Medical Policy

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***Current Policy Effective Date: 1/1/24**
(See policy history boxes for previous effective dates)

Title: Serum Markers for the Diagnosis and Care of Inflammatory Bowel Disease

Description/Background

Serological markers, which are used to identify antibodies in the blood with some diseases, have been proposed as a means to distinguish between Crohn's disease versus ulcerative colitis and inflammatory bowel disease (IBD) versus non-IBD. Such antibodies are typically formed in response to an infection (against a given microorganism), against other foreign proteins, or to one's own proteins (in instances of autoimmune disease). Serological tests may be performed for diagnostic purposes when an infection is suspected and in many other situations.

Inflammatory bowel disease (IBD) is a term for 2 conditions (Crohn's disease and ulcerative colitis) that are characterized by chronic inflammation of the gastrointestinal (GI) tract. The exact cause is unknown, but there appears to be a genetic component. Individuals with a family history of IBD are at a higher risk of developing the disease. A defective immune system is believed to be the culprit. Environmental triggers cause inflammation of the GI tract as a result of improper immune response.

Crohn's disease (CD) most often affects the portion of the small intestine before the large intestine/colon but can affect any part of the GI tract from the mouth to the anus. The inflammation in Crohn's disease may affect multiple layers of the GI walls. Ulcerative colitis (UC) is characterized by inflammation of the large intestine and rectum with inflammation being present only in the innermost layer of the lining.

IBD is prevalent in children as well as adults. The incidence of IBD is 100 to 200 per 100,000 individuals in North America and Europe and has recently increased rapidly in several countries. Crohn's disease was first reported by Burrill Crohn et al (1922) and was called regional ileitis. According to the Centers for Disease Control and prevention (2019), in 2015 an estimated 1.3% of adults in the United States reported being diagnosed with either Crohn's

disease or ulcerative colitis, and the incidence and prevalence are rising. Ulcerative colitis has a prevalence of 35-100 cases per 100,000 in the United States.

Individuals with IBD produce particular antibodies. Several serological markers for UC and CD have been identified and investigated. Two such markers, discussed below, have been extensively studied for their role in the diagnosis of IBD and also for their ability to differentiate between CD and UC. In addition, a panel of markers with the use of an algorithm is being studied in the identification of specific subtypes of IBD that have different clinical courses.

Perinuclear anti-neutrophilic cytoplasmic antibodies (pANCA) and anti-Saccharomyces cerevisiae antibodies (ASCA) are 2 serum autoantibodies that have been investigated as initial markers in diagnosing IBD and distinguishing between CD and UC. It is believed that these serological markers may potentially decrease the need for extensive diagnostic workup and invasive imaging. Testing for pANCA is available in most clinical laboratories, while ASCA is not widely available.

pANCA is positive in 60-70% of patients with known ulcerative colitis. It is present in up to 40% of patients with CD. ASCA is positive in 50-70% of CD patients and in 6-14% of those with ulcerative colitis. High titers of ASCA, or the presence of both IgG and IgA antibodies for ASCA, are associated with fibrostenosing and penetrating forms of this disease.

In addition to pANCA and ASCA, a number of new antibodies have recently been discovered, and data on their clinical significance has been rapidly increasing. As a result, assays incorporating other serum markers have been developed for use in conjunction with pANCA and ASCA in an effort to improve the diagnostic capabilities of serologic testing for IBD. Other serum markers associated with IBD include antibodies against outer membrane porin C (anti-OmpC), Pseudomonas fluorescens bacterial sequence I2 (anti-I2), and bacterial flagellin (anti-CBir1). Additionally, the following anti-glycan antibodies have been investigated for their diagnostic value and for assessing their association with disease severity in IBD:

- AMCA (Anti-Mannobioside Carbohydrate Antibody)
- ALCA (Anti-Laminaribioside Carbohydrate include Antibody)
- ACCA (Anti-Chitobioside Carbohydrate Antibody)
- Anti-L (Anti Laminarin)
- Anti-C (Anti-Chitin)

Currently, Prometheus® Inc. offers 2 diagnostic systems that use combinations of tests in addition to pANCA and/or ASCA to aid in the diagnosis of IBD: (1) the PROMETHEUS® Crohn's Prognostic test, and (2) the PROMETHEUS® IBD sgi Diagnostic™ test. These systems initially use an enzyme linked immunoabsorbent assay (ELISA) test to screen for ANCA or ASCA. Positive ANCA tests are further analyzed by indirect immunofluorescence to determine the specific staining pattern. When a perinuclear pattern is obtained (pANCA), specific enzyme reagents are then used to distinguish between true positives and fixation artifacts. After a positive screen for ASCA, the serum specimens are further analyzed by an ELISA microplate assay. Positive specimens are identified when the antibody level exceeds a predetermined cut-off point.

According to Prometheus Inc., "Prometheus® Crohn's Prognostic test is the first and only test that combines proprietary serologic and genetic (serogenetic) markers in a logistic regression

model to provide individualized probabilities for developing disease complications after diagnosis in patients with Crohn's disease. This test may allow physicians to stratify their CD patients according to their risks of developing complications over time and personalize the disease treatment plan for the patients."

The Prometheus® IBD sgi Diagnostic™ test, as defined by Prometheus, is a "next generation IBD test and the first and only test that combines serologic, genetic, and inflammatory markers in a proprietary Smart Diagnostic Algorithm. This test helps physicians differentiate between IBD and non-IBD and CD vs. UC in 1 comprehensive blood test." The Prometheus® IBD sgi Diagnostic™ test includes 3 major classes of biomarkers: serological, genetic, and inflammatory. Several serological markers are evaluated, including pANCA, ASCA and immunoglobulin G, anti-OmpC, anti-CBir1, anti-Fla-X, anti-A4-Fla2, ANCA-IgG, and deoxyribonuclease-sensitive pANCA. Since some genetic factors are thought to influence immune responses, and this assay also includes evaluation of *ATG16L1, STAT3, NKX2-3, and ECM1*. Inflammatory markers included in the Prometheus IBD sgi Diagnostic are vascular endothelial growth factor (VEGF), intercellular adhesion molecule (ICAM), vascular cell adhesion protein (VCAM), C-reactive protein (CRP), and serum amyloid A (SAA).

There is insufficient evidence in the current medical literature to support the use of serological markers for the diagnosis of IBD. Further studies are needed to establish the prognostic value of serological markers in screening and monitoring patients with IBD. It is not clear that the use of these tests will obviate standard diagnostic procedures (e.g., endoscopy and biopsy) in the evaluation of patients with suspected IBD.

Regulatory Status:

Laboratory tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1988. Premarket approval from the U.S. Food and Drug Administration (FDA) is not required as long as the assay is performed in a laboratory facility that observes CLIA regulations.

Medical Policy Statement

The use of serological markers and/or test panels incorporating a combination of antibodies or algorithms incorporating antibodies, inflammatory and genetic markers to diagnose inflammatory bowel disease, distinguish between ulcerative colitis and Crohn's disease or determine the prognosis of inflammatory bowel disease is experimental/investigational. While these tests may be safe, their effectiveness in these clinical indications has not been scientifically established.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

84999

Rationale

This policy was originally based on a 1999 TEC Assessment (1) that evaluated anti-neutrophilic cytoplasmic antibody (ANCA) and anti-Saccharomyces cerevisiae antibody (ASCA) in the following three clinical situations:

- The use of both tests as a first screen in patients with clinical signs and symptoms suggestive of inflammatory bowel disease (IBD) but who have not undergone confirmatory tests such as contrast radiographic studies of colonoscopy with biopsy. In this setting the sensitivity of the test, as averaged among studies, is 38% with an average specificity of 94%. The low sensitivity of the test indicates that a negative result will not be clinically helpful. A positive result indicates that IBD is likely, but it is difficult from the available data to reliably estimate the positive predictive value in a population presenting with signs and symptoms of IBD.
- ANCA as a confirmatory test for ulcerative colitis, and ASCA as a confirmatory test for Crohn's disease.
  In this setting, the average specificity of ANCA and ASCA is 90% and 94%, respectively, but the TEC Assessment concluded that this specificity is not likely to be high enough to confirm the diagnosis such that additional testing would not be necessary.
- The use of both tests to distinguish between Crohn's disease and ulcerative colitis in patients who have completed the standard workup, including pathologic evaluation of gastrointestinal biopsies.
- In this setting, the pooled sensitivity of the test is 84%. This sensitivity, although relatively high, would still result in a significant number of patient misclassifications. In addition, in the studies the patients had either established ulcerative colitis or Crohn's disease, and this is not the population of clinical interest.

Reese et al (2006) published a meta-analysis of studies that evaluated the diagnostic accuracy of ASCA and ANCA in inflammatory bowel disease. It included studies that compared ASCA or ANCA sensitivity and specificity to a "gold standard" (clinical, radiologic, endoscopic and/or histologic diagnosis). Studies included patients who ultimately had a diagnosis of ulcerative colitis and/or Crohn's disease. A total of 60 eligible studies were identified; there were 3841 ulcerative colitis patients, 4019 patients with Crohn's disease, and 3748 controls. Fifteen studies had a control group of healthy controls, 14 had a control group of individuals with non-IBD conditions, 14 had both types of control groups, and 15 studies had no control group (characteristics of two studies were not reported). For the diagnosis of ulcerative colitis, the

authors examined the sensitivity and specificity of ANCA in different combinations with ASCA, and for Crohn's disease, they looked at ASCA in different combinations with ANCA. For ulcerative colitis, the most sensitive test combination was an ANCA-positive test without information regarding ASCA status; the pooled sensitivity was 55.3% and specificity was 88.5%. The most sensitive test for Crohn's disease was ASCA immunoglobulin (IgG)-positive or IgA-positive in sera that were ANCA-negative. The pooled sensitivity was 55% with a specificity of 93%. The tests were also examined for their ability to distinguish between Crohn's disease and ulcerative colitis. The most sensitive test for differentiating between the two conditions was the presence of either ANCA or ASCA antibodies of any class. The combined sensitivity and specificity in this situation were 62.6% and 92.6%, respectively. The authors did a sensitivity analysis and found that including only high-quality studies (n=18) did not significantly change the findings. They did not stratify their findings by prospective versus retrospective studies or by type of control group (i.e., healthy controls vs. patients with conditions other than IBD).

Most studies have included populations of patients with established ulcerative colitis and Crohn's disease. An exception is Joossens et al (2002) which identified 97 patients with indeterminate colitis followed up prospectively. A definitive diagnosis of ulcerative colitis was made in 11 patients; 7 of 11 were ANCA positive and ASCA negative. A diagnosis of Crohn's disease was made in 10 patients; 8 of 10 were ANCA negative and ASCA positive. Approximately half of the patients with indeterminate colitis did not have positivity for either serum marker.

Several articles attempted to correlate titers of ANCA and/or ASCA with disease activity. Mow et al (2004) investigated whether serologic antibodies were associated with disease complications. In this case series of 303 patients with Crohn's disease, certain antibodies were associated with fibrostenosis or perforating disease. In a study conducted in Scotland, Russell et al (2009) evaluated the association between ASCA status and disease phenotype. The study included a total of 301 patients (197 with Crohn's disease, 76 with ulcerative colitis, and 28 with indeterminate colitis). In multivariate analysis, they found a significant association between ASCA positivity and a higher likelihood of oral Crohn's disease (adjusted odds ratio [OR] =22.2, 95% confidence interval [CI] =3.4-142.9) and the presence of hypoalbuminemia (adjusted OR=4.78, 95% CI=1.40-16.4). Confidence intervals were wide, indicating a high degree of uncertainty. In both the Mow and Russell studies, it is unclear how this information would be used in the management of the patient.

Sutton et al (2000) and Annese et al (2001) evaluated the presence of serum markers in unaffected relatives of patients with IBD, reporting positive results in approximately 25–50% of family members. However, these studies did not report on the incidence of IBD in relatives with positive antibodies. Zholudev et al (2004) reported on 2 additional antibodies that have also been studied, Escherichia coli outer membrane porin C (anti-OmpC) and I2 antibody. The same limitations in the published literature apply to these antibodies.

A study by Schoepfer et al (2008) studied the results of various testing in 64 patients to compare the accuracy of fecal markers (i.e., PhiCal Test, IBD-SCAN) , C-reactive protein, blood leukocytes, and antibody panels (ASCA and pANCA) for discriminating IBD from irritable bowel syndrome and to define a "best test." The authors concluded PhiCal Test and IBD-SCAN are highly accurate for discriminating IBD from irritable bowel syndrome. Additional diagnostic accuracy is only marginal when the PhiCal Test and IBD-SCAN are combined with

ASCA and pANCA. ASCA and pANCA have a high specificity for IBD; however, they should not be primarily measured for discriminating IBD from irritable bowel syndrome, as their additional value to fecal leukocyte markers in this issue is only marginal.

Papp et al (2007) discussed the expansion of the panel of serologic markers for IBD. An increasing amount of data are available on newly discovered antibodies (i.e., Anti-OmpC, Anti-12, Anti-CBir1, and antiglycan antibodies) directed against various microbial antigens. However, ASCA and P-ANCA remain the most widely investigated. The authors noted that the role of the assessment of various antibodies in the current IBD diagnostic algorithm is often questionable due to limited sensitivity. They concluded that further prospective clinical studies are needed to establish the clinical role of serologic tests in IBD.

Mokhtarifar et al (2013) published a study regarding the diagnostic value of atypical-P-ANCA and ASCA and their relationship to ulcerative colitis (UC) and Crohn's disease (CD) were evaluated. There were 97 patients enrolled in the study, 72 diagnosed with UC and 25 with CD. The control group consisted of 40 healthy individuals. ASCA was determined by enzyme-linked immunosorbent assay (ELISA) and atypical-P-ANCA by indirect immunofluorescence assay (IIF). The results were as follows: "For CD, the sensitivity of ASCA was 16% and its specificity was 97%. ASCA had a specificity of 90% in UC patients. The atypical P-ANCA test had a sensitivity of 44% and specificity of 86% for UC. The positive predictive value (PPV) for atypical P-ANCA in UC patients was 78% and for the negative predictive value (NPV), it was 58%.There was no correlation between ASCA and atypical P-ANCA results and the location of gastrointestinal (GI) involvement in CD (p=0.61) and UC (p=0.28) patients." The researchers concluded that ASCA and atypical P-ANCA markers are not useful for IBD screening. Additionally, the researchers noted that the study suggests that "atypical P-ANCA is a useful parameter to differentiate UC from CD. However, ASCA is of limited value for screening and differentiating UC from CD."

Mitsuyama et al (2014) stated that various non-invasive tests have been studied to screen for patients with CD, and were found to have limited accuracy and sensitivity, particularly in Asian populations. The investigators explored the possible diagnostic utility of antibodies to the CD peptide (ACP) in patients with CD. In a multi-center study using ELISA, serum ACP levels were determined in 196 patients with CD, 210 with UC, 98 with other intestinal diseases, 132 with other inflammatory diseases, and 183 healthy controls; and then examined for correlation to clinical variables. The diagnostic utility of ACP was evaluated by ROC analysis and compared with ASCA. Levels of ACP were significantly elevated in the CD patients, but not in the other groups that included UC, other intestinal diseases, other inflammatory diseases and the healthy controls. Among these other groups, ACP levels were not significantly different. In the CD patients, ACP had a higher sensitivity and specificity (63.3 % and 91.0 %, respectively) than ASCA (47.4 % and 90.4 %). Levels of ACP were negatively associated with disease duration, but not with Crohn's Disease Activity Index (CDAI), disease location, or medical treatment. The authors concluded that ACP, a newly proposed serologic marker, was significantly associated with CD and was highly diagnostic. They stated that further investigation is needed across multiple populations of patients and ethnic groups, and more importantly, in prospective studies to ascertain the clinical value of ACP.

Bonneau et al (2015) published a systematic review of studies examining the clinical utility of newer serological markers (ACCA, ALCA, AMCA, anti-L and anti-C), anti-GP2 and anti-GM-CSF Ab) in the diagnosis, prognosis and therapeutic monitoring of IBD.(16) Anti-glycan, anti-

GP2 and anti-GM-CSF Ab are especially associated with CD and seem to be correlated with complicated disease phenotypes even if results differ between studies. Although anti-glycan Ab and anti-GP2 Ab have low sensitivity in diagnosis of IBD, they could identify a small number of CD patients not detected by other tests such as ASCA. Anti-glycan Abs are associated with a progression to a more severe disease course and a higher risk for IBD-related surgery. Anti-GP2 Ab could particularly contribute to better stratify cases of pouchitis. Anti-GM-CSF Ab seems to be correlated with disease activity and could help predict relapses. Although these serological markers may be useful in the diagnosis and monitoring of IBD, more prospective studies are needed.

Takedatsu et al (2018) investigated associations with clinical data in new methodology with chemiluminescence enzyme immunoassay. Serum proteinase three antineutrophil cytoplasmic antibodies (PR3-ANCA) titres were assessed in 102 patients with ulcerative colitis (UC), 67 patients with Crohn's disease (CD), 44 controls with other intestinal diseases and 66 healthy controls. The diagnostic role of PR3-ANCAs was evaluated by receiver operating characteristic (ROC) analysis. PR3-ANCA titres were significantly higher in patients with UC than in those with CD patients, patients with intestinal diseases (intestinal controls) and healthy controls (all $p < 0.001$). ROC analysis demonstrated an area under the curve of 0.85 (95% Confidence interval: 0.83-0.87) and showed that the manufacturer's cut-off value (3.5 U/mL) had a sensitivity of 39.2% and specificity of 96.6% for UC. There was a significant difference between PR3-ANCA-positive and negative patients with regard to disease duration ($p < 0.05$) and disease severity ($p < 0.01$). The authors concluded that PR3-AMCA titres role as serological markers for inflammatory bowel disease (IBD) remains uncertain and further prospective studies are needed across multiple populations of patients and ethnic groups.

Chen (2020) reviewed data on serological biomarkers for IBD. PubMed was searched using predefined key words on relevant literature of serum biomarkers regarding diagnosis, evaluation of therapeutic efficacy, surveillance of disease activity, and assessment of prognosis of IBD. Serological biomarkers that are well-established and widely used (e.g., C-reactive protein), newly discovered biomarkers (e.g., cytokines, antibodies, and non-coding RNAs), and also recently advancements in serological biomarkers (e.g., metabolomics and proteomics) that are used in different aspects of IBD were reviewed. Authors concluded that IBD biomarkers are far from ideal. Because individual biomarkers lack specificity or sensitivity, the combination of different biomarkers such as Crohn’s disease classifier, mucosal healing index, and Ulcerative Colitis Response Index may enhance the effectiveness in evaluating disease course. Further studies are required to identify new biomarkers that have low cost and improved availability. More attention should be paid to predicting complicated disease before disease progression and assessing the risks of re-hospitalization and postoperative recurrence. It should be noted that the methods for identifying new biomarkers and clinical trial endpoints should be rigorous and standardized. The assessment of disease activity and response to therapies needs to be objective. Newly discovered markers should be confirmed in multicenter international collaborations before they are applied to clinical practice.

Summary

A number of studies have examined the association between serologic markers and inflammatory bowel disease. Systematic reviews have found relatively low sensitivity and moderately high specificity. Moreover, the clinical utility of these assays has not been demonstrated. No studies demonstrated the use of these markers in lieu of a standard workup for IBD. A number of authors claim that these markers can be used to avoid invasive testing,

but no studies demonstrated an actual decrease in the number of invasive tests through the use of serum markers. These technologies are investigational for diagnosing and monitoring inflammatory bowel disease; the evidence is insufficient to evaluate the impact on net health outcomes.

Further, available studies have failed to show the clinical effectiveness of the use of serological markers, next generation test panels incorporating a combination of antibodies, or algorithms incorporating antibodies, inflammatory and genetic markers to diagnose inflammatory bowel disease, distinguish between UC and CD or determine the prognosis of IBD.

Supplemental Information

TECHNOLOGY ASSESSMENTS, GUIDELINES, AND POSITION STATEMENTS

The Institute for Clinical Systems Improvement (ICSI)
In 2002, ICSI released a technology assessment, "Serum Antibodies for the Diagnosis of Inflammatory Bowel Disease (IBD): pANCA for Ulcerative Colitis (UC) and ASCA for Crohn's Disease (CD)." The following is a summary of the key findings. … "With regard to serum antibodies for diagnosing inflammatory bowel disease (IBD) the ICSI Technology Assessment Committee finds:

1. The clinical utility of serological testing is not yet established for the diagnosis of inflammatory bowel disease in patients presenting with symptoms suggestive of IBD (Conclusion Grade III).
2. The clinical utility of serological testing is not yet established for differentiating between UC and CD in patients with inflammatory bowel disease (Conclusion Grade II).
3. Although serum testing is a safe procedure, risks are associated with false negative and false positive test results. Consequences due to false negative and false positive test results have not been evaluated.
4. There are well-established radiologic, histologic, and endoscopic techniques for diagnosing IBD and differentiating CD and UC.
5. There appears to be a high inter-laboratory variability of sensitivities and specificities."

American College of Gastroenterology
Guidelines from the American College of Gastroenterology (ACG) on Management of Crohn's disease (2009) reported, "The diagnosis of CD is based on a composite of endoscopic, radiographic, and pathological findings documenting focal, asymmetric, transmural, or granulomatous features. The sequence of diagnostic maneuvers is based on presenting symptoms, physical findings, and basic laboratory abnormalities (grade C).(14) Currently, the measurement of genetic mutations in patients with CD remains a research tool that is not yet proven to be of clinical benefit for the general assessment of diagnosis, guidance of patient care, or prediction of response to specific medical therapies. The use of genetic testing is currently not recommended in the caring of patients with CD (level C). Additionally, serological studies evaluating antibodies against Saccharomyces cerevisiae, antineutrophil cytoplasmic antibodies, antibodies directed against CBir1, OmpC are evolving to provide adjunctive support for the diagnosis of CD but are not sufficiently sensitive or specific to be recommended for use as a screening tools."

ACG grade A recommendations indicate that there is consistent level I evidence (randomized controlled trials), grade B indicates that the evidence would be level II or III, which are cohort studies or case–control studies. Grade C recommendations are based on level IV studies, meaning case series or poor-quality cohort studies, and grade D recommendations are based on level V evidence, meaning expert opinion.

Another guideline from the ACG on Ulcerative Colitis (UC) (2010) reported, “Perinuclear antineutrophil cytoplasmic antibodies (pANCA) have been identified in 60 – 70% of UC patients but are also found in up to 40% of patients with CD.(8) These pANCA – positive CD patients typically have a clinical phenotype resembling left -sided UC, so pANCA detection alone is of little value in distinguishing between UC and Crohn’s colitis. However, reactivity to CBir1, an anti-flagellin antibody, is preferentially present in pANCA-positive CD patients as compared with pANCA-positive UC patients, 44% vs. 4%, respectively. The low sensitivity of pANCA for the diagnosis of UC prevents it from serving as a useful diagnostic tool. However, their specificities may make these assays useful in the occasional patient in whom no other clinical or pathologic features allow a differential diagnosis between UC and Crohn’s colitis. Although this distinction is not always crucial, it may have important consequences in terms of counseling, prognosis, and the choice of medical and surgical therapies.”

In 2018, the ACG (12) updated their guidelines for the management of Crohn’s disease as follows:

Diagnosis

“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.”

Routine laboratory investigation

Initial laboratory investigation should include evaluation for inflammation, anemia, dehydration, and malnutrition.

In patients who have symptoms of active Crohn's disease, stool testing should be performed to include fecal pathogens, Clostridium difficile testing, and may include studies that identify gut inflammation such as a fecal calprotectin.

Genetic testing

Genetic testing is not indicated to establish the diagnosis of Crohn's disease

Serologic markers of IBD

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

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. Anti-glycan antibodies

are more prevalent in CD than in ulcerative colitis but have a low sensitivity, making their use in diagnosis less helpful.

ACG (2021) updates do not mention the use of serological assays in the diagnosis or management of irritable bowel syndrome.(9)

In 2023 the ACG updated its guidelines regarding celiac disease diagnosis, management, and screening. Updates do not mention the use of serological assays in children 3 years and older. For patients aged 2 years and younger, immunoglobulin IgA anti-TTG is the preferred single test for CD detection, and testing for CD in children with IgA should be performed using IgG-based antibodies.(7)

American Gastroenterological Association
No guideline or position statement on the use of serum antibodies for the diagnosis of inflammatory bowel disease was found on its public website. 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.

British Society of Gastroenterology
The British Society of Gastroenterology (2019) released a consensus guideline for inflammatory bowel disease (IBD) in adults. Stool cultures, clostridium difficile, flexible or rigid sigmoidoscopy, biopsy and a full ileocolonoscopy, usually within the first year, were recommended to confirm a diagnosis of ulcerative colitis versus Crohn's disease and give information that may help to predict future disease course. The use of serum antibodies was not mentioned.

Government Regulations
National:
There is no national coverage determination for these tests.

Local:
Prometheus IBD sgi Diagnostic Policy (L37539); Effective date: 3/19/18; Revision date: 12/29/22

This is a non-coverage policy for the Prometheus IBD sgi Diagnostic test. The intended use of this test is to aid healthcare providers in the differentiating inflammatory bowel disease (IBD) vs non-IBD, and CROHN's disease (CD) vs ulcerative colitis (UC) in a comprehensive blood test.

The test includes nine serological markers: ASCA IgA, ASCA IgG, anti-OmpC IgA, anti-CBir1 IgG, anti-A4 Fla2 IgG, anti-FlaX IgG, IBD-specific pANCA autoantibody, IBD-specific pANCA IFA (perinuclear pattern), IBD-specific pANCA IFA DNAse Sensitivity; four genetic immune response markers (SNPs): ATG16L1, STAT3, NKX2-3, and ECM1; and five inflammatory biomarkers: ICAM-1, VCAM-1, VEGF, CRP, and SSA. A proprietary Smart Diagnostic Algorithm interprets patterns among the multiple assay values to produce an IBD score. The test results are reported as "consistent with IBD" (consistent with UC; consistent with CD, or

inconclusive for UC vs CD) or “not consistent with IBD”. In addition to the algorithmic test interpretation, the results of the 17 biomarkers are also individually reported.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Fecal Calprotectin
- Measurement of Serum Antibodies to Infliximab and Adalimumab
- Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 8/3/23, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
2/24/03	2/24/03	2/27/03	Joint policy established
6/9/04	6/09/04	5/27/04	Routine maintenance
7/1/06	5/1/06	3/27/06	Routine maintenance
11/1/07	8/21/07	10/27/07	Routine maintenance
3/1/09	12/9/08	12/28/08	Routine maintenance
9/1/10	6/15/10	6/29/10	Routine maintenance
3/1/12	12/13/11	12/21/11	Routine maintenance
9/1/13	6/19/13	6/26/13	Routine maintenance; Rationale section and references updated; MPS revised for clarity; policy position unchanged.
9/1/14	6/17/14	7/14/14	Routine maintenance; added information on commercial IBD tests; modified MPS to incorporate various serum markers; references updated, added ACG guidelines.
1/1/16	10/13/15	10/27/15	Routine maintenance
1/1/17	10/11/16	10/11/16	Routine maintenance
1/1/18	10/19/17	10/19/17	Routine maintenance
1/1/19	10/16/18	10/16/18	Routine maintenance
1/1/20	10/15/19		Routine maintenance Retirement recommendation rejected
1/1/21	10/20/20		Routine maintenance
1/1/21	10/19/21		Routine maintenance
1/1/23	10/18/22		Routine maintenance (slp)
1/1/24	10/17/23		• Routine maintenance (slp) • Vendor Managed: Avalon • Title changed FROM: Serum markers for the diagnosis of inflammatory bowel disease TO: Serum markers for the diagnosis and care of inflammatory bowel disease

Next Review Date: 4th Qtr, 2024

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: SERUM MARKERS FOR THE DIAGNOSIS AND CARE OF INFLAMMATORY BOWEL DISEASE

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.