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Serological Testing for Inflammatory Bowel Disease (IBD)

Table of Contents

Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

This medical policy has become inactive as of the end date above. There is no current active version and this policy is not to be used for current claims adjudication or business purposes.

Testing for serological markers for the diagnosis and/or management of inflammatory bowel disease (IBD) **is considered experimental, investigational and/or unproven.** Tests include, but are not limited to the following:

- Anti-neutrophilic cytoplasmic antibody (ANCA), perinuclear anti-neutrophilic cytoplasmic antibody (pANCA);
- Anti-saccharomyces cerevisiae antibody (ASCA);
- Anti-outer membrane porin C (anti-OmpC) antibody;
- Anti-CBir1 flagellin (anti-CBir1) antibody;
- Anti-laminaribioside carbohydrate IgG (ALCA);
- Anti-chitobioside carbohydrate IgA (ACCA);
- Anti-synthetic mannoside antibodies (AΣMA or AMCA);
- Pseudomonas-associated sequence I2 (Anti-I2).

IBD diagnostic testing combining serologic, genetic, and inflammatory markers (e.g., Prometheus® IBD sgi Diagnostic®, Prometheus® Crohn's Prognostic) **is considered experimental investigational and/or unproven.**

Policy Guidelines

The following codes may be submitted for the Prometheus® IBD sgi Diagnostic® testing: 81479 (multiple units), 82397 (multiple units), 83520 (multiple units), 86140, 88346, 88350.

The following codes may be submitted for the Prometheus® Crohn's Prognostic testing: 81401, 83520 (multiple units), 88346, 88350.

These procedure codes are considered experimental, investigational and/or unproven when submitted for either of the tests mentioned.

Description

Inflammatory bowel disease (IBD) is a general term used to describe diseases that cause inflammation of the intestines. Crohn's disease (CD) and ulcerative colitis (UC) are the two major IBDs. In CD, inflammation usually occurs in the lower part of the small intestine (distal ileum) but may affect any part of the digestive tract. The inflammation in CD extends deep into the affected tissue, in contrast to UC, which causes inflammation and ulcers in the top layers of the lining of the colon and rectum. Inflammation in CD is asymmetrical and segmental, with areas of both healthy and diseased tissue, in contrast to UD where inflammation is symmetrical and uninterrupted from the rectum proximally.

Both CD and UC are chronic and affect men and women on an approximately equal basis. These diseases are seen most commonly in northern Europe and North America. Approximately 20 percent of individuals with CD have a blood relative with some form of IBD. The onset of CD is usually between ages 15 and 30 with a second smaller peak of incidence between 50 and 70. Since many of the symptoms of CD and UC are similar, diagnosis is often difficult, time consuming, and invasive. Approximately 10-15 percent of cases are not initially classifiable and is referred to as "indeterminate colitis." (2) Over time, about half of these patients are eventually classified as CD or UC.

Clinical management of CD and UC requires repeated assessments; endoscopy with histological examination remains the gold standard for detecting and quantifying intestinal inflammation. Several laboratory tests have been studied but to date, a disease marker is not yet available. In recent years, research has drawn attention to fecal markers owing to their specificity for intestinal inflammation, ease of sample collection, availability of commercial immunoassays and convenience. These biologic markers have been used to assess IBD patients for the purposes of their clinical management and response to treatment.

Perinuclear anti-neutrophilic cytoplasmic antibody (pANCA) and anti-saccharomyces cerevisiae antibody (ASCA) are serological markers that have been proposed as tools to assist in diagnosing IBD, differentiating UC from CD in patients with indeterminate colitis, and determining therapy and monitoring response to treatment. Anti-neutrophilic cytoplasmic antibody (ANCA) has been used in the diagnosis and classification of various vasculitis-associated and autoimmune disorders and has been associated with renal manifestations of small vessel vasculitis with rapidly progressing glomerulonephritis. pANCA is an antibody directed against the cytoplasmic components of neutrophils with a perinuclear staining pattern. Serum pANCA has been reported to be present in 20–85% of patients with UC, and in 2–28% of patients with CD. Elevated levels of serum pANCA in UC patients are believed to be caused by pANCA production in the colonic mucosa. (3)

Anti-saccharomyces cerevisiae antibody (ASCA) is an antibody that reacts to a component of yeast commonly found in food. ASCA has been detected in the serum of a majority of CD patients, but fewer UC patients. The origin of ASCA is not clear, nor is it known why this antibody occurs in only a subset of patients with CD. ASCA has been detected in approximately 39–76% of CD patients, and up to 15% in UC patients. (3)

Several additional antibodies have been described as serological markers for IBD, including anti-outer membrane porin C (anti-OmpC) and anti-CBir1 flagellin (anti-CBir1). These antibodies are directed against luminal bacterial components seen in IBD. Anti-OmpC, directed against the outer membrane porin C of Escherichia coli, is reportedly seen more often in patients with a mixed family history of CD and UC as opposed to those with a family history of only UC. The antigens CBir1, A4-Fla2, and Fla-X are flagellin subunit proteins linked to Clostridium cluster XIVa. Anti-CBir1 is an antibody to flagellin from Clostridium species and is reported to be found in approximately 6% of UC patients and 50% of patients with CD and may be associated with more complicated disease. Pseudomonas-associated sequence I-2 (Anti-I2 is a bacterial DNA fragment and has been identified in lamina propria mononuclear cells of active CD patients. Anticarbohydrate antibodies have also been used in IBD management, including antilaminaribioside carbohydrate IgG (ALCA), antichitobioside carbohydrate IgA (ACCA), and anti-synthetic mannoside antibodies AΣMA or AMCA). ALCA, ACCA, and AMCA are similar to ASCA in that they are antibodies to sugars on the surface of microorganisms. ALCA and ACCA are reported to be associated with CD and are found in 17–28% of CD patients. AΣMA is an antibody against synthetic oligomannose epitopes and is found to be positive in 24% of patients with CD who were negative for ASCA and had a lower sensitivity but higher specificity compared to ASCA. (2, 3)

Combined serological testing has been proposed as a screening method for patients who present with signs and symptoms of IBD, and as a method to differentiate CD from UC. Prometheus® Biosciences (San Diego, CA) offers a variety of proprietary diagnostic tests for a variety of disorders, including one for the differentiation of IBD vs. non-IBD. Prometheus® IBD sgi Diagnostic® includes the 9 serological markers ASCA IgA, ASCA IgG and proprietary markers anti-Fla-X, anti-A4-Fla2, anti-CBir1, anti-OMPC, and DNAse-sensitive pANCA. This test uses

algorithmic technology to improve the predictive accuracy to provide added clarity in diagnosing IBD. (5)

Combined serological testing has also been proposed as a method of determining the risk for disease-related complications in patients with CD. Prometheus Crohn's Prognostic, combines proprietary serogenetic markers and serologic markers, including Anti-I2 and many of the assays included in the Prometheus® IBD sgi Diagnostic panel. The test employs a logistic regression model to provide probabilities for developing disease complications in patients diagnosed with CD. (6)

Regulatory Status
Laboratory tests are not regulated by the U.S. Food and Drug Administration. Laboratories performing clinical tests must be certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

Rationale

Laboratory studies can be valuable in assisting with the management of inflammatory bowel disease (IBD); however, no laboratory test is specific enough to adequately and definitively establish the diagnosis of IBD. It has been suggested that serologic studies may be used to help diagnose IBD and to differentiate Crohn disease (CD) from ulcerative colitis (UC), but they are not recommended for routine diagnosis of either. (3)

Perinuclear antineutrophil cytoplasmic antibodies (pANCA) have been identified in some patients with UC, and anti-Saccharomyces cerevisiae antibodies (ASCA) have been found in patients with CD. The combination of positive pANCA and negative ASCA has high specificity for ulcerative colitis, whereas the inverse pattern—positive ASCA, negative pANCA—is more specific for CD. However, false-positive (and false-negative) results are not uncommon; therefore, at this time, serologic markers cannot be used to definitively rule in or exclude IBD. (3)

A variant of CD involving the colon may result in a positive pANCA test, which could complicate the diagnosis. Serum response to anti-CBir1, an antibody associated with the presence of IBD, has been shown to differentiate pANCA-positive results with UC versus UC-like CD. (3)

A higher number of positive ASCA may indicate a great risk of complications such as strictures and fistulas in patients with CD, as well as a higher risk for surgery. However, serologic markers do not appear to predict response to medical therapy and there is currently insufficient evidence to recommend the use of antibody testing to predict responses to medical treatment or surgery in patients. (3)

In 2006 Bossuyt conducted a review focusing on the value of antibodies for diagnosing IBD, differentiating CD from ulcerative colitis, indeterminate colitis, monitoring disease, defining

clinical phenotypes, predicting response to therapy, and as subclinical markers. Pancreatic antibodies and newly identified anti-microbial antibodies (anti-outer membrane porin C, anti-I2, and anti-flagellin) were also reviewed. The role of atypical pANCAs and ASCAs as diagnostic serologic markers for IBD appears to be limited, however, mainly because of their lower sensitivity. A positive test result for either pANCAs or ASCAs modestly influences pretest–posttest probability in distinguishing IBD from non-IBD, and a negative test result has no clinical value. The combined use of atypical pANCA and ASCA test results substantially affects pretest–posttest probability in distinguishing UC from CD in patients with IBD. The pANCA+/ASCA- combination is specific for UC, whereas the ASCA+/pANCA- combination is specific for CD. This may be of help in patients in whom distinction between CD and UC is not obvious with the classic diagnostic tools (patient history, radiologic examination, endoscopy, and biopsy). The discriminative value of ASCAs and pANCAs to predict definitive diagnosis (CD or UC) in patients with indeterminate colitis is modest. Almost 50% of these patients do not develop ASCA or pANCA antibodies. The author concluded future studies should unravel whether this seronegative subgroup of patients represents a separate clinical entity. Serial measurement of pANCAs and ASCAs is not useful. Titers of both antibodies are stable over time and do not correlate with disease activity. The assays that detect atypical pANCAs and ASCAs lack standardization, which leads to large interlaboratory variation. Efforts should be undertaken to harmonize these assays, and future research should aim to identify the main autoantigens targeted by atypical pANCAs. (4)

Pancreatic antibodies are specific markers for IBD. Their sensitivity, however, is limited (30%). Microbial target antigens (OmpC, I2, and the flagellin CBir1) have been described in patients with CD. There is evidence that the number and magnitude of immune responses to different microbial antigens are associated with the severity of the disease course. This should be confirmed by additional studies. The author concluded future studies should further explore the potential to cluster patients in more homogeneous subgroups based on antibody responses. Correlating serologic markers with genotypes and clinical phenotypes should enhance understanding of the pathophysiology of IBD. Hopefully this will lead to the introduction of new and accurate tools for diagnosis, stratification, and follow-up of patients with IBD. (4)

Kaul et al. (2012) performed a systematic review (n=14 studies) and meta-analysis (n=9/14 studies) of the evidence evaluating the diagnostic ability of the anti-glycan antibodies (ASCA/gASCA, AMCA, ALCA, ACCA, Anti-L, Anti-C) to differentiate IBD from non-IBD and CD from UC, as well as their association with disease complications and/or need for surgery in IBD. Studies were primarily retrospective and were included if they compared the performance of at least two of the six anti-glycan antibody markers in at least one of the following outcomes: differentiating IBD from non-IBD; CD from UC; IBD-related complication; or need for IBD-related surgery. The mean age of the IBD patients ranged from 29 to 47 years, with mean duration of disease ranging from five to 12 years. For individual antibodies, ASCA was reported to have the highest diagnostic performance in differentiating conditions:

- IBD versus healthy: Diagnostic odds ratio (DOR), 21.1; 95% CI, 1.8-247.3; sensitivity 44.0%; specificity 96.4%;

- CD versus UC: DOR, 10.2; 95% CI, 7.7-13.7; sensitivity 56.6%; specificity 88.1%;
- CD versus other gastrointestinal disorders: DOR, 10.3; 95% CI, 5.0-21.0; sensitivity 52.8%; specificity 90.0%;
- CD versus healthy: DOR, 2.7; 95% CI, 0.3-21.6; sensitivity 53.0%; specificity 70.4%.

ASCA had the highest sensitivity compared to the other anti-glycan markers for diagnosis of both CD (52.8- 56.6% versus 15.0-27.8%) and CD related surgery (60.2% versus 43.9-47.3%) or complications (70.8% versus 42.3-54.5%). For specificity all individual markers performed similarly (88-95%). The authors noted that although individual studies suggested that the combination of at least two markers had a better diagnostic value, this meta-analysis indicated that the combination of markers performs only slightly better than any individual marker. Limitations of this review include the retrospective design of studies included and the lack of data demonstrating improved clinical outcomes. Although results indicated that the measurement of serological antibodies may have some value in differentiating IBD conditions, additional well designed controlled studies are needed to demonstrate clinical utility and impact on health outcomes. (7)

A prospective study (n=169 patients/523 samples) by Hamilton et al. in 2017 evaluated the role of serological antibodies in predicting recurrence after CD resection. Subjects were prospectively tested for serologic antibody presence (e.g., pANCA, ASCA, IgA/IgG, anti-OmpC, anti-CBir1, anti-A4-Fla2, anti-Fla-X) and titer perioperatively, and at 6, 12 and 18 months postoperatively. Colonoscopy was performed at 18 months postoperatively. Quartile sum score (range 6-24), logistic regression analysis, and correlation with phenotype, smoking status and endocsocpic outcome were assessed. Patients with ≥2 previous resections were found to be more likely to be anti-OmpC positive (p=0.001). Recurrence at 18 months was associated with anti-Fla-X positivity at baseline (p=0.033) and 12 months (p=0.04). Patients who were positive (n=28) for all four antibacterial antibodies (anti-CBir1, anti-OmpC, anti-A4-Fla2, and anti-Fla-X) at baseline were more likely to experience recurrence at 18 months than those who were negative (n=32) for all four antibodies (p=0.034). The baseline quartile sum score for all six antimicrobial antibodies was higher in patients with severe recurrence at 18 months, adjusted for clinical risk factors (p=0.039). It was concluded that pre-operative serologic screening may help to identify patients at increased risk for CD recurrence. (8)

In 2020, Chen et al. performed a review of the available data on serological biomarkers for IBD. Noting that serum pANCA have been widely studied and are accepted to be UC specific, it can differentiate UC from CD. However, the sensitivity of pANCA in the evaluation of patients with suspected UC is rather low; and pANCA are significantly increased in UC patients and in CD patients with “UC-like” features. Nearly 25% of CD patients with left-sided colitis identified endoscopically or histopathologically and with symptoms similar to UC present with increased levels of pANCA, which limits the utility of pANCA in the subclassification of IBD. Study has shown that an increased titer of ASCA is associated with genes involved in bacterial sensing and autophagy. ASCA are also a risk marker for early disease onset, fibrostenosing, and internal-penetrating disease behavior. However, the expression of ASCA is relatively low in patients with isolated colonic CD. Moreover, it should be noted that the expression of ASCA varies in

different ethnic populations: the prevalence and titers of ASCA are significantly lower in Asian CD patients than Caucasian CD patients. The levels of antibodies to the cell wall carbohydrate epitopes of bacteria, such as laminaribioside carbohydrate (ALCA), chitobioside (ACCA), and mannobioside carbohydrate (AMCA), are higher in patients with CD compared with patients with UC and healthy subjects (30). However, the combination of these antibodies and ASCA were not useful for the subclassification of IBD. The authors concluded that despite a great deal of study, current IBD markers are far from ideal; and further studies are required to identify new biomarkers that have improved availability. Newly discovered markers should be confirmed in multicenter international collaborations before they are applied to clinical practice. (9)

Gao and Zhang in 2021 studied the use of serological markers for the diagnosis of Crohn's disease (10). In the study, 196 suspected CD patients were enrolled, and ELISA was used to study the expression of various biomarkers including ASCA-IgG, ASCA-IgA, AYMA-IgG, AYCA-IgA, FI2Y-IgG, and pANCA. Overall, ASCA was found to be the most accurate serological marker for the differential diagnosis of CD. It was also noted that a combination of markers resulted in a higher sensitivity and NPV. There was no relation noted between the expression of ASCA and disease behavior at diagnosis.

In 2022, Nakov et al. (11) performed a review of current studies related to IBS and IBD biomarker diagnosis and management, including how to distinguish IBS – a disorder of the gastrointestinal tract - from IBD – 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." The authors noted a limitation in the development of biomarkers for IBS is that this is not one disease; and establishing a biomarker that can identify all patients with IBS is extremely unlikely. IBS biomarkers are disappointing due to small study populations and the challenges of ruling out other organic diseases with modest accuracy.

Practice Guidelines and Position Statements

The American College of Gastroenterology (ACG) 2018 Clinical Guidelines on Management of CD in Adults state that "routine use of serologic markers of IBD to establish the diagnosis of Crohn's disease is not indicated." (1)

The 2019 ACG Clinical Guidelines on UC in Adults have a strong recommendation, with very low quality of evidence against the use of serologic antibody testing to establish or rule out a diagnosis of UC and to determine the prognosis of UC. These guidelines specifically state:

- "We recommend against serologic antibody testing to establish or rule out a diagnosis of ulcerative colitis (strong recommendation, very low quality of evidence).
- We recommend against serologic antibody testing to determine the prognosis of ulcerative colitis (strong recommendation, very low quality of evidence)." (12)

Summary of Evidence

There have been numerous studies and reviews of various serological biomarkers purported to be useful in the diagnosis and management of inflammatory bowel disease (IBD). None of the literature has shown how the use of serological markers can be applied to clinical practice and improve the health outcome of patients. The literature is insufficient to support the use of serological markers in the diagnosis and management of IBD. Therefore, testing of these markers is considered experimental, investigational and/or unproven in the diagnosis and management of IBD.

Coding

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

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	81401, 81479, 82397, 83516, 83520, 86021, 86036, 86037, 86140, 86255, 86256, 88346, 88350
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
12/31/2025	Document became inactive.
06/15/2025	Reviewed. No changes.
04/01/2024	Document updated with literature review. Coverage unchanged. References 10 and 11 added; others revised.
03/15/2023	Reviewed. No changes.
08/15/2022	Document updated with literature review. Coverage unchanged. No references added, some updated.
04/01/2021	Reviewed. No changes.
09/01/2020	Document updated with literature review. The following tests were added to the experimental, investigational and/or unproven statement: Anti-I2; Anti-aminaribioside carbohydrate IgG (ALCA); Anti-chitobioside carbohydrate IgA

	(ACCA); Anti-synthetic mannoside antibodies (AΣMA or AMCA); and Pseudomonas-associated sequence I2 (Anti-I2). Prometheus® Crohn's Prognostic added to the diagnostic testing combining serologic, genetic and inflammatory markers as experimental, investigational and/or unproven. Rationale and references revised. Title changed from Serological Markers for the Diagnosis and Management of Inflammatory Bowel Disease.
07/01/2019	Reviewed with literature review. Coverage unchanged.
03/01/2017	Reviewed. No changes.
04/15/2016	Document updated with literature review. Coverage unchanged.
09/01/2015	Reviewed. No changes.
03/01/2014	Document updated with literature review. Title changed from Biologic Markers for Diagnosis and Management of Inflammatory Bowel Disease (IBD). Policy no longer addresses fecal markers. The following was added to the experimental investigational and/or experimental listing of testing: anti-outer membrane porin C (anti-OmpC) antibody and anti-CBir1 flagellin (anti-CBir1) antibody. In addition, the following was also added: IBD diagnostic testing combining serologic, genetic, and inflammatory markers (eg, Prometheus® IBD sgi Diagnostic™) is considered experimental investigational and/or unproven.
04/01/2011	Document updated with literature review. Title changed from Serum Antibodies for the Diagnosis of Inflammatory Bowel Disease (IBD) to Biologic Markers for Diagnosis and Management of Inflammatory Bowel Disease (IBD) CPT/HCPCS code(s) updated. Coverage was unchanged.
02/15/2010	Routine update of policy with literature review, no change in coverage.
01/01/2008	Revised/updated entire document