MEDICAL POLICY

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MEDICAL POLICY DETAILS	
Medical Policy Title	**Serum Antibodies for the Diagnosis of Inflammatory Bowel Disease**
Policy Number	**2.02.19**
Category	**Technology Assessment**
Original Effective Date	**05/21/03**
Committee Approval Date	**04/15/04, 02/17/05, 01/21/10, 11/17/11, 12/20/12, 12/19/13, 11/20/14, 11/19/15, 11/17/16**
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Product Disclaimer	• *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), medical policy criteria apply to the benefit.* • *If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.* • *If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.* • *If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.*

POLICY STATEMENT

I. Based upon our criteria and assessment of the peer-reviewed literature, the use of serologic markers (including, but not limited to *anti-neutrophil cytoplasmic antibodies* (ANCA) and/or *anti-Saccharomyces cerevisiae* (ASCA); antibodies of outer membrane porin C of the bacteria *Eschericia coli* (anti-OmpC); *Pseudomonas* fluorescens-associated sequence I2 (anti-I2); flagellin CBir1 (anti-cBir1); *antichitobioside* antibodies (ACCA IgA); *antilaminaribioside* antibodies (ALCA IgG); and *antimannobioside* antibodies (AMCA IgG)) has not demonstrated a benefit to patient outcomes and, therefore, is considered **not medically necessary** for all indications including, but not limited to:
   A. to diagnose and monitor patients with inflammatory bowel disease (IBD); or
   B. to distinguish ulcerative colitis (UC) from Crohn's disease (CD).

Refer to Corporate Medical Policy #11.01.15 Medically Necessary Services

POLICY GUIDELINES

Laboratories performing clinical tests must be certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

DESCRIPTION

Inflammatory bowel disease (IBD) is a chronic disease of the gastrointestinal tract that consists of two related diseases, ulcerative colitis (UC) and Crohn's disease (CD). Although UC and CD are generally considered distinctive forms of IBD, their clinical presentations commonly overlap. Furthermore, for approximately 10-15% of patients with IBD, the distinction between UC and CD cannot be made with certainty. These patients are given a diagnosis of indeterminate colitis (IC). A correct diagnosis of IBD, especially the differentiation between CD and UC is highly important in determining treatment and prognosis. The diagnostic work-up of patients with IBD is relatively complicated, and

endoscopic exam and biopsy are currently crucial components of the diagnosis. Less invasive, accurate diagnostic tools to distinguish between UC, CD, and cases of indeterminate colitis are needed.

It has been proposed that serological markers for IBD can be utilized, both to differentiate UC from CD, and to define patient subgroups (e.g., location of the disease, such as proximal versus distal bowel involvement). Other potential uses include determination of disease severity, prediction of response to anti-tumor necrosis factor (TNF) therapy, and identification of the susceptibility to IBD among family members of an affected individual. Anti-neutrophil cytoplasmic antibodies (ANCA) and anti-*Saccharomyces cerevisiae* antibodies (ASCA) have been the most extensively studied serological markers for use in the diagnosis of IBD. ANCA are a group of antibodies, which are specific for granulocyte antigens. Anti-neutrophil cytoplasmic antibodies with perinuclear staining (pANCA) have been most commonly described in IBD and have been linked with UC. Other antibodies that have recently been associated with CD include anti-OmpC, anti-cBir1, Anti-I2, ACCA, ALCA, and AMCA. Increased amounts and levels of an antibody's response have been suggested to predict a more complicated course of disease. Large prospective studies are needed, to validate these findings.

Recent data suggest that the presence of serological biomarkers might represent a genetic susceptibility, because patients who have positive antibodies may carry mutations in the NOD2/CARD15 gene or in toll-like receptor genes. However, future studies of larger cohorts with well-defined clinical characteristics and patient populations are needed, to determine the validity of this relationship.

The PROMETHEUS IBD sgi Diagnostic aims to help identify IBD and differentiates between UC and CD. It may also assess a patient's risk for more aggressive disease. The test includes the proprietary and patented serologic markers anti-CBir1, Anti-OmpC and DNAse-sensitive pANCA process as well as, the markers ASCA IgA (ACCA) and IgG (ALCA and AMCA). The sgi Diagnostic test also includes the ATG16L, ECM1, mkX2-3, and STAT3 genetics and inflammation markers such as VEGF, ICAM-1, VACAM-1, CRP, and SAA. The Smart Diagnostic Algorithm technology produces an IBD score; results are reported as consistent with IBD (consistent with ulcerative colitis, consistent with CD, or inconclusive for ulcerative colitis vs. CD) or not consistent with IBD. The test is intended for use in patients with clinical suspicion of IBD.

RATIONALE

While the specificity of these tests is relatively high (82-100%), the sensitivity is low (32 -50%), which indicates that a negative result will not be clinically helpful. The ANCA and/or ASCA test results, alone or in combination with the new serological markers, cannot be relied upon for confirmation of a diagnosis; thus, patients will often still require the standardized work-up, including colonoscopy and biopsy. Studies do not demonstrate any correlation between the presence of these antibodies and disease activity or duration.

The use of serological markers for patients with IBD has not been shown to improve health outcomes by reducing the need for other tests nor has it been proven to increase the accuracy of diagnosis for these patients. Large-scale prospective studies are required, to ascertain the predictive value and cost-effectiveness of the use of these serology markers in the screening and monitoring of IBD patients.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/appropriate = (NMN).*

CPT Codes

Code	Description
There are no specific CPT codes for this test; 81479, 82397, 83516 83520, 86140, 88346 or 88350 may be used for billing PROMETHEUS IBD sgi Diagnostic. **These codes are not specific to PROMETHEUS IBD.**	
81479	Unlisted molecular pathology procedure
82397	Chemiluminescent assay
83516	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
86140	C-reactive protein;
88346	Immunofluorescence, per specimen; initial single antibody stain procedure
88350	Immunofluorescence, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)

HCPCS Codes

Code	Description
No specific code	

ICD10 Codes

Code	Description
K50.00-K50.919	Crohn's disease [regional enteritis] (code range)
K51.00-K51.919	Ulcerative colitis (code range)

REFERENCES

*Annes V, et al. familial expression of anti-Saccheromyces cerevisiae mannan antibodies in Crohn's disease and ulcerative colitis: a GISC study. Am J Gastroenterol 2001;96(8):2407-12.

*Bernstein CN, et al. Development of an assay for antibodies to Saccharomyces cerevisiae: easy, cheap, and specific for Crohn's disease. Can J Gastroenterol 2001 Aug;15(8):499-504.

*Bonneau J, et al. Systematic review: new serological markers (anti-glycan, anti-GP2, anti-GM-CSF-Ab) in the prediction of IBD patient outcomes. Autoimmun Rev 2015 Mar;14(3):231-45.

*Desir B, et al. Utility of serum antibodies in determining clinical course in pediatric Crohn's disease. Clin Gastroenterol Hepatol 2004 Feb;2(2):139-146.

*Dotan I. New serologic markers for inflammatory bowel disease diagnosis. Dig Dis 2010;28(3):418-23.

*Fengming Y, et al. Biomarkers of inflammatory bowel disease. Dis Markers 2014:710915.

*Forcione DG, et al. Anti-saccharomyces cerevisiae antibody (ASCA) positivity is associated with increased risk for early surgery in Crohn's disease. Gut 2004 Aug;53(8):1117-22.

*Iskandar HN, et al. Biomarkers in inflammatory bowel disease: current practices and recent advances. Transl Res 2012 Apr;153(4):313-25.

*Kaul A, et al. Serum anti-glycan antibody biomarkers for inflammatory bowel disease diagnosis and progression: a systematic review and meta-analysis. Inflamm Bowel Dis 2012 Oct;28(10):1872-84.

*Kevans D, et al. Serological markers associated with disease behavior and response to anti-tumor necrosis factor therapy in ulcerative colitis. J Gastroenterol Hepatol 2015 Jan;30(1):64-70.

*Kim BG, et al. Diagnostic role of anti-Saccharomyces mannan antibodies combined with antineutrophil cytoplasmic antibodies in patients with inflammatory bowel disease. Dis Colon Rectum 2002 Aug;45(8):1062-9.

*Lichtenstein GR, et al. Combination of genetic and quantitative serological immune markers are associated with complicated Crohn's disease behavior. Inflamm Bowel Dis 2011 Dec;17(12):2488-96.

*Mitsuyama K, et al. Antibody markers in the diagnosis of inflammatory bowel disease. World J Gastroenterol 2016 Jan 21;22(3):1304-10.

*Papp M, et al. Serological studies in inflammatory bowel disease: how important are they? Curr Opin Gastroenterol 2014 Jul;30(4):359-64.

*Peng C., et al. Serum biomarkers for inflammatory bowel disease. Front Med 2020 Apr;7:123.

*Ryan JD, et al. Predicting complicated Crohn's disease and surgery: phenotypes, genetics, serology, and psychological characteristics of a population-based cohort. Aliment Pharmacol Ther 2013 Aug;38(3):274-83.

*Schoepfer AM, et al. Discriminating IBD from IBS: comparison of the test performance of fecal markers, blood leukocytes, CRP, and IBD antibodies. Inflamm Bowel Dis 2008; 14(1):32-9.

*Sipeki N, et al. Prevalence, significance, and predictive value of antiphopholipid antibodies in Crohn's disease. World J Gastroenterol 2015 Jun 14;21(22):6952-64.

*Smids C, et al. The value of serum antibodies in differentiating inflammatory bowel disease, predicting disease activity and disease course in the newly diagnosed patient. Scand J Gastroenterol 2017 Oct;52(10):1104-1112.

*Torres J, et al. Predicting outcomes to optimize disease management in inflammatory bowel diseases. J Crohns Colitis 2016 Dec;10(12):1385-1394.

*Vermeire S, et al. Classification of inflammatory bowel disease: the old and the new. Curr Opin Gastroenterol 2012 Jul;29(4):321-6.

*Vermeire S, et al. (Auto)Antibodies in Inflammatory Bowel Diseases. Gastroenterol Clin N Am 2008;37:429-38.

*Vermeire S, et al. Comparative study of ASCA (Anti-saccharomyces cerevisiae antibody) assays in inflammatory bowel disease. Gastroenterol 2001 Mar; 120 (4):827-33.

*Zholudev A, et al. Serologic testing with ANCA, ASCA and anti-OmpC in children and young adults with Crohn's disease and ulcerative colitis: diagnostic value and correlation with disease phenotype. Am J Gastroenterol 2004 Nov;99(11):2235-41.

*Key Article

KEY WORDS

Anti-neutrophil cytoplasmic antibodies, ANCA, Anti-*Saccharomyces cerevisiae,* ASCA, Crohn's disease, Inflammatory bowel disease, Prometheus Labs, Serological markers, Ulcerative colitis.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

Based on our review, Serological Diagnosis of Inflammatory Bowel Disease or Prometheus IBD is not addressed in National or Regional Medicare coverage determinations or policies.