MEDICAL POLICY

POLICY TITLE	SERUM ANTIBODY MARKERS FOR DIAGNOSING AND MONITORING INFLAMMATORY BOWEL DISEASE (FORMERLY SERUM ANTIBODY MARKERS FOR DIAGNOSING INFLAMMATORY BOWEL DISEASE)
POLICY NUMBER	MP 2.222

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**3/1/2024**

I. POLICY

Determination of anti-neutrophil cytoplasmic antibody (ANCA) and anti-*Saccharomyces cerevisiae* antibody (ASCA) is considered **investigational** in the workup and monitoring of patients with inflammatory bowel disease.

There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with these procedures.

Cross-references:

MP 2.329 Measurement of Serum Antibodies to Selected Biologic Agents
MP 2.218 Pharmacogenomic and Metabolite Markers for Patients with Inflammatory Bowel Disease Treated with Thiopurines
MP 2.277 Miscellaneous Genetic and Molecular Diagnostic Tests
MP 5.033 Wireless Capsule Endoscopy to Diagnose Disorders of the Small Bowel, Esophagus, and Colon

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:
https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

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III. DESCRIPTION/BACKGROUND

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Two serum antibodies, anti-neutrophilic cytoplasmic antibodies (ANCA) and anti-*Saccharomyces cerevisiae* (ASCA) have been associated with inflammatory bowel disease (IBD). These antibodies may have potential use in the diagnosis of IBD, differentiating types of IBD, and predicting response to treatment.

Background

Inflammatory bowel disease (IBD) can be subdivided into ulcerative colitis and Crohn's disease, both of which present with symptoms of diarrhea and abdominal pain. The definitive diagnosis can usually be established by a combination of radiographic, endoscopic, and histologic criteria, although in 10–15%, the distinction between ulcerative colitis and Crohn's disease cannot be made with certainty.

The serum antibodies, ANCA and ASCA, have several potential uses. They can be used as diagnostic tests to improve the efficiency and accuracy of diagnosing IBD to decrease the extent of the diagnostic workup or to avoid invasive tests. As a diagnostic test, they might also be useful in differentiating between ulcerative colitis and Crohn's disease in cases of indeterminate colitis. A second potential use is to classify subtypes of IBD by location of disease (i.e., proximal vs. distal bowel involvement) or by disease severity, thereby providing prognostic information. It has also been proposed that these markers may predict response to anti-tumor necrosis factor (TNF) therapy or identify susceptibility to IBD among family members of an affected individual.

PROMETHEUS® IBD sgi Diagnostic™ is Prometheus' 4th-generation IBD diagnostic test and combines serologic, genetic, and inflammation markers, hence "sgi", in the proprietary Smart Diagnostic Algorithm for added diagnostic clarity. This test uses pattern recognition to assess 17 assay results, including proprietary biomarkers anti-CBir1, anti-OmpC, anti-FlaX, anti-A4-Fla2, and DNAse-sensitive pANCA. This test has replaced the PROMETHEUS® IBD Serology 7.

Recent studies have identified serologic- and genetic correlates of aggressive CD that is characterized by fistula formation, fibrostenosis, and the need for surgical intervention. Prometheus has developed a blood test that aims to identify patients with CD who are likely to experience an aggressive disease course.

Crohn's Prognostic (Prometheus Therapeutics & Diagnostics) is a panel of 6 serologic (n=3) and genetic (n=3) biomarkers. Serologic markers include ASCA IgA, ASCA IgG and priority markers anti-CBir1, anti-I2, anti-OMPC, and DNAse sensitive pANCA. Genetic markers include NOD2 variants (SNPS 8, 12, 13). Limited information about the test is available on the manufacturer's website. An UpToDate article titled "Clinical Spectrum of Antineutrophil cytoplasmic autoantibodies" states that "The pathogenetic significance of these antibodies is unclear. The titers of ANCA do not vary with the activity or severity of the disease and, in ulcerative colitis, do not fall after colectomy."

Regulatory Status

Serum testing for ANCA and ASCA does not require U.S Food and Drug Administration (FDA) approval.

IV. RATIONALE

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SUMMARY OF EVIDENCE

A number of studies have examined the association between the serologic markers ASCA and ANCA 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 use of serum markers. These technologies are investigational for the diagnosis and monitoring of inflammatory bowel disease given the insufficient evidence to evaluate the impact on net health outcome.

V. DEFINITIONS

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NA

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice, and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore, not covered:

Procedure Codes								
81401	81479	81599	82397	83516	83520	84999	86021	86036
86037	86255	86671	88346	88350				

IX. REFERENCES

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1. *Reese GE, Constantinides VA, Simillis C, et al. Diagnostic precision of anti-Saccharomyces cerevisiae antibodies and perinuclear antineutrophil cytoplasmic antibodies in inflammatory bowel disease. Am J Gastroenterol 2006; 101(10):2410-22.*
2. *Joossens S, Reinisch W, Vermeire S et al. The value of serologic markers in indeterminate colitis: a prospective follow-up study. Gastroenterology 2002; 122(5):1242-7.*
3. *Mow WS, Vasiliauskas EA, Lin YC, et al. Association of antibody responses to microbial antigens and complications of small bowel Crohn's disease. Gastroenterology 2004; 126(2):414-24.*
4. *Russell RK, Ip B, Aldhous MC. Anti- Saccharomyces cerevisiae antibody status is associated with oral involvement and disease severity in Crohn disease. J Pediatr Gastroenterol Nutr 2009; 48(2):161-7.*
5. *Sutton CL, Yang H, Li Z et al. Familial expression of anti- Saccharomyces cerevisiae mannan antibodies in affected and unaffected relatives of patients with Crohn's disease. Gut 2000; 46(1):58-63.*
6. *Annese V, Andreoli A, Andriulli A, et al. Familial expression of anti- Saccharomyces cerevisiae Mannan antibodies in Crohn's disease and ulcerative colitis: a GISC study. Am J Gastroenterol 2001; 96(8):2407-12.*
7. *Zholudev A, Zurakowski D, Young W, 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; 99(11):2235-41.*
8. *Schoepfer AM, Trummler M, Seeholzer P, 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.*
9. *Papp M, Norman GL, Altorjay I et al. Utility of serological markers in inflammatory bowel diseases: gadget or magic? World J Gastroenterol 2007; 13(14):2028-36.*

10. *Snapper, S, Podolsky, D. Immune and microbial mechanisms in the pathogenesis of inflammatory bowel disease. In: UpToDate Online Journal [serial online]. Waltham, MA: UpToDate; updated February 10, 2022. Literature review current through Feb 2022. www.uptodate.com.*
11. *Falk R and Merkel P. Clinical Spectrum of anti-neutrophil cytoplasmic antibodies. In: UpToDate Online Journal [serial online]. Waltham, MA: UpToDate; updated January 3, 2022. Literature review current through Feb 2022. www.uptodate.com.*
12. *Nestlé Health Science Press Release. Prometheus Launches Next Generation IBD Diagnostic Test. 2011;*
13. *Lichtenstein, Gary R MD, FACG1; Loftus, Edward V MD, FACG2; Isaacs, Kim L MD, PhD, FACG3; Regueiro, Miguel D MD, FACG4; Gerson, Lauren B MD, MSc, MACG (GRADE Methodologist)5,†; Sands, Bruce E MD, MS, FACG6 ACG Clinical Guideline: Management of Crohn's Disease in Adults, American Journal of Gastroenterology: April 2018 - Volume 113 - Issue 4 - p 481-517.*
14. *Rubin, David T. MD, FACG1; Ananthakrishnan, Ashwin N. MD, MPH2; Siegel, Corey A. MD, MS3; Sauer, Bryan G. MD, MSc (Clin Res), FACG (GRADE Methodologist)4; Long, Millie D. MD, MPH, FACG5 ACG Clinical Guideline: Ulcerative Colitis in Adults, The American Journal of Gastroenterology: March 2019 - Volume 114 - Issue 3 - p 384-413.*
15. *Lee WI, Subramaniam K, Hawkins CA, Randall KL. The significance of ANCA positivity in patients with inflammatory bowel disease. Pathology. 2019;51(6):634-639. doi:10.1016/j.pathol.2019.07.002*
16. *Singh, S., Ananthakrishnan, A., Nguyen, N., Cohen, B., & Velayos, F. S., et. al (2023, March). AGA Clinical Practice Guideline on the Role of Biomarkers for the Management of Ulcerative Colitis. Gastroenterology.*
17. *Prometheus Laboratories. (2023, June 6). Crohn's prognostic. Crohn's Prognostic. https://prometheuslabs.com/disease-tests/crohns-prognostic/*
18. *Blue Cross Blue Shield Association Medical Policy Reference Manual. 2.04.17, Serum Antibodies for the Diagnosis of Inflammatory Bowel Disease. Archived June 2010.*

X. POLICY HISTORY

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MP 2.222	**CAC 6/24/03**
	CAC 5/31/05
	CAC 5/30/06 Consensus
	CAC 3/27/07
	CAC 3/25/08 Consensus
	CAC 3/31/09 Consensus
	CAC 5/25/10 Adopted BCBSA Criteria
	CAC 4/26/11 Consensus
	CAC 6/26/12 Consensus, no change to policy statements, references updated.
	7/25/13 Admin coding review completed.

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	CAC 9/24/13 Consensus, no change to policy statements, references updated
	CAC 3/25/14 Consensus, no change to policy statements. References updated.
	CAC 3/24/15 Consensus review. No changes to the policy statements. References and rationale updated. Coding reviewed.
	CAC 3/29/16 Consensus review. No change to policy statements. References and rationale reviewed. Coding reviewed.
	Admin Update 11/15/16 Variation Reformatting
	CAC 3/28/17 Consensus review. No change to the policy statements. References and rationale reviewed**.** Coding reviewed.
	1/03/18 Consensus review. Policy statement unchanged. Cross-Reference, Rationale, and Reference sections updated.
	1/16/19 Consensus review. No change to the policy statements. References reviewed. Rationale revised.
	1/23/2020 Consensus review. No change to policy statements. References updated. Coding reviewed.
	1/5/2021 Consensus review. No change to policy statements. Updated name of MP 2.329 for Cross-Reference. Updated Background with most current Prometheus test. References updated. Coding reviewed. Added codes 81479, 82397, 83516, 83520, 86021, 86140, 86671, 88346, and 88350.
	3/11/2022 Consensus review. Added codes 86036 and 86037. Removed 86140. No change to policy statement. Cross references, FEP, references updated.
	9/6/2023 Consensus review. Changed title to include 'monitoring'. Added Prometheus Crohn's Prognostic test information to background and associated codes to coding table. Updated references.
	1/19/2024 Administrative update. Clinical benefit added.

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