Inflammatory bowel disease (IBD) is a class of inflammatory bowel disorders comprised of two major disorders: ulcerative colitis and Crohn disease each with distinct pathologic and clinical characteristics (Peppercorn & Kane, 2017c).

Ulcerative colitis (UC) is a chronic inflammatory condition characterized by relapsing and remitting episodes of inflammation limited to the mucosal layer of the colon (Silverberg et al., 2005) beginning at the rectum and may extend proximal and continuous fashion to involve other parts of the colon (Peppercorn & Kane, 2017b).

Crohn’s disease (CD) is characterized by patchy transmural inflammation (skip lesions) of the gastrointestinal tract resulting in sinus tracts, and ultimately microperforations and fistulae (Silverberg et al., 2005). It may also lead to fibrosis and strictures, and to obstructive clinical presentations that are not typically seen in ulcerative colitis (Gasche et al., 2000; Peppercorn & Kane, 2017a).

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

Reimbursement is not allowed for laboratory testing for the diagnosis of inflammatory bowel disease.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Laboratory Testing for the Diagnosis of Inflammatory Bowel Disease is covered

Not applicable.

When Laboratory Testing for the Diagnosis of Inflammatory Bowel Disease is not covered

1. Reimbursement is not allowed for the use of serologic markers including, but not limited to, the following in the workup and monitoring of individuals with inflammatory bowel disease:
   a. anti-neutrophil cytoplasmic antibody (ANCA),
   b. anti-Saccharomyces cerevisiae antibody (ASCA),
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c. perinuclear anti-neutrophilic cytoplasmic antibody (pANCA),
d. antibody to Escherichia coli outer membrane porin C (anti-OmpC),
e. antibody to Pseudomonas fluorescens-associated sequence I2 (anti-I2),
f. anti-CBir1 flagellin antibody (anti-cBir1),
g. antichitobioside antibodies (ACCA IgA),
h. antilaminaribioside antibodies (ALCA IgG),
i. antimannobioside antibodies (AMCA IgG)
j. pyruvate kinase M2 (PKM2)

2. Reimbursement is not allowed for the use of diagnostic algorithm-based testing, including testing that combines serologic, genetic, and inflammation markers (such as Prometheus® testing) for the diagnosis or monitoring of individuals with inflammatory bowel disease, including Crohn’s disease and ulcerative colitis.

3. Reimbursement is not allowed for genetic testing for inflammatory bowel disease, including Crohn’s disease and ulcerative colitis.

**Policy Guidelines**

**Background**

The diagnoses of Crohn's disease (CD) and ulcerative colitis (UC) depend on a combination of clinical, laboratory, radiographic, endoscopic, and histological criteria (Malatjalian, 1987). Differential diagnosis can be challenging but is highly important toward treatment and prognosis. Serological markers could be of value in differentiating CD from UC cases of indeterminate colitis, and in predicting the disease course of IBD (Peeters et al., 2001).

Investigations based on animal models have led to the current theory that chronic intestinal inflammation is the result of an aberrant immunologic response to commensal bacteria within the gut lumen (Blumberg, Saubermann, & Strober, 1999; Strober, Fuss, & Blumberg, 2002). Immune responses toward commensal enteric organisms have been investigated in CD and UC (Akasaka et al., 2015; D’Haens et al., 1998). Patients with IBD can have a loss of tolerance to specific bacteria antigens and autoantigens. These distinct antibody response patterns may indicate unique pathophysiological mechanisms for the progression of this complicated disease and may underlie the basis for the development of specific phenotypes (Lan et al., 2002; Peeters et al., 2001).

A number of these autoantibodies detected in patients with IBD have shown promise as diagnostic or prognostic indicators (Dubinsky et al., 2008; Ferrante et al., 2007; Mow et al., 2004). Antineutrophil cytoplasmic antibodies (pANCA) and antibodies to *Saccharomyces cerevisiae* (ASCA) have been proposed as a means for diagnosing IBD and differentiating CD from ulcerative colitis (Peeters et al., 2001). The sensitivity of the antibody tests alone or in combination was in the range of 40 to 60 percent, and the specificity was greater than 90 percent for distinguishing patients with IBD from controls (Reinald et al., 2006; Ruemmele et al., 1998; Sandborn et al., 2000). However, its utility in indeterminate bowel disease is uncertain (Joossens et al., 2002; Peeters et al., 2001). Additionally, ASCA were present in 50 percent of patients with celiac disease, and described in cystic fibrosis and intestinal tuberculosis, suggesting that they may reflect a nonspecific immune response in small bowel disease (Condino et al., 2005; Granito et al., 2005). Antibodies to the *E. coli* outer membrane porin Omp have also been identified as a potential serologic marker of IBD (Cohavy et al., 2000; Mow et al., 2004; Nakamura & Bousvaros, 2001; Zhuludev, Zurakowski, Young, Leichtner, & Bousvaros, 2004). Additional antibody tests under investigation include laminaribioside, chitobioside, or mannan (Dotan et al., 2006), and CBir1 flagellin (Targan et al., 2005). The accuracy and predictive value of antibody tests is uncertain (Wang, Shi, & Peng, 2017) and the prevalence of these antibodies in patients with a variety of inflammatory diseases affecting the gut has not been well studied. Thus, antibody tests should only be used as an adjunct to conventional testing and clinical diagnosis and should not be used as screening modalities (Peppercorn & Kane, 2017a).

Genetic studies have identified over 200 distinct susceptibility loci for irritable bowel disease with a significant portion of these overlapping with Crohn’s and ulcerative colitis (Jostins et al., 2012; Liu et al., 2015). Most of these are located within introns which more likely modulate the expression of proteins, and at that only mildly given that each only confers a slight increase in risk (Snapper & Abraham, 2018). Altogether, the known loci only explain ~13% of variation in disease liability (Jostins et al., 2012). These results indicate that the genetic architecture of IBD represents that of multifactorial complex...
traits where a combination of multiple genes, along with the environment, lead to disease (Liu & Anderson, 2014). Given the low predictive value of individual genetic markers and high number of putative risk alleles genetic testing does not currently offer much in terms of clinical utility (Lichtenstein et al., 2018; Liu & Anderson, 2014; McGovern, Kugathas, & Cho, 2015; Shirts, von Roon, & Tebo, 2012).

Laboratory evidence of inflammation is common in IBD. Fecal calprotectin, lactoferrin, ESR and CRP have each been correlated with disease activity (Lewis, 2011; Menees, Powell, Kurlander, Goel, & Chey, 2015), but are not specific. Additional inflammatory markers including vascular endothelial growth factor, intercellular adhesion molecule, vascular adhesion molecule, and serum amyloid A offer no significant advantage (Shirts et al., 2012). Fecal calprotectin has been shown to be useful to help differentiate the presence of IBD from irritable bowel syndrome and in monitoring disease activity and response to treatment (Lichtenstein et al., 2018).

Bile acid deficiency as indicated by serum 7α-hydroxy-4-cholesten-3-one (7C4) has been documented in patients with IBD (Donato, Lueke, Kenyon, Meeusen, & Camilleri, 2018; Vijayvargiya et al., 2018). This test has shown utility as an alternative test to measuring bile acids in stool (Walters & Pattni, 2010), but is not recommended in the workup for IBD.

Efforts improve the predictive value of IBD testing, serologic, genetic, and inflammation markers for IBD have been combined and analyzed as panels (Plevy et al., 2013). The clinical validity and utility of antibody tests and panels of combinations of serologic tests for the diagnosis of IBD and the disease course and severity are still uncertain (Benor et al., 2010; Coukos et al., 2012; Kaul et al., 2012; Sura, Ahmed, Cheifetz, & Moss, 2014; Wang et al., 2017). Thus, these tests should only be used as an adjunct to conventional testing and clinical diagnosis and should not be used as screening modalities.

Clinical Validity and Utility

Peppercorn and Kane (2017) published a review on the diagnosis of Crohn disease in adults. Regarding use of serologic markers, the authors stated that “Although commercially available, the accuracy and predictive value of antibody tests and panels of combinations of serologic tests for the diagnosis of IBD and the disease course and severity continue to be elucidated. Furthermore, the prevalence of these antibodies in patients with a variety of inflammatory diseases affecting the gut has not been well studied. Thus, antibody tests should only be used as an adjunct to conventional testing and clinical diagnosis and should not be used as screening modalities.”

Mitsuyama et al (2016) reviewed the current status of antibody markers, including microbial antibodies, autoantibodies and peptide antibodies for IBD. They concluded that “At present, no single marker with qualities that are satisfactory for the diagnosis and treatment of IBD has been identified, although panels of some antibodies are being evaluated with keen interest.”

Mitsuyama et al (2014) conducted a multicenter study to explore the possible diagnostic utility of antibodies to the CD peptide (ACP) in patients with CD which found that “ACP levels 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. Antibody levels in 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 %). ACP levels were negatively associated with disease duration, but not with CDAI, disease location, or medical treatment.”

Kaul et al (2012) performed a meta-analysis/systemic review aimed to evaluate the diagnostic value, as well as the association of anti-glycan biomarkers with IBD susceptible gene variants, disease complications, and the need for surgery in IBD. They found “Individually, anti-Saccharomyces cervisiae antibodies (ASCA) had the highest DOR for differentiating IBD from healthy (DOR 21.1; 1.8-247.3; two studies), and CD from UC (DOR 10.2; CI 7.7-13.7; seven studies). For combination of ≥2 markers, the DOR was 2.8 (CI 2.2-3.6; two studies) for CD-related surgery, higher than any individual marker, while the DOR for differentiating CD from UC was 10.2 (CI 5.6-18.5; three studies) and for complication was 2.8 (CI 2.2-3.7; two studies), similar to individual markers.” The authors concluded that: “ASCA had the highest diagnostic value among individual anti-glycan markers. While anti-chitobioside carbohydrate antibody (ACCA) had the highest association with complications, ASCA and ACCA associated equally with the need for surgery. Although in most individual studies the combination of ≥2 markers had a better diagnostic value as well as higher association with complications and the need for surgery, we found the combination performing slightly better than any individual marker in our meta-analysis.”
Schoepfer et al (2008) aimed to determine the accuracy of fecal markers, C-reactive protein (CRP), blood leukocytes, and antibody panels for discriminating IBD from IBS. They found that “Overall accuracy of tests for discriminating IBD from IBS: IBD-SCAN 90%, PhiCal Test 89%, LEUKO-TEST 78%, Hexagon-OBTI 74%, CRP 73%, blood leukocytes 63%, CD antibodies (ASCA+/pANCA- or ASCA+/pANCA+) 55%, UC antibodies (pANCA+/ASCA-) 49%. ASCA and pANCA had an accuracy of 78% for detecting CD and 75% for detecting UC, respectively. The overall accuracy of IBD-SCAN and PhiCal Test combined with ASCA/pANCA for discriminating IBD from IBS was 92% and 91%, respectively.”

**Applicable Federal Regulations**

This test is considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories. LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA’88).

As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

**Guidelines and Recommendations**

**Practice 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 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 and Consequences due to false negative and false positive test results have not been evaluated.”

**American Gastroenterological Association (AGA)**

No guideline or position statement from AGA on the use of immunologic or genetic markers for the diagnosis of inflammatory bowel disease was found. The AGA assessment algorithms used for both Crohn’s disease and ulcerative colitis do not include genetic testing or combinatorial serologic-genetic testing approaches, such as the Prometheus® methodology (AGA, 2018).

**2018 American College of Gastroenterology (Lichtenstein et al., 2018)**

The ACG published guidelines (Lichtenstein et al., 2018) on the management of Crohn’s disease which state:

The diagnosis of Crohn’s disease (CD) is based on a combination of clinical presentation and endoscopic, radiologic, histologic, and pathologic findings that demonstrate some degree of focal, asymmetric, and transmural granulomatous inflammation of the luminal GI tract. Laboratory testing is complementary in assessing disease severity and complications of disease. There is no single laboratory test that can make an unequivocal diagnosis of CD. The sequence of testing is dependent on presenting clinical features.

Initial laboratory investigation should include evaluation for inflammation, anemia, dehydration, and malnutrition.
Fecal calprotectin is a helpful test that should be considered to help differentiate the presence of IBD from irritable bowel syndrome (strong recommendation, moderate level of evidence).

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

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

The ACG guidelines on Ulcerative Colitis in adults (Kornbluth & Sachar, 2010) state:

The low sensitivity of pANCA for the diagnosis of UC prevents it from serving as a useful diagnostic tool.

**2015 World Gastroenterology Organisation (WGO) (Bernstein et al., 2016)**

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

**2007 Working Group of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the Crohn’s and Colitis Foundation of America (Bousvaros et al., 2007)**

A clinical report (Bousvaros et al., 2007) found that:

Multiple studies have also been published on the role of serology in CD and UC, in both adults and children. The anti-neutrophil cytoplasmic antibody (pANCA) is identified in approximately 75% of patients with ulcerative colitis, and up to 20% of patients with CD. ASCA is present in 40% to 80% of patients with CD, seems to preferentially identify CD of the ileum and cecum, and may predict risk of ileocecal resection. Thus, the presence of a positive ASCA antibody in a patient with IBD strongly suggests the diagnosis of CD. However, patients with CD limited to the colon often have an ANCA-positive serotype similar to patients with UC; therefore, a positive ANCA does not differentiate between UC and Crohn’s colitis.

The value of serology in the patient with IC remains a topic of study. In the largest prospective study of serological markers of IC, 97 patients with IC underwent serological testing and were observed prospectively; of these 97, 31 patients were reclassified as either UC or CD. According to the authors, a positive ASCA and a negative ANCA were associated with development of CD in 8 of 10 patients. However, the majority of patients with IC remained seronegative for both ASCA and ANCA.

Genetic testing cannot as yet reliably differentiate UC from CD of the colon. The NOD2 genotyping test reliably identifies 25% of patients with CD, but these patients typically have fibrostenosing CD of the terminal ileum and can be readily differentiated from UC by conventional radiographic and endoscopic means multiple studies have demonstrated that NOD2 mutations are generally not seen in individuals with UC.

**Billing/Coding/Physician Documentation Information**
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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81401, 81479, 82397, 83516, 83520, 86140, 88346, 88350

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Lewis, J. D. (2011). The Utility of Biomarkers in the Diagnosis and Therapy of Inflammatory Bowel Disease. Gastroenterology, 140(6), 1817-1826 e1812. doi:10.1053/j.gastro.2010.11.058


Specialty Matched Consultant Advisory Panel review 11/2019

Medical Director review 11/2019

Policy Implementation/Update Information

1/1/2019 New policy developed. BCBSNC will not provide coverage for laboratory testing for the diagnosis of inflammatory bowel disease because it is considered investigational. BCBSNC does not provide coverage for investigational services or procedures. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

10/1/19 Policy statement revised to read: Reimbursement is not allowed for laboratory testing for the diagnosis of inflammatory bowel disease. Wording revised in the Not Covered section. “Investigational” changed to read “Reimbursement is not allowed…” Deleted coding grid. Notification given 10/1/2019 for effective date 12/2/2019. (an)
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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.