Inflammatory Bowel Disease Biomarker Testing

MOL.TS.359.A
v2.0.2025

Biomarker testing for inflammatory bowel disease (IBD) is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure addressed by this guideline	Procedure code
Crohn's Prognostic	81401, 83520, 86021, 86255
IBD sgi Diagnostic	81479, 82397, 83520, 86140, 86255, 88346, 88350
PredictSURE IBD	0203U

Criteria

Requests for testing of blood or other body fluids in the evaluation and management of inflammatory bowel disease are reviewed using the following criteria. Please note that this guideline does not address anatomic pathology examinations of gastrointestinal biopsies, imaging by any modality, or other assessments of the intestinal tract.

IBD sgi Diagnostic

CPT 81479, 82397, 83520, 86140, 86255, 88346, 88350

Medical necessity requirements

This testing is considered experimental, investigational, or unproven.

Crohn's Prognostic

CPT 81401, 83520, 86021, 86255

Medical necessity requirements

This testing is considered experimental, investigational, or unproven.

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PredictSURE IBD

CPT 0203U

Medical necessity requirements

The clinical utility of PredictSURE IBD in the setting of inflammatory bowel disease (evaluation, diagnosis, monitoring) has not been demonstrated. This testing is considered experimental, investigational, or unproven.

Billing and Reimbursement

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

PredictSURE IBD

CPT 0203U

PredictSURE IBD testing is not reimbursable.

What is inflammatory bowel disease?

Inflammatory bowel disease (IBD) is a chronic, idiopathic, lifelong inflammatory disease of the gastrointestinal tract, characterized by recurrent episodes of abdominal pain, weight loss, diarrhea, and bloody stools.[1]

The two main forms of IBD are Crohn's disease and ulcerative colitis. These two entities are distinguished by their clinical, radiographic, endoscopic, and pathological features. This distinction may, in some cases, be challenging; however, an accurate diagnosis is critical in determining prognosis and therapy. Crohn's disease usually involves the terminal ileum, cecum, perianal region, and colon in a discontinuous pattern, whereas ulcerative colitis involves the rectum and either part of or the entire colon in a continuous fashion.[1] Histologically, these two entities are differentiated by the degree of intestinal involvement. Crohn's disease characteristically displays transmural inflammation with a granulomatous component, fissures, ulceration, and perforation leading to strictures and fibrosis; Ulcerative colitis is typically limited to the mucosa and submucosa, with cryptitis, crypt abscesses, and crypt architectural distortion.

As many as 50% of individuals with inflammatory bowel disease will experience an extra-intestinal manifestation of their disease, which may occur before the onset of the primary illness.[2] A myriad of extra-intestinal manifestations (EIM) may occur, and includes uveitis, primary sclerosing cholangitis, and ankylosing spondylitis, among others. The risk of developing an EIM is higher in Crohn's disease than in ulcerative colitis, and increases with the duration of the primary disease.

An additional critical relationship of long-standing IBD is the increased risk for colorectal carcinoma, necessitating endoscopic surveillance for the early detection of mucosal dysplasia.[3] The incidence of colorectal cancer is approximately 18% after 30 years of colitis, but studies have demonstrated a decreasing risk with improved therapy and surveillance.[3] Hence, laboratory testing, as a component of care, may be critical in the accurate diagnosis of IBD, therapeutic monitoring, assessment of disease activity, and cancer surveillance.

Endoscopy has played a fundamental role in the diagnosis, management, and treatment of inflammatory bowel disease, and in cancer surveillance of individuals with IBD.[4] Laboratory testing, as a component of care, may also be critical for obtaining an accurate diagnosis of IBD. Many laboratory tests have been developed as potential aids in the diagnosis and management of inflammatory disorders, including inflammatory bowel disease. Non-invasive testing for the evaluation of inflammatory bowel disease has not replaced common parameters derived from endoscopic, radiologic, and histopathologic evaluations. However, research in inflammatory bowel disease has uncovered several potential serologic and genetic markers for clinical use. These include inflammatory biomarkers, mediators of tissue damage, and antibodies to commensal gut organisms.

Advances in endoscopy and therapy have led to an evolution in disease management for both ulcerative colitis and Crohn's disease.[5,6] Clinical guidelines recommend that treatment decisions be based on several levels of care, including patient reported outcomes and inflammatory burden, the latter which may be assessed by endoscopy and markers of inflammation.[5,6] Laboratory testing is used in the therapeutic monitoring, assessment of disease activity, and cancer surveillance for individuals with IBD.

Test Information

Testing for inflammatory bowel disease may include serologic or biomarker testing.

The laboratory tests discussed in this guideline have proposed roles in the diagnosis and management of inflammatory bowel disease. Some of the tests described have established roles in the diagnosis or monitoring of other disorders. This guideline does not address anatomic pathology examinations of gastrointestinal biopsies, imaging by any modality, or other assessments of the intestinal tract.

Anti-neutrophil cytoplasmic antibodies (ANCA)

Anti-neutrophil cytoplasmic antibodies are detected by immunofluorescence using ethanol-fixed neutrophils. The cytoplasmic ANCA (cANCA) pattern is represented by a pattern of granular cytoplasmic fluorescence, whereas the peripheral-ANCA (p-ANCA) pattern is perinuclear. ANCA are often detected in individuals with autoimmune vasculitis. P-ANCA may be observed in those with IBD.

Anti-Saccharomyces cerevisiae IgG and IgA (ASCA)

ASCA antibodies are detected by enzyme-linked immunosorbent assay or enzyme immunoassay (EIA). ASCA may be found in individuals with inflammatory bowel disease.

Anti-OmpC antibody

Anti-OmpC antibody is directed against the outer membrane porin of *Escherichia coli*, and is detected by enzyme-linked immunosorbent assay (ELISA). It may be found in some individuals with IBD.

Cytolethal distending toxin B antibody and vinculin antibody

These antibodies, detected by ELISA, may be found in individuals with irritable bowel syndrome (IBS). The tests are proposed as an aid in distinguishing IBS from IBD.

Serum mannose-binding lectin

Mannose-binding lectin is an immune component that binds to mannose residues on a variety of microorganisms, triggering the complement pathway and resulting in opsonization. Mannose-binding protein is also an acute phase reactant. Abnormal mannose-binding protein concentrations have been found in individuals with infectious disorders such as tuberculosis, hepatitis B, and in autoimmune disorders.

Proteinase-3 antibody

Proteinase-3 is a 29-kD serine protease that exists in neutrophils. Antibodies to proteinase-3 may be detected in individuals with Wegener's Granulomatosis. Proteinase-3 antibody (IgG) is detected by enzyme immunoassay or a multiplex assay using microspheres coated with proteinase-3 antigen, with subsequent antibody detection by laser photometry.

Serum amyloid A (SAA)

Serum amyloid A has been proposed as a possible biomarker to evaluate mucosal healing in Crohn's disease. SAA may be measured by latex agglutination and ELISA, and has been a component of a multiplex vascular injury panel.

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CBir1 (flagellin-like antigen) antibody

CBir1 is a flagella component of indigenous bacteria in a mouse colitis model.[7] Anti-CBir1 antibody is detected by ELISA, and may be found in individuals with inflammatory bowel disease, non-IBD colitis, and ankylosing spondylitis.

I2 antibody

This antibody is directed against *Pseudomonas fluorescens* – associated sequence I2, and may be detected in individuals with IBD and non-IBD colitis. It is detected by ELISA.

Anti-glycan antibodies: Anti-chitobioside antibody (ACCA), anti-laminaribioside antibody (ALCA), anti-mannobioside antibody (AMCA)

Anti-glycan antibodies are reactive against cell wall components of microorganisms. Anti-glycan antibodies are measured using enzyme immunoassay. They have been proposed as aids in the diagnosis of inflammatory bowel disease, and in the differential diagnosis of Crohn's disease and ulcerative colitis.

Pyruvate kinase M2 (PKM2)

Serum PKM2 is measured by ELISA. Elevated levels of PKM2 have been detected in individuals with IBD.

IBD sgi Diagnostic™

This commercial proprietary assay combines serologic, genetic, and inflammatory biomarkers in a testing algorithm as an aid in differentiating IBD from IBS, and ulcerative colitis from Crohn's disease. The test includes 9 serological markers including anti-Fla-X, anti-A4-Fla2, anti-CBir1, anti-OMPC, and DNAse-sensitive pANCA, genetic evaluation of ATG16L1, STAT3, NKX2-3, and ECM1. Inflammatory markers include VEGF, ICAM, VCAM, CRP, and SAA.

Crohn's Prognostic™

This commercial proprietary assay combines serologic testing (anti-CBir1, anti-OMPC, DNAse sensitive pANCA) and genetic markers (NOD2 variants SNPs 8,12,13) and employs an algorithm to quantify the probability of disease complications over time.

Crohn's Monitr™

This commercial proprietary assay tests for 13 biomarkers (hsCRP, SAA, carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM 1), vascular cell adhesion molecule 1 (VCAM 1), interleukin-7, transforming growth factor-alpha, angiopoietin 1 and 2, matrix metalloproteinase 1 (MMP 1), MMP 2, MMP 3, MMP 9,

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and extracellular matrix metalloproteinase inducer (EMMPRIN)) and uses a proprietary algorithm to assess the severity of disease.

Fecal calprotectin

Calprotectin is a calcium and zinc binding protein present in the cytoplasm of granulocytes. There are several commercial, Food and Drug Administration (FDA)-cleared or automated immunoassay assays available to quantify human fecal calprotectin. The methodologies include enzyme linked immunoassays (ELISA), chemiluminescence immunoassays (CLIA), fluoroenzyme immunoassays (FEIA), and particle-enhanced turbidimetric immunoassays (PETIA).[8] Automated immunoassays for measuring fecal calprotectin, and point-of-care tests, are available commercially. Fecal calprotectin's proposed use is as an aid in identifying gastrointestinal disease, assess disease activity, and to monitor treatment.

Fecal lactoferrin, qualitative and quantitative

Fecal lactoferrin is an iron-binding glycoprotein that is a major component of secondary granules in neutrophils. It is detected by ELISA.

PredictSURE IBD

The PredictSURE IBD test is a reverse-transcriptase quantitative polymerase chain reaction performed on whole blood of untreated IBD patients, evaluating expression of 15 informative genes and 2 reference genes. The CD8 T cell gene expression signature generated is analyzed by a proprietary algorithm, which aims to predict which IBD patients will have a more aggressive disease course.

Guidelines and Evidence

The biomarkers listed below have proposed uses in the evaluation of inflammatory bowel disease. Guidelines on biomarker use in the setting of IBD by the American Gastroenterological Association stated conditional recommendations only for select biomarkers (fecal lactoferrin, fecal calprotectin, C-reactive protein) with a certainty of evidence graded from very low to moderate.[9,10]

Anti-neutrophil cytoplasmic antibodies (ANCA)

Anti-neutrophil cytoplasmic antibodies are classified according to staining pattern: cytoplasmic (c-ANCA) and perinuclear (p-ANCA). In inflammatory bowel disease, p-ANCA may be detected, and the antigen is thought to be histone 1, and a possible cross-reactant to antigens present in gut flora. p-ANCA is detected in 60-70% of ulcerative colitis cases, 10-15% of Crohn's disease cases, and less than 5% of non-IBD colitis cases.[7]

In individuals with an established diagnosis of IBD, an Australian retrospective cross-sectional study demonstrated the presence of ANCA in a high percentage of participants, but ANCA did not add value in disease subtyping.[11] Other retrospective studies demonstrated that p-ANCA may be detected more often in individuals with an established diagnosis of ulcerative colitis than in those with Crohn's disease or indeterminate colitis.[12,13] However, ANCA testing in the evaluation of IBD had low sensitivity.[14]

The American College of Gastroenterology, in its guideline for the management of Crohn's disease in adults, stated:[6]

- "Because of the heterogeneous nature of IBD there has been extensive research directed toward finding immunologic markers that would assist in disease diagnosis. These studies have focused on antibodies to microbial antigens and autoantibodies…"
- "Routine use of serologic markers of IBD to establish the diagnosis of Crohn's disease is not indicated."

Similarly, in its guideline for the management of ulcerative colitis (UC), the ACG stated:[5]

- "Serologic markers such as perinuclear antineutrophil cytoplasmic antibodies (pANCAs) may be found in up to 70% of patients with UC, and combination of negative anti–Saccharomyces cerevisiae antibodies with elevated pANCA levels has been proposed to facilitate establishing a diagnosis of UC. However, the pooled sensitivity of antibody testing for diagnosis of UC is low, and such markers are not used for establishing or ruling out a diagnosis of UC. Although pANCA positivity has also been associated with treatment refractory UC, the evidence supporting this is limited, and there is currently no role for such testing to determine the likelihood of disease evolution and prognosis."

Proteinase-3 antibody

Studies demonstrated that proteinase-3 antibodies are more often detected in ulcerative colitis than in Crohn's disease, however the utility of the test in managing IBD is yet to be established. In a retrospective study using a chemiluminescence assay, antibody to proteinase-3 had a sensitivity of 52.1% for ulcerative colitis.[12] In one study, proteinase-3 antibody levels were higher in individuals with ulcerative colitis, but the test demonstrated moderately poor sensitivity.[15] Similar results were found in other studies.[16,17] In a retrospective cohort study, anti-proteinase 3 was also found to be specific for ulcerative colitis in children, but with similar sensitivity (58%) as in adults.[13]

The ACG Clinical Guidelines for the management of Crohn's disease or ulcerative colitis in adults did not address proteinase-3 antibody testing.[5,6]

The utility of proteinase-3 antibody testing in altering therapeutic decisions, reducing disease complications, or reducing the need for more invasive testing has not been established.

Serum amyloid A (SAA)

Serum amyloid A (SAA) has been proposed to be a more sensitive biomarker of inflammation compared to CRP.[18] In a cross-sectional study of Crohn's disease, high SAA levels correlated with a lack of mucosal healing.[18] In another study, SAA was moderately correlated (r=0.64 and 0.42) with clinical indices of Crohn's disease activity.[19] In a study of individuals with ulcerative colitis in clinical remission, SAA correlated better (r=0.61) with the Mayo Endoscopic Score than CRP (r=0.35), but yielded only marginally better sensitivity.[20]

The ACG Clinical Guidelines for the management of Crohn's disease or ulcerative colitis in adults did not address serum amyloid A testing.[5,6]

The utility of serum amyloid A testing in altering therapeutic decisions, reducing disease complications, or reducing the need for more invasive testing has not been established.

Anti-Saccharomyces cerevisiae IgG and IgA (ASCA)

The presence of antibodies to the baker's yeast Saccharomyces cerevisiae (ASCA) has been posited as a marker for Crohn's disease and inflammatory bowel disease (IBD).[21]

ASCA may be detected in approximately 60-70% of individuals with Crohn's disease, 10-15% of individuals with ulcerative colitis, and less than 5% of those with non-IBD colitis.[7] However, the ASCA test has not emerged as a recommended test in any clinical presentation. It remains speculative that ASCA antibodies are associated with the development of IBD.[22]

There are reports of ASCA testing being used in conjunction with perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) testing in the context of IBD and Crohn's disease. According to one report, the combination of a positive ASCA test with a negative p-ANCA test had a positive predictive value of 96% and a specificity of 97% for Crohn's disease.[23] It is important to note that both p-ANCA and ASCA antibodies are found in other diseases, such as autoimmune liver disease, primary sclerosing cholangitis and gluten-sensitive enteropathy. Therefore, their role as diagnostic serological markers for IBD is limited.

One frequently cited study concerning ASCA as a marker concluded that ASCA (and p-ANCA) antibodies likely precede the clinical diagnosis of IBD.[21] If true, the presence of ASCA would not be useful in diagnosing IBD or Crohn's disease but would likely only function as a pre-marker for disease, with presumptive utility only with regard to risk of progression. For these reasons ASCA testing has not become commonplace.

Clinical guidelines did not provide any recommendation for ASCA testing in regard to evaluating for IBD. Specifically, for Crohn's disease:[6]

- "Routine use of serologic markers of IBD to establish the diagnosis of Crohn's disease is not indicated."

And for ulcerative colitis:[5]

- "We recommend against serologic antibody testing to establish or rule out a diagnosis of UC (strong recommendation, very low quality of evidence)" and "We recommend against serologic antibody testing to determine the prognosis of UC (strong recommendation, very low quality of evidence)."

Anti-OmpC antibody

IgA anti-OmpC antibody was present in approximately 55% of individuals with Crohn's disease, 5-10% of individuals with ulcerative colitis, and up to 36% of those with indeterminate colitis.[7] In a retrospective study of 135 children with IBD, anti-OmpC had a low sensitivity for Crohn's disease and ulcerative colitis.[24] In an observational study of 117 individuals with indeterminate colitis and at least of one-year follow-up after serologic testing, anti-OmpC antibody demonstrated low sensitivity and suboptimal specificity for a subsequent diagnosis of Crohn's disease or ulcerative colitis.[25] A separate study of indeterminate colitis found that anti-OmpC antibody contributed marginally to serologic testing for IBD.[26]

In a Chinese study, anti-OmpC antibody was detected in individuals with IBD, as well as in those with gastrointestinal tuberculosis and other gastrointestinal disorders.[27] In another study, anti-OmpC was found in over 15% of normal controls.[28] As an isolated test, anti-OmpC did not appear to have value in the diagnosis of IBD. Serologic markers, including OmpC, were also not a reliable predictor of outcome in ulcerative colitis.[29] Prospective studies are also necessary to determine whether use of anti-OmpC in a multi-marker panel can be used to distinguish ulcerative colitis from Crohn's disease.[28]

One potential clinical application for anti-OmpC antibody is as a biomarker for anti-TNF therapy response in ulcerative colitis. In a retrospective study of 230 individuals with ulcerative colitis, anti-OmpC positivity was associated with a lack of response to infliximab.[30] However, additional studies are necessary to support the use of anti-OmpC testing as a therapeutic guide.

Cytolethal distending toxin B antibody and vinculin antibody

Historically, the diagnosis of diarrhea-predominant irritable bowel syndrome (IBS-D) has been a clinical one, resting on characteristic clinical findings (e.g. chronic diarrhea) and exclusion of other etiologies such as inflammatory bowel disease (IBD) and celiac disease. Distinguishing between IBS-D and other causes of diarrhea remains a challenge, due to the broad differential diagnosis and lack of specific biomarkers for many entities, and workup may be extensive and costly.[31]

Some investigations demonstrated that a subset of IBS-D occurs after an episode of acute infectious gastroenteritis. In rat models of post-infectious IBS, antibodies reactive with the Campylobacter jejuni toxin cytolethal distending toxin B (Cdtb) cross react with the cell adhesion protein vinculin, found in the interstitial cells of Cajal and in myenteric

ganglia.[32] Anti-CtdB and anti-vinculin antibodies have been investigated as potential biomarkers for IBS-D.[33]

Several case-control studies investigated the utility of anti-CtdB and anti-vinculin in the diagnosis of IBS-D.[33,34] The studies found that mean anti-CtdB titers appeared higher in individuals with IBS-D than in healthy controls, but with substantial overlap in results between the two populations. In a community study, the difference did not reach significance.[35] In the largest study, with 2375 individuals with IBS, the difference was significant, though the effect size was modest for most participants.[33] The area under the receiver-operator curve for anti-CtdB was 0.81, and at an optimized cutoff, the sensitivity was 92% and the specificity 44%.

Studies of anti-vinculin produced conflicting results. In a community study, there was no significant difference between anti-vinculin titers in healthy individuals and those with IBS-D.[35] In another study, the difference was significant.[33] The latter study also investigated whether anti-CtdB and anti-vinculin could distinguish between IBS-D and IBD or celiac disease. It found that mean anti-CtdB and anti-vinculin titers were not significantly elevated in IBD, but were in celiac disease, indicating that elevated anti-CtdB and anti-vinculin did not distinguish between IBS-D and celiac disease.[33]

The American Gastroenterological Association (AGA) published evidence-based recommendations on the laboratory evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome in adults.[36] Recommendations varied in strength according to the quality of the clinical evidence. With regard to serologic testing for diagnosis of IBD, and specifically anti-CtdB and anti-vinculin, the recommendations stated, “No recommendation; knowledge gap.” Citing Pimentel et al. and a 30-person study conducted in Mexico, the authors continued:[33,37]

- "The available data are sparse but suggest that the contemporary tests lack the diagnostic accuracy needed for routine use. In addition, the case-control design of the studies and the study setting used (secondary and tertiary care) likely inflate the estimates of the test characteristics compared to what is expected in a general population. The specificity in the 2 studies available for the technical review was in the 90% range, meaning that a positive test would indicate a high likelihood of IBS-D. However, the low sensitivity (20%-40%) would not be sufficient to employ these tests in routine use. More data will be helpful in determining the proper roles of these and similar tests."

Other studies demonstrated that anti-CdtB and anti-vinculin lacked the sensitivity and specificity to discriminate functional GI syndromes.[35,37]

The utility of cytolethal distending toxin B antibody and vinculin antibody testing in altering therapeutic decisions, reducing disease complications, or reducing the need for more invasive testing has not been established.

Serum mannose-binding lectin

There were limited studies evaluating the use of serum mannose-binding lectin (MBL) in the clinical setting. In a study of children with IBD, mannose-binding lectin concentrations were lower in both Crohn's disease and ulcerative colitis, compared to controls.[38] In two adult studies, serum MBL did not appear to be beneficial in the diagnosis of IBD.[39,40] In another study, serum MBL was not associated with disease course or therapeutic response.[41]

The utility of serum mannose-binding lectin testing in altering therapeutic decisions, reducing disease complications, or reducing the need for more invasive testing has not been established.

CBir1 (flagellin-like antigen) antibody

Antibody directed against CBir1 was more prevalent in Crohn's disease than in ulcerative colitis, and was found in approximately 8% of non-IBD colitis cases.[7] In one study assessing the performance of anti-CBir1 as a serologic panel component, anti-CBir1 was detected in 39.5% of individuals with Crohn's disease, and 17.4% of individuals with ulcerative colitis.[28] A similar study also demonstrated low sensitivity of anti-CBir1 for Crohn's disease.[27] In a retrospective cohort study, high levels of anti-Cbir1 IgG were associated with a greater likelihood of active Crohn's disease.[42] A study of ankylosing spondylitis demonstrated that those also having IBD had higher levels of CBir1 antibody compared to those without IBD.[43] In children with IBD, CBir1 antibody may be detected in those negative for other serological markers and in younger individuals, and is more likely to be found in individuals with ulcerative colitis that develop pouchitis.[44-46] In a study of 601 adults with ulcerative colitis, anti-CBir1 antibody was not associated with severe disease, proximal disease extension, or colectomy.[29]

The ACG Clinical Guidelines for the management of Crohn's disease or ulcerative colitis in adults did not address CBir1 antibody testing.[5,6]

I2 antibody

I2 IgA antibody was detected in approximately 55% of individuals with Crohn's disease,10% of those with ulcerative colitis, and in 20% of non-IBD colitis cases.[7]

Studies assessing the clinical utility of I2 antibody were limited. In a retrospective cohort study of Crohn's disease, individuals with I2 antibody were more likely to have fibrosing Crohn's disease and to require small bowel surgery.[47] In another study, anti-I2 was associated with a clinical response to fecal diversion in individuals with proctocolitis and perianal disease.[48] In the pediatric population, anti-I2 has low sensitivity and specificity for IBD.[48]

The ACG Clinical Guidelines for the management of Crohn's disease or ulcerative colitis in adults did not address I2 antibody testing.[5,6]

The utility of I2 antibody testing in altering therapeutic decisions, reducing disease complications, or reducing the need for more invasive testing has not been established.

Anti-glycan antibodies: anti-chitobioside antibody (ACCA), anti-laminaribioside antibody (ALCA), anti-mannobioside antibody (AMCA)

Anti-glycan antibodies were implicated in the pathogenesis of IBD. Anti-glycan antibodies were detected in up to 30.5% of pediatric Crohn's disease cases, and were present in Crohn's disease cases that are negative for other biomarkers.[49,50]

In one cohort study, anti-glycan antibodies had a greater association with Crohn's disease than with ulcerative colitis.[51] In another cohort study, increasing levels of anti-glycan antibodies in Crohn's disease were associated with disease complications and the need for surgical intervention.[52] However anti-glycan antibody testing had limited use because of low sensitivity.[6]

The utility of anti-glycan antibody testing in altering therapeutic decisions, reducing disease complications, or reducing the need for more invasive testing has not been established.

Pyruvate kinase M2 (PKM2)

There were limited studies of the role of serum PKM2 in the evaluation of IBD. In one study, serum PKM2 levels were six times higher in newly diagnosed IBD, but PKM2 values did not correlate with disease activity indices.[53]

There were not any published studies evaluating the clinical utility of serum PKM2 in the diagnosis or management of individuals with IBD.

IBD sgi Diagnostic

There were not any published independent studies evaluating the utility of IBD sgi Diagnostic in the diagnosis or management of individuals with IBD.

Crohn's Prognostic

There were not any published independent studies evaluating the utility of Crohn's Prognostic in the diagnosis or management of individuals with IBD.

Crohn's Monitr

One study reported on the development and validation of this test.[54] Blood samples from 278 individuals with Crohn's disease were used to develop the test of 13 proteins, the result of which is reported as an endoscopic healing index (EHI). The test was validated using 2 independent cohorts. Test specificity using the two cohorts was 69% and 36.6%

using a cutoff EHI of 20 points, and 100% and 87.8% using a cutoff EHI of 50 points. The AUROC for the test did not differ significantly from that of fecal calprotectin.

There were not any published independent studies evaluating the utility of Crohn's Monitr in the diagnosis or management of individuals with IBD.

Fecal calprotectin

Fecal calprotectin is a non-invasive marker used with the aim of distinguishing IBD from other intestinal disorders, and for the diagnosis of IBD, monitoring therapeutic response, and determining the need for endoscopy.[55,56] Some studies found fecal calprotectin to correlate with endoscopic findings or predict relapse. In individuals with Crohn's disease, fecal calprotectin correlated moderately (r=0.45) with a simple endoscopic score.[57] In a meta-analysis of 8 prospective studies, fecal calprotectin essentially excluded IBD in individuals with irritable bowel syndrome (IBS) symptoms when less than 40 ug/g, however it did not reliably distinguish between IBS and healthy controls, and had a maximum predictive value for IBD of 78.7%.[58] There was also significant heterogeneity among the studies. In a second meta-analysis of cohort and case-control studies, fecal calprotectin yielded a pooled sensitivity of 0.88 and specificity of 0.73 when compared to endoscopy.[56] Similar results were obtained in a meta-analysis of eight pediatric IBD studies.[59]

One systematic review was of six prospective studies that evaluated the usefulness of monitoring fecal calprotectin to predict disease relapse. Although two consecutively increased levels appeared to be the best predictor for relapse, the studies demonstrated significant heterogeneity, and poor consistency with regards to the definition of relapse and the reference standard used. Probabilities of relapse and remission were as high as 83% and 33%, respectively; whether therapeutic decisions or health outcomes were affected was not addressed.[60]

A National Institute for Health Research technology assessment concluded that fecal calprotectin could be a highly sensitive test for detecting IBD, concluding that a negative test result could exclude IBD in most cases.[61] The systematic review included studies predominantly of referral populations, limiting generalizability of the study results. A separate meta-analysis assessed the efficacy of fecal calprotectin as a diagnostic marker for IBD in individuals with gastrointestinal symptoms.[62] The authors concluded that individuals with a fecal calprotectin below the cut-off level would not need to proceed to colonoscopy. In that meta-analysis, the pooled sensitivity and specificity from 19 studies was 0.882 and 0.799, respectively.

An expert joint panel of the European Crohn's and Colitis Organisation (ECCO) and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) published comprehensive guidelines for the diagnosis and monitoring of IBD in 2019.[63] Calprotectin studies to assess intestinal inflammation in IBD were discussed:

- "Faecal calprotectin [FC], a neutrophil-derived protein, appears to be the most sensitive marker of intestinal inflammation in IBD…An exact cut-off value that distinguishes between IBD and functional bowel diseases does not exist. However, good diagnostic accuracy can potentially be obtained at a cut-off value of 150 µg/g, as recently suggested in a meta-analysis."
- "A more accurate surrogate marker of [mucosal healing] is faecal calprotectin [FC]. There is a strong correlation between endoscopic inflammation and FC in UC. In a study with 52 patients, FC correlated with clinical Mayo score [$r = 0.63$; $p < 0.0001$]."
- "In one of the more recently published studies, patients with both UC and CD provided faecal samples every third month and were prospectively followed until the first clinical relapse…This study revealed that FC levels start rising approximately 3 months before a relapse becomes clinically apparent, and confirmed the observations of the aforementioned systematic review."

The AGA clinical practice guidelines provided a conditional recommendation for fecal calprotectin testing in the evaluation of functional diarrhea and diarrhea-predominant IBS in adults:[36]

- "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."

In a subsequent guideline, the AGA provided conditional recommendations for fecal calprotectin testing in the setting of ulcerative colitis, albeit with a low or very low level of evidence.[9]

For the evaluation of irritable bowel syndrome, the American College of Gastroenterology recommended fecal calprotectin "in patients without alarm features and with suspected IBS and diarrhea symptoms to rule out inflammatory bowel disease".[66]

The British Society of Gastroenterology consensus guidelines stated:[67]

- "We recommend that, for patients aged 16–40 presenting in primary care with chronic diarrhoea and symptoms that may be consistent with either IBD or IBS, faecal calprotectin is a useful screening tool with a high negative predictive value. If significantly elevated, patients should have an infective cause excluded and be referred for further investigation (GRADE: strong recommendation, moderate-quality evidence. Agreement: 97.9%)."

Several studies examined the value of fecal calprotectin in predicting IBD relapse. Depending upon the cutoff value chosen, IBD subtype, time to remission, and study endpoint, sensitivity for relapse ranged from 32% to 100%, and specificity from 24% to 91%.[68] In a single center, retrospective cohort study of individuals with IBD in remission, fecal calprotectin levels at baseline were higher in those that experienced disease relapse, however only close to 50% of the participants underwent endoscopy during the 6-month follow-up period.[69] In a multi-center cohort study, fecal calprotectin levels

were again found to be a predictor of relapse following therapeutic de-escalation, however cut-off levels for fecal calprotectin were retrospectively determined, and 35 of 98 (35.7%) of individuals with fecal calprotectin levels < 100 µg/g experienced relapse within 12 months.[70] In a prospective study of Crohn's disease treated with infliximab, fecal calprotectin measurement at 14 weeks could not predict relapse at 1 year.[71] In a prospective observational study, fecal calprotectin of 100 µg/g had a sensitivity of 91.7% and specificity of 57.1% for histologic remission of ulcerative colitis.[72]

The British Society of Gastroenterology guidelines stated:[67]

- "…more evidence is also needed of the role of faecal calprotectin or other biomarkers as non-invasive surrogates for mucosal healing"
- "We suggest that patients in whom anti-TNF therapy is withdrawn should be observed for evidence of relapse. Monitoring of faecal calprotectin may be helpful in this context as levels may rise before clinical relapse occurs (GRADE: weak recommendation, low-quality evidence. Agreement: 97.9%)."
- "We suggest that patients presenting with features of orofacial granulomatosis (OFG) and gastrointestinal symptoms, raised inflammatory markers or raised faecal calprotectin should have the gastrointestinal tract investigated for inflammation (GRADE: weak recommendation, very low-quality evidence. Agreement: 100%)."
- "We suggest that, in the event of symptomatic recurrence following ileocolonic resection for Crohn's disease, an assessment of mucosal inflammation may be performed with ileocolonoscopy. Faecal calprotectin and/or cross-sectional imaging may be used if ileocolonoscopy is not possible or acceptable, but may not be sensitive enough to detect localised inflammation (GRADE: weak recommendation, low-quality evidence. Agreement: 97.4%)."

The European Society for Paediatric Gastroenterology and Nutrition Gastroenterology Committee stated:[73]

- "Although faecal calprotectin may be considered as a tool to differentiate functional gastrointestinal disorders from organic diseases, it has not proven its value in this respect apart from identifying possible inflammatory bowel disease within these common clinical presentations… Other than inflammatory bowel disease, the applicability of faecal calprotectin measurement in gastrointestinal inflammatory and immune-mediated conditions remains to be defined."

Randomized controlled trials examining the role of fecal calprotectin with well-defined cutoff values in predicting IBD relapse may clarify the inconsistencies among prior studies.

The CALM study was a multicenter, randomized, open label controlled phase 3 trial comparing endoscopic and clinical outcomes in moderate to severe Crohn's disease managed with a tight control algorithm that included the use of biomarkers versus clinical management.[74] The study revealed better outcomes in individuals managed by symptoms and biomarker results than by symptoms alone. One limitation of this

industry-funded study was that 26% of the participants managed by tight-control and 24% managed by symptoms only discontinued the study; statistical analysis did not account for endpoints of participants that discontinued the study. Treatment failure criteria, not including biomarker values, also were different between the two groups. Exclusion criteria utilizing biomarker values contributed selection bias to the study. The study's design of not blinding investigators and participants to treatment did not establish that fecal calprotectin values were independent from other variables in driving medical management or outcomes. Additional study limitations negatively influenced the significance of the investigators' conclusions.

Studies of fecal calprotectin testing in the post-operative setting produced inconsistent results, and its use in the post-operative setting requires further investigation.[75] Studies examining the use of fecal calprotectin in assessing the presence of pouchitis demonstrated moderately good correlation with endoscopic and clinical findings, but did not establish an impact on management.[55]

Fecal lactoferrin

Like calprotectin, fecal lactoferrin is a non-invasive biomarker used with the aim of distinguishing IBD from IBS and assessing mucosal healing and disease relapse in IBD.

In a meta-analysis involving both fecal biomarkers, pooled sensitivities and specificities for IBD compared to endoscopy were similar.[56] In a tertiary center study, fecal lactoferrin was significantly higher in individuals with IBD compared to those with IBS and healthy controls.[76] Additional studies demonstrated that the accuracy of fecal lactoferrin was similar to that of fecal calprotectin in distinguishing active IBD from inactive IBD and IBS.[77,78]

The AGA clinical practice guidelines provided a conditional recommendation for fecal lactoferrin testing in the evaluation of functional diarrhea and diarrhea-predominant IBS in adults:[36]

- "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."

In a subsequent guideline, the AGA similarly provided conditional recommendations for fecal lactoferrin testing in the setting of ulcerative colitis, albeit with a low or very low level of evidence.[9]

The utility of fecal lactoferrin testing in altering therapeutic decisions, reducing disease complications, or reducing the need for more invasive testing was not established.

PredictSURE IBD

There were no published randomized control studies examining the clinical utility of the PredictSURE IBD test. The benchmark study for this test was a prospective study of a

validation cohort of 123 individuals with active IBD recruited from four United Kingdom hospital based IBD specialty clinics over an 8-year period.[79] Disease activity status was confirmed by serum CRP, calprotectin, or endoscopy. The study did not employ a non-diseased comparison population. Participants identified by the algorithm as having a high probability of aggressive disease were more likely to receive escalated therapy. The data analysis did not stratify the study population by disease history (new diagnosis vs prior diagnosis) or disease activity indicator (CRP, calprotectin, endoscopic findings).

A similar, earlier study examined the likelihood of therapy escalation in a cohort of 77 individuals with IBD, 52% of which had newly diagnosed disease.[80] Subgroups of participants with CD or UC defined by transcriptional signatures of CD8 positive T cells demonstrated differing proportions requiring therapy escalation, however follow-up was inconsistent among and between groups, and there was no subgroup analysis of those with newly diagnosed disease and those with existing disease.

A separate prospective cohort study of 112 treatment-naïve pediatric IBD patients and 19 healthy controls examined the role of CD8 positive T-cell transcription signatures and DNA methylation in disease activity and outcome. Although there was an association between CD8 positive T-cell gene expression and IBD, there was no association with disease outcome.[81]

In a technology briefing, the National Institute for Health and Care Excellence stated:[82]

- "…PredictSURE IBD may be a helpful test to determine the most appropriate treatment for people with ulcerative colitis; however, there is limited evidence to support that."

The utility of PredictSURE IBD testing in altering therapeutic decisions, reducing disease complications, or reducing the need for more invasive testing has not been established.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for inflammatory bowel disease biomarker testing will ensure that testing will be available to those members most likely to benefit from the information provided by the assays. For those not meeting criteria, it ensures alternate management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

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