

Ben-Shachar, et al. (2019) evaluated the impact of genotype variations on serological biomarkers. The authors examined three *NOD2* variants (1007fs, G908R, R702W) and an *ATG16L1* variant (A300T). Then, the authors analyzed the antiglycan antibodies anti-*Saccharomyces cerevisiae* (ASCA), antilaminaribioside (ALCA), antichitobioside (ACCA), and antimannobioside carbohydrate (AMCA). A total of 308 IBD patients were included, "130 with Crohn's Disease (CD), 67 with ulcerative

colitis (UC), 111 with UC and an ileal pouch (UC-pouch), and 74 healthy controls." ACCA was found to be "positive" in 28% of CD patients with the *ATG16L1* A300T variant, compared to only 3% in patients without the variant. ASCA was found to be positive in 86% of patients with the 1007fs variant, compared to 36% without the variant. UC-pouch patients with the 1007fs variant were also found to have "elevated" ASCA and ALCA levels compared to those without (50% vs 7% and 50% vs 8% respectively). The authors also found that the genetic variants were not associated with serologic responses in healthy controls and "unoperated" UC patients. The authors concluded that "Genetic variants may have disease-specific phenotypic (serotypic) effects. This implies that genetic risk factors may also be disease modifiers."[66]

Ahmed et al. (2019) examined the association between six serological markers and Crohn's Disease (CD) activity. The six markers evaluated were "ASCA-IgA, ASCA-IgG, anti-OmpC IgA, anti-CBir1 IgG, anti-A4Fla2 IgG and anti-FlaX IgG." A total of 135 patients were included. The authors found that CD patients with high anti-Cbir1 IgG at baseline were 2.06 times more likely to have active clinical disease. The other five autoantibodies were not found to have significant impact on clinical courses. The authors concluded that "High levels of anti-Cbir1 IgG appear to be associated with a greater likelihood of active CD. Whether routine baseline testing for anti-Cbir1 IgG to predict a more active clinical course is warranted needs more research."[67,68]

In a cross-sectional study, Campbell, et al. (2021) assessed the clinical performance of the LIAISON Calprotectin Assay in differentiating inflammatory bowel disease (IBD) from irritable bowel syndrome (IBS) against the Genova Diagnostics PhiCal test. A total of 240 patients were included in the study, in which 102 patients had IBD, 67 had IBS, and 71 had other GI disorders. Median fecal calprotectin levels were higher in IBD patients (522 µg/g) compared to IBS patients (34.5 µg/g). The LIAISON assay showed good correlation with the PhiCal test, holding a positive percent agreement of 97.8% and a negative percent agreement of 94.4%. Overall, the LIAISON Calprotectin Assay is efficient with a time to the first result of 35 minutes and "is a sensitive marker for distinguishing IBD from IBS with a cutoff of ~100 µg/g."[69]

Nakov, et al. (2022) performed a review of current studies related to IBS and IBD biomarker diagnosis and management, including how to distinguish IBS from IBD (as a note, IBS is a disorder of the gastrointestinal tract while IBD constitutes inflammation or destruction of the bowel wall. Crohn's disease and ulcerative colitis fall under an IBD etiology). The authors focused on the most clinically validated biomarkers to-date and summarized the biological rationale, diagnostic, and clinical value. The authors wrote, "there are well-established serological markers that help differentiate IBS from IBD. These include ASCA, which facilitates the differential diagnosis of Crohn's disease (CD) and ulcerative colitis (UC), predominantly in the disease's early stages. The serum concentration of ASCA is considerably higher in patients with CD than in those with UC. Thus, ASCA can be employed in differentiating organic disease from IBS." They also noted "the other autoantibodies that can be used in distinguishing IBS from IBD are the anti-neutrophil cytoplasmic antibody. They target antigens present in neutrophils and are positive in 50–80% of the UC patients."[70]

Johnson, et al. (2022) compared fecal calprotectin and pancreatic elastase assays, aiming to understand the differences between the tests and manufacturers. Data from proficiency tests performed in Germany between 2015 and 2020 was included in the study. Fecal calprotectin assays had a "high degree of variability" between tests from the eight manufactures included. Pancreatic elastase assays were "harmonized" without significant variability between tests from the five

manufacturers included. The authors concluded that "both calprotectin and pancreatic elastase assays could be improved by standardization efforts."[71]

Reese, et al. (2006) performed a meta-analysis of dozens of studies to assess the diagnostic precision of ASCA and pANCA in pinpointing irritable bowel disease, as well as the role of these serum antibodies in differentiating Crohn's from ulcerative colitis. Using 60 different studies, comprising 3,841 UC and 4,019 CD patients, they calculated sensitivity, specificity, and likelihood ratio for different test combinations. The ASCA+ with PANCA- test had the highest sensitivity for Crohn's disease at 54.6%; the specificity was 92.8%. The sensitivity and specificity of pANCA+ tests for ulcerative colitis were 55.3% and 88.5%, respectively. Sensitivity and specificity or pANCA+ were improved in a pediatric subgroup when combined with an ASCA test. In the pediatric cohort, sensitivity was 70.3% and specificity was 93.4%. In conclusion, the authors write that "ASCA and pANCA testing are specific but not sensitive for CD and UC, but that it may be particularly useful for differentiating between CD and UC in the pediatric population."[22]

Vestergaard, et al. (2023) studied the pre-clinical phase of IBS to investigate biological changes that precede the diagnosis of IBD aiming to improve early diagnosis and intervention. The study included over 20000 individuals, including population controls and IBD patients 10 years before diagnosis. The researchers measured 17 hematological and biochemical parameters. "We observe widespread significant changes in multiple biochemical and hematological parameters that occur up to 8 years before diagnosis of Crohn's disease (CD) and up to 3 years before diagnosis of ulcerative colitis." More specifically, "8 years before a diagnosis of CD, levels of leukocytes, neutrophils, and platelets remained significantly higher in CD cases compared to controls" and "3 years before UC diagnosis, cases had higher levels of CRP, leukocytes, neutrophils, eosinophils, and platelets compared to controls." The authors concluded that the results reveal "an opportunity for earlier intervention, especially in CD."[72]

Mourad, et al. (2024) studied the clinical use of fecal calprotectin when testing for suspected IBD. The retrospective study included data from 447 patients who had FC tests. Overall, 56% of the patients has positive FC above 50 µg/g. Of the 447 patients, 81 were diagnosed with IBD and 146 were diagnosed with IBS. The use of FC for patients with IBD had a sensitivity of 79.0%, a specificity of 49.2%, a positive predictive value of 25.5%, and a negative predictive value of 91.3%. The authors concluded that "the use of FC plays an important role in the diagnosis of IBD and in limiting overutilization of healthcare resources. However, in our real-world experience, the accuracy of the test was found to be poor in differentiating IBD from other gastrointestinal diseases."[73]

Guidelines and Recommendations

American Gastroenterological Association (AGA)

No guideline or position statement from AGA on specific use of immunologic or genetic markers for the diagnosis of inflammatory bowel disease was found. The AGA assessment algorithms used for both Crohn's disease and ulcerative colitis do not include genetic testing or combinatorial serologic-genetic testing approaches, such as the Prometheus® testing methodology.[74,75]

In 2021, the AGA published a guideline on the medical management of severe luminal and perianal fistulizing Crohn's disease.[76] While the guideline focuses on therapeutic approaches (i.e., different drug classes for Crohn's disease), it does make a statement on perceived future research needs and

evidence gaps. AGA notes: “There remains an urgent need for improved patient-specific predictors, clinical and biologic, of response and harm to a particular drug or drug class to improve the rational choice of initial and second-line therapeutic agents in a given patient. The need is especially great in special populations, such as those with fistulizing disease or aggressive and recurrent fibro stenosing disease. Overall, the data on risk-stratifying individual patients into low and high risk of disease complications and disability remain poor.”[76]

Regarding the laboratory evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome in adults (IBS-D), AGA recommends the following:

“1. In patients presenting with chronic diarrhea, AGA suggests the use of either fecal calprotectin or fecal lactoferrin to screen for inflammatory bowel disease (IBD).

2. In patients presenting with chronic diarrhea, AGA suggests against the use of erythrocyte sedimentation rate or C-reactive protein to screen for IBD.

3. In patients presenting with chronic diarrhea, AGA recommends testing for Giardia.

4. In patients presenting with chronic diarrhea with no travel history or recent immigration from high-risk areas, AGA suggests against testing for ova and parasites (other than Giardia).

5. In patients presenting with chronic diarrhea, AGA recommends testing for celiac disease with immunoglobulin A (IgA) tissue transglutaminase and a second test to detect celiac disease in the setting of IgA deficiency.

6. In patients presenting with chronic diarrhea, AGA suggests testing for bile acid diarrhea.

7. In patients presenting with chronic diarrhea, AGA makes no recommendation for the use of currently available serologic tests for diagnosis of irritable bowel syndrome (IBS).”[77]

A 2021 clinical practice guideline from AGA recommends the below as best practice advice for the diagnosis of IBD in elderly patients:

“1. A diagnosis of inflammatory bowel disease (IBD) (Crohn’s disease, ulcerative colitis) should be considered in older patients who present with diarrhea, rectal bleeding, urgency, abdominal pain or weight loss because up to 15% of new diagnoses of IBD occur in individuals older than 60 years.

2. Fecal calprotectin or lactoferrin may help prioritize patients with a low probability of IBD for endoscopic evaluation. Individuals presenting with hematochezia or chronic diarrhea with intermediate to high suspicion for underlying IBD, microscopic colitis or colorectal neoplasia should undergo colonoscopy.

3. In elderly patients with segmental left-sided colitis in the setting of diverticulosis, consider a diagnosis of segmental colitis associated with diverticulosis in addition to the possibility of Crohn’s disease or IBD-unclassified.”[78]

In 2023, the AGA released the following recommendations for the use of biomarkers in the management of ulcerative colitis:

- “In patients with UC in symptomatic remission, AGA suggests a monitoring strategy that combines biomarkers and symptoms, rather than symptoms alone.
- In patients with UC in symptomatic remission, AGA suggests using fecal calprotectin <150 µg/g, normal fecal lactoferrin, or normal C-reactive protein (CRP) to rule out active inflammation and avoid routine endoscopic assessment of disease activity.

- In patients with UC in symptomatic remission but elevated stool or serum markers of inflammation (fecal calprotectin >150 µg/g, elevated fecal lactoferrin, elevated CRP), AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment.
- In patients with UC with mild symptoms, with normal stool or serum markers of inflammation (fecal calprotectin <150 µg/g, normal fecal lactoferrin, normal CRP), AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment.
- In patients with symptomatically active UC, AGA suggests an evaluation strategy that combines biomarkers and symptoms, rather than symptoms alone, to inform treatment adjustments.
- In patients with UC with moderate to severe symptoms suggestive of flare, AGA suggests using fecal calprotectin >150 µg/g, elevated fecal lactoferrin, or elevated CRP to rule in active inflammation and inform treatment adjustment and avoid routine endoscopic assessment solely for establishing presence of active disease.
- In patients with UC with mild symptoms, with elevated stool or serum markers of inflammation (fecal calprotectin >150 µg/g, elevated fecal lactoferrin, or elevated CRP), AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment.
- In patients with UC, AGA makes no recommendation in favor of, or against, a biomarker-based monitoring strategy over an endoscopy-based monitoring strategy to improve long-term outcomes."[79]

The AGA published a practice update on functional gastrointestinal symptoms in patients with IBD. The following best practice advice recommendations on fecal calprotectin were given regarding the diagnosis and management of functional gastrointestinal symptoms in patients IBD:

- "Best practice advice 1: 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).
- Best practice advice 2: In those patients with indeterminate fecal calprotectin levels and mild symptoms, clinicians may consider serial calprotectin monitoring to facilitate anticipatory management."[80]

American College of Gastroenterology (ACG)

The ACG published guidelines on the management of Crohn's disease which state:

- "The diagnosis of Crohn's disease (CD) is based on a combination of clinical presentation and endoscopic, radiologic, histologic, and pathologic findings that demonstrate some degree of focal, asymmetric, and transmural granulomatous inflammation of the luminal GI tract. Laboratory testing is complementary in assessing disease severity and complications of disease. There is no single laboratory test that can make an unequivocal diagnosis of CD. The sequence of testing is dependent on presenting clinical features."
- "Initial laboratory investigation should include evaluation for inflammation, anemia, dehydration, and malnutrition."
- "In patients who have symptoms of active CD, stool testing should be performed to include fecal pathogens, *Clostridioides difficile* testing, and studies that identify gut inflammation such as an FC."
- "Genetic testing is not indicated to establish the diagnosis of CD."

- "Genetic variants, including HLADQA1*05, HLA-DRB1*03, nudix hydrolase 15 (NUDT15), and thiopurine methyltransferase (TPMT), can affect individual treatment response and identify potential risks for adverse effects of drug therapy in CD. These are clinically useful in disease management and should be measured in select patients."
- "Routine use of serologic markers of IBD to establish the diagnosis of CD is not indicated."
- "Fecal calprotectin is a helpful test that should be considered to help differentiate the presence of IBD from irritable bowel syndrome (IBS) (strong recommendation, moderate level of evidence)."
- "Fecal calprotectin and fecal lactoferrin measurements may have an adjunctive role in monitoring disease activity. Fecal markers may have a role in noninvasively monitoring disease activity in CD [Crohn's disease]. Studies have shown that both fecal lactoferrin and fecal calprotectin are sensitive markers of disease activity and correlate with a number of endoscopic activity indices such as the colonic SES-CD. There have been several studies that suggest that levels of fecal calprotectin can be used to monitor patients for postoperative recurrence after ileocolic resection for Crohn's disease. Levels of >100 μ g/g indicate endoscopic recurrence with a sensitivity in the range of 89%. In patients with an infliximab-induced remission, fecal calprotectin of >160 μ g/g has a sensitivity of 91.7% and a specificity of 82.9% to predict relapse… The presence of biomarkers of disease activity can be assessed (such as CRP, fecal calprotectin) but should not exclusively serve as end point for treatment as normalization of the biomarker can occur despite having active mucosal inflammation/ulceration… Although not specific for CD activity, determination of serum CRP and/or fecal calprotectin is suggested as a useful laboratory correlate with disease activity assessed by the CDAI."[81]

The Crohn's Disease Activity Index (CDAI) is a tool that can provide a numerical value in assessing Crohn's disease; however, fecal calprotectin is not a criterion of the index. Within the supplemental information of the guidelines, the authors state, "This is a weighted subjective tool that includes scores for liquid bowel movements per day, general wellbeing, abdominal pain and extra-intestinal manifestations. This index does require 7 days of measurements making it difficult to use in the clinic setting. Due to the subjective nature of some of the measurements it is not an optimal tool for measuring disease activity and is generally not used in routine clinical practice."[38]

The guidelines do not address the frequency of fecal calprotectin testing for adjunctive monitoring.

The 2025 updates to the ACG Clinical Guideline for the Management of Crohn's disease in adults recommends "We recommend the use of FC (cutoff >50–100 μg/g) to differentiate inflammatory from noninflammatory disease of the colon (Strong recommendation; moderate level of evidence)," explaining that "in patients who have symptoms of active CD, stool testing should be performed to include fecal pathogens, *Clostridioides difficile* testing, and studies that identify gut inflammation such as an FC."[81]

The ACG guidelines on Ulcerative Colitis in adult's state:

- ‘‘We recommend stool testing to rule out *Clostridioides difficile* in patients suspected of having UC (Strong recommendation, very low quality of evidence)."
- "We recommend against serologic antibody testing to establish or rule out a diagnosis of UC (strong recommendation, very low quality of evidence)."
- "We recommend against serologic antibody testing to determine the prognosis of UC (strong recommendation, very low quality of evidence)."

- The ACG also mentions perinuclear antineutrophil cytoplasmic antibodies (pANCAs) as a proposed serological marker, but they observe that "there is currently no role for such testing to determine the likelihood of disease evolution and prognosis" and that the marker has low sensitivity for diagnostic purposes.
- Overall, "the yield of genetic or serologic markers in predicting severity and course of UC has been modest at best, and their use cannot be recommended in routine clinical practice based on available data."
- "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."[82]

The ACG also recommends:

- "Stool testing to rule out *Clostridioides difficile (C. diff)* in patients suspected of having UC (strong recommendation, very low quality of evidence)."
- Recommends against "serologic antibody testing to establish or rule out a diagnosis of UC (strong recommendation, very low quality of evidence)."
- Recommends against serologic antibody testing to determine the prognosis of UC (strong recommendation, very low quality of evidence)."[83]

In 2025, the ACG updated their guidelines on ulcerative colitis in adults. They recommend:

- "Definitions of disease severity are needed to guide treatment decisions; definitions should be based on (i) patient-reported outcomes (bleeding, normalization of bowel habits, bowel urgency), (ii) the inflammatory burden (endoscopic assessment including extent and severity, and markers of inflammation including fecal calprotectin [FC], C-reactive protein [CRP], and serum albumin), (iii) disease course (need for hospitalization, need for steroids, failure to respond to medications), and (iv) disease impact (HRQoL and social functioning)."
- "Disease assessment and monitoring in response to therapy and during maintenance and periods of suspected relapse may be performed with FC, CRP, endoscopic assessment with flexible sigmoidoscopy or colonoscopy, and/or intestinal ultrasound."
- "We recommend the use of FC in UC to assess response to therapy, to evaluate suspected relapse, and during maintenance (Strong recommendation, moderate quality of evidence)."[82]

The ACG released guidelines on management of IBS in adults. They recommend that fecal calprotectin, either fecal calprotectin 1 or fecal lactoferrin 2 and C-reactive protein 1, be checked in patients with suspected IBS and diarrhea symptoms to rule out inflammatory bowel disease. ACG includes two fecal-derived markers of intestinal inflammation, fecal lactoferrin (FL) and fecal calprotectin (fCal), are both diagnostically useful and could be superior to serologic tests such as CRP or ESR regarding discriminating IBD from IBS. "In summary, fCal and FL are safe, noninvasive, generally available, and can identify IBD with good accuracy." The recommendations also state:

- "We recommend that serologic testing be performed to rule out celiac disease (CD) in patients with IBS and diarrhea symptoms.
- We suggest that either fecal calprotectin or fecal lactoferrin and C-reactive protein be checked in patients without alarm features and with suspected IBS and diarrhea symptoms to rule out inflammatory bowel disease.

- We recommend against routine stool testing for enteric pathogens in all patients with IBS."[84]

European Crohn's and Colitis Organization (ECCO)

The ECCO states that the Montréal classification of CD is advocated. Therefore, "genetic tests or serological markers should currently not be used to classify CD in clinical practice." ECCO notes that fecal calprotectin may be used in the initial laboratory investigation. Fecal calprotectin is also observed to be an emerging surrogate marker for mucosal healing but has not demonstrated a clear predictive value. Fecal calprotectin may also help in monitoring disease activity.[85]

In a 2017 update for UC, ECCO states that "the routine clinical use of genetic or serological molecular markers is not recommended for the classification of ulcerative colitis." ECCO also notes that the most widely studied marker is the pANCAs, but they have "limited sensitivity" and "their routine use for the diagnosis of UC and for therapeutic decisions is not clinically justified." They state that fecal calprotectin should be included in an initial investigation of UC. ECCO considers fecal calprotectin an "accurate" marker of colonic inflammation and "a useful non-invasive marker in the follow-up of UC patients."[86]

The ECCO also published a "harmonization of the approach to Ulcerative Colitis Histopathology." A section titled "Correlation of Histological Scores with Biomarkers" is included. However, only fecal biomarkers (such as fecal lactoferrin and calprotectin) are mentioned, with no mention of serological biomarkers.[87]

The 2019 ECCO also published the "ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment." While the guideline mainly focused on therapeutic agents, it does advocate for identification of important biomarkers to biologic effect. ECCO writes, "there is a clear need to identify biomarkers that could guide therapeutic choices, and to conduct appropriately sized head-to-head trials that could allow for the identification of patient subgroups who would benefit from a given biologic over the other."[88] The 2024 update does not include any statements about laboratory testing.[89]

The ECCO expounds on their guidelines for the prevention, diagnosis, and management of infections in inflammatory bowel disease in a series of statements. A list of the relevant guidance is captured below.

- "Serological screening for hepatitis A, B, C, HIV, Epstein-Barr virus, cytomegalovirus, varicella zoster virus, and measles virus [in the absence of documented past infection or vaccination for the latter two] is recommended for all IBD patients at baseline [EL4] and especially before or during immunosuppressive treatment [EL1]. A Pap smear for human papillomavirus screening is also recommended [EL1]"
- "Immunohistochemistry [IHC], possibly tissue polymerase chain reaction [PCR], or both, are essential for confirming active CMV infection [colitis] in IBD and should be the standard tests [EL2]. Findings and potential interventions should be discussed in the clinical context"
- "Immunosuppressed female IBD patients should undergo annual cervical cancer screening [EL3]"
- "Routine prophylactic HPV vaccination is recommended for both young female and young male patients with IBD [EL2]."[90]

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

Working with the European Society of Gastrointestinal and Abdominal Radiology (ESGAR), ECCO has developed a list of laboratory parameters for the initial diagnosis of known IBD and the detection

of its complications. These relevant provisions of these new diagnostic consensus guidelines are included below.

- "Statement 1.1. ECCO-ESGAR Diagnostics GL [2018]
- A single reference standard for the diagnosis of Crohn's disease [CD] or ulcerative colitis [UC] does not exist. The diagnosis of CD or UC is based on a combination of clinical, biochemical, stool, endoscopic, cross-sectional imaging, and histological investigations [EL5]"
- "Statement 1.2. ECCO-ESGAR Diagnostics GL [2018]
- Genetic or serological testing is currently not recommended for routine diagnosis of CD or UC [EL3]"
- "Statement 1.3. ECCO-ESGAR Diagnostics GL [2018]
- On diagnosis, complementary investigations should focus on markers of disease activity [EL2], malnutrition, or malabsorption [EL5]. Immunization status should be assessed. Consider screening for latent tuberculosis [EL5]."[43]

When monitoring known IBD cases, the following guidelines were provided:

- "Response to treatment in active ulcerative colitis [UC] should be determined by a combination of clinical parameters, endoscopy, and laboratory markers such as C-reactive protein [CRP] and faecal calprotectin [EL1]
- In patients with UC who clinically respond to medical therapy, mucosal healing [MH] should be determined endoscopically or by faecal calprotectin [FC] approximately 3 to 6 months after treatment initiation [EL5]."

It should also be noted that "Serological markers may be used to support a diagnosis, though the accuracy of the best available tests [pANCA and ASCAs] is rather limited and hence ineffective at differentiating colonic CD from UC. Similarly, the additional diagnostic value of antiglycan and antimicrobial antibodies, such as anti-OmpC and CBir1, is small."

A relevant portion of "**Table 1.** Markers of disease activity for monitoring asymptomatic IBD patients" is shown below:[43]

	Validity*	Responsiveness to changes in condition	Signal-to-noise ratio**	Practicality
Endoscopy	Gold standard	Gold standard	Gold standard	Low
Faecal calprotectin	Good	Good Rises quickly in case of relapse;	Moderate Risk of false-positive results	High Possible reluctance of

		falls rapidly with successful treatment		patients for repeated stool collection

* Correlation with gold standard; ** ability to differentiate changes in condition from background variability

European Crohn's and Colitis Organization (ECCO) and European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)

This joint guideline was published regarding "Management of Paediatric Ulcerative Colitis" Although there was no mention of serological markers, the guideline did make this comment on "very early-onset inflammatory bowel disease presenting as colitis," which is as follows:

- "Unusual disease evolution, history of recurrent infections, HLH [hemophagocytic lymphocytic histiocytosis], and non-response to multiple IBD medications may indicate an underlying genetic defect which should prompt genetic and/or immunological analyses at any age during childhood."[91]

World Gastroenterology Organization (WGO)

Concerning the use of p-ANCA and ASCA to diagnose UC and CD, the WGO states, "These tests are unnecessary as screening tests, particularly if endoscopy or imaging is going to be pursued for more definitive diagnoses. p-ANCA may be positive in Crohn's colitis and hence may not be capable of distinguishing CD from UC in otherwise unclassified colitis. ASCA is more specific for CD. These tests may have added value when there may be subtly abnormal findings, but a definitive diagnosis of inflammatory bowel disease is lacking. They may also be helpful if considering more advanced endoscopic techniques such as capsule endoscopy or double-balloon endoscopy, such that a positive ASCA test may provide stronger reasons for evaluating the small bowel." Later, the WGO also notes, "There are several other antibody tests, mostly for microbial antigens, that increase the likelihood of CD either singly, in combination, or as a sum score of the ELISA results for a cluster of antibodies. These tests are costly and not widely available. The presence of these antibodies, including a positive ASCA, would increase the likelihood that an unclassified IBD-like case represents Crohn's disease."[92]

Working Group of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the Crohn's and Colitis Foundation of America

A clinical report noted that:

- "A positive ANCA does not differentiate between UC and Crohn colitis."
- "Genetic testing cannot as yet reliably differentiate UC from CD of the colon."[93]

The Working Group also observed that in the largest study of prospective markers for UC, most patients remained seronegative for both ASCA and ANCA.

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN)

The NASPGHAN published a guideline regarding the management of patients with "Very Early-Onset Inflammatory Bowel Disease (VEO-IBD)." This guideline defines this cohort as a patient of the pediatric

IBD population presenting under six years of age. The guideline makes the following remarks on evaluation of IBD in this population:

- "…genetic sequencing is often necessary to identify the specific monogenic forms of VEO-IBD, or to confirm a suspected defect."
- "Targeted panels should be performed first in cases of infantile onset IBD, when the phenotype is consistent with a known defect, history of consanguinity, and abnormal immunology studies."
- "Currently, WES is most often performed in the setting of a negative targeted panel, however, there are select cases in which WES may be indicated instead of a targeted panel, such as those patients who present with a phenotype that is not previously described."
- "At this time, WGS should be reserved for cases in which WES is negative, yet there remains a high suspicion of a monogenic defect given the young age of onset, disease severity, family history, and complex phenotype including associated autoimmunity."
- "In general, the gene defects that have been detected with the highest frequency in patients with VEO-IBD can prompt specific targeted therapies that include defects that lead to CGD (NADPH complex defects), IL-10R and XIAP."[94]

National Institute for Health and Care Excellence (NICE)

The NICE published guidance on fecal calprotectin testing which included the following recommendations:

- "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 and appropriate quality assurance processes and locally agreed care pathways are in place for the testing."[95]

The NICE does not mention any serological or genetic biomarkers in its reviews of management of UC or CD.[96,97]

British Society of Gastroenterology (BSG)

The BSG published guidelines on the "management of inflammatory bowel disease [IBD] in adults." In it, they made the following comments regarding use of biomarkers in IBD:

- "…more evidence is also needed of the role of faecal calprotectin or other biomarkers as non-invasive surrogates for mucosal healing."
- "Further studies are required to evaluate the use of drug levels and biomarkers to determine personalized dosing for patients."
- "If a response [to treatment] is unclear, then measurement of biomarkers, serum C-reactive protein and faecal calprotectin, or comparison of disease activity scores or PROMs with baseline values, may be helpful."
- "We suggest that genetic testing for monogenic disorders should be considered in adolescents and young adults who have had early onset (before 5 years of age) or particularly aggressive, refractory or unusual IBD presentations (GRADE: weak recommendation, very low-quality evidence."[98]

In 2021, the BSG released guidelines on management of irritable bowel syndrome. The BSG suggests that "all patients presenting with symptoms of IBS for the first time in primary care should have a full

blood count, C reactive protein or erythrocyte sedimentation rate, coeliac serology and, in patients <45 years of age with diarrhea, a faecal calprotectin to exclude inflammatory bowel disease. Local and national guidelines for colorectal and ovarian cancer screening should be followed, where indicated."[99]

World Society of Emergency Surgery and the American Association for the Surgery of Trauma

The WSES and AAST released joint guidelines on the management of inflammatory bowel disease in the emergency setting. When assessing an acute abdomen in patients with IBD, "laboratory tests including full blood count, electrolytes, liver enzymes, inflammatory biomarkers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and serum albumin and pre-albumin (to assess nutritional status and degree of inflammation) are mandatory."[100]

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in-house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

In March 2006, the PhiCal™ (Genova Diagnostics) quantitative ELISA test for measuring concentrations of fecal calprotectin in fecal stool was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) processes. This test is indicated to aid in the diagnosis of inflammatory bowel disease (IBD) and to differentiate IBD from irritable bowel syndrome (IBS); it is intended to be used in conjunction with other diagnostic testing and clinical considerations.[101] On December 26, 2018, a successor device called "LIAISON Calprotectin, LIAISON Calprotectin Control Set, LIAISON Calprotectin Calibration Verifiers, LIAISON Q.S.E.T. Buffer, LIAISON Q.S.E.T. Device" was approved. The new description is as follows: "The DiaSorin LIAISON® Calprotectin assay is an in vitro diagnostic chemiluminescent immunoassay (CLIA) intended for the quantitative measurement, in human stool, of fecal calprotectin, a neutrophilic protein that is a marker of mucosal inflammation. The LIAISON® Calprotectin assay can be used as an aid in the diagnosis of inflammatory bowel diseases (IBD), specifically Crohn's disease and ulcerative colitis, and as an aid in differentiation of IBD from irritable bowel syndrome (IBS). Test results are to be used in conjunction with information obtained from the patients' clinical evaluation and other diagnostic procedures. The test has to be performed on the LIAISON® XL Analyzer."[102]

In January 2014, CalPrest® (Eurospital SpA, Trieste, Italy) was cleared for marketing by the FDA through the 510(k) processes. According to the FDA summary, CalPrest® "is identical" to the PhiCal™ test "in that they are manufactured by Eurospital S.p.A. Trieste, Italy. The only differences are the name of the test on the labels, the number of calibrators in the kit and the dynamic range of the assay." CalPrest®NG (Eurospital SpA) was cleared for marketing in November 2016.[103]

On October 16, 2018, the FDA approved the QUANTA Flash Calprotectin and Fecal Extraction Device. The device's intended use is as follows: "QUANTA Flash Calprotectin is a chemiluminescent immunoassay for the quantitative determination of fecal calprotectin in extracted human stool samples. Elevated levels of fecal calprotectin, in conjunction with clinical findings and other laboratory tests, can aid in the diagnosis of inflammatory bowel disease (IBD) (ulcerative colitis and Crohn's disease), and in the differentiation of IBD from irritable bowel syndrome (IBS)." This device has a predicate device, which was approved in 2017.[102]

On December 26, 2018, the FDA approved the LIAISON Calprotectin Assay. The device's intended use is as follows: "The DiaSorin LIAISON® Calprotectin assay is an in vitro diagnostic chemiluminescent immunoassay (CLIA) intended for the quantitative measurement, in human stool, of fecal calprotectin, a neutrophilic protein that is a marker of mucosal inflammation. The LIAISON® Calprotectin assay can be used as an aid in the diagnosis of inflammatory bowel diseases (IBD), specifically Crohn's disease and ulcerative colitis, and as an aid in differentiation of IBD from irritable bowel syndrome (IBS). Test results are to be used in conjunction with information obtained from the patients' clinical evaluation and other diagnostic procedures."[104]

On September 24, 2019, BUHLMANN Laboratories AG received FDA approval for the Buhlmann FCAL Turbo and CALEX Cap fecal calprotectin extraction device. This device is to be used in conjunction with the automated calprotectin test, BÜHLMANN fCAL® turbo. The BÜHLMANN fCAL® turbo is an in vitro diagnostic assay which quantitatively measures fecal calprotectin.[105]

Rapid fecal calprotectin tests, such as CalproSmart™, are available internationally for use as point-of-care testing, but these have not been approved for use in the U.S. by the FDA.

II. Applicable Codes

Code	Description	Comment
81401	Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using non-sequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)	
81479	Unlisted molecular pathology procedure	
82397	Chemiluminescent assay	
83516	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method	
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified	
83630	Lactoferrin, fecal; qualitative	
83993	Calprotectin, fecal	
86021	Antibody identification; leukocyte antibodies	
86036	Antineutrophil cytoplasmic antibody (ANCA); screen, each antibody	
86037	Antineutrophil cytoplasmic antibody (ANCA); titer, each antibody	
86255	Fluorescent noninfectious agent antibody; screen, each antibody	

86671	Antibody; fungus, not elsewhere specified	
88346	Immunofluorescence, per specimen; initial single antibody stain procedure	
88350	Immunofluorescence, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)	
0164U	Gastroenterology (irritable bowel syndrome [IBS]), immunoassay for anti-CdtB and anti-vinculin antibodies, utilizing plasma, algorithm for elevated or not elevated qualitative results Proprietary test: ibs-smart™ Lab/Manufacturer: Gemelli Biotech	
0176U	Cytolethal distending toxin B (CdtB) and vinculin IgG antibodies by immunoassay (ie, ELISA) Proprietary test: IBSchek® Lab/Manufacturer: Commonwealth Diagnostics International, Inc	
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 Proprietary test: PredictSURE IBD™ Test Lab/Manufacturer: KSL Diagnostics	
0598U	Gastroenterology (irritable bowel syndrome), IgG antibodies to 18 food items by microarray-based immunoassay, whole blood or serum, report as elevated (positive) or normal (negative) antibody levels. Proprietary test: inFoods® IBS Test Lab/Manufacturer: Ethos Laboratories, Biomerica	

Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

III. Definitions

Term	Meaning

IV. Related Policies

Policy Number	Policy Description
PO-RE-051	Celiac Disease Testing
PO-RE-053	Fecal Analysis in The Diagnosis of Intestinal Dysbiosis
PO-RE-054	Fecal Calprotectin Testing in Adults
PO-RE-063	General Inflammation Testing

Procedure codes appearing in Reimbursement Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

V. Reference Materials

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VI. Revision History

Revision Date	Summary of Changes
09/04/2025	Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria: Combined contents of G2061-Fecal Calprotectin Testing in Adults with this policy. Results in the addition of new CC1 and CC2: "1) Fecal calprotectin or fecal lactoferrin testing (see Note 1) MEETS COVERAGE CRITERIA for any of the following situations: a) For the differential diagnosis between non-inflammatory gastrointestinal disease (e.g., IBS) and inflammatory gastrointestinal disease (e.g., IBD). b) To monitor individuals with IBD (e.g., assess for response to therapy or relapse).

	2) For all other situations not described above, fecal calprotectin and fecal lactoferrin testing DOES NOT MEET COVERAGE CRITERIA." Former CC2, now CC4, edited for clarity. Now reads: "5) The use of multianalyte serum biomarker panels (with or without algorithmic analysis) that are designed to distinguish between IBD and non-IBD or that are designed to diagnose or monitor IBD (e.g. ibs-smart™, IBSchek®, PredictSURE IBD™ Test, Prometheus® testing) DOES NOT MEET COVERAGE CRITERIA." New Note 1: "Note 1: Fecal calprotectin is the preferred biomarker. If fecal calprotectin and fecal lactoferrin are ordered at the same time, only fecal calprotectin will be approved." Added CPT code 83630, 83993; 0598U (effective date 10/1/2025)
09/04/2024	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following edits were made for clarity: CC2 edited for clarity, now reads: "2) For the diagnosis or monitoring of individuals with IBD, the use of diagnostic algorithm-based testing (e.g. ibs-smart™, PredictSURE IBD™ Test, Prometheus® testing) DOES NOT MEET COVERAGE CRITERIA." Removed CC3, as genetic testing can be managed/denied by the general germline policy, M2145: "3) Genetic testing for IBD DOES NOT MEET COVERAGE CRITERIA."

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