MEDICAL POLICY

POLICY TITLE	SERUM ANTIBODY MARKERS FOR DIAGNOSING INFLAMMATORY BOWEL DISEASE
POLICY NUMBER	MP-2.222

Original Issue Date (Created):	**August 9, 2002**
Most Recent Review Date (Revised):	**March 25, 2014**
Effective Date:	**June 1, 2014**

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 conclusion concerning the health outcomes or benefits associated with these procedures.

Cross-reference:
MP-2.329 Measurement of Serum Antibodies to Infliximab and Adalimumab
MP-2.218 Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines
MP-5.033 Wireless Capsule Endoscopy as a Diagnostic Technique in Disorders of the Small Bowel, Esophagus, and Colon

II. PRODUCT VARIATIONS

TOP

[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

- [N] Capital Cares 4 Kids
- [N] PPO
- [N] HMO
- [N] SeniorBlue HMO
- [N] SeniorBlue PPO
- [N] Indemnity
- [N] SpecialCare
- [N] POS
- [Y] FEP PPO*

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*The FEP program dictates that all drugs, devices or biological products approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational. Therefore, FDA-approved drugs, devices or biological products may be assessed on the basis of medical necessity.

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.

The Prometheus© IBD Serology 7 (Prometheus© Inc., San Diego, CA) is a quantitative analysis of biomarkers for IBD prediction and differentiation. Prometheus© IBD Serology 7 is only offered at Prometheus©. This system uses a 2-step process to diagnose IBD and to differentiate between ulcerative colitis and Crohn's disease. The first step is a panel of 4 markers intended to maximize the sensitivity and negative predictive value of the test. Patients who test positive on the initial screen are further analyzed by a set of proprietary markers and enzyme reagents to distinguish between true positive results and artifacts of fixation. In this way, the Prometheus© system is intended to increase the specificity of the test compared to other laboratories. The company also markets a testing strategy for predicting response to anti-TNF therapy and to monitor therapy.

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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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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.

The policy was updated regularly with searches of the MEDLINE database. The most recent literature search was performed for the period April 2009 through April 2010. Following is a summary of the key updated literature:

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In 2006, a meta-analysis of studies that evaluated the diagnostic accuracy of ASCA and ANCA in inflammatory bowel disease was published. (2) 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 2 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. which identified 97 patients with indeterminate colitis followed up prospectively. (3) 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 and colleagues investigated whether serologic antibodies were associated with disease complications. (4) 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 and colleagues evaluated the association between ASCA status and disease phenotype. (5) 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.

Other studies evaluated the presence of serum markers in unaffected relatives of patients with IBD (6, 7), 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. Two additional antibodies have been also been studied, Escherichia coli outer membrane porin C (anti-OmpC) and I2 antibody. (8) However, the same limitations in the published literature apply to these antibodies.

A study by Schoepfer and colleagues 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." (9) 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.

A review article published in 2007 discussed the expansion of the panel of serologic markers for IBD. (10) 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.

Summary

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.

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).” (11) 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 Gastroenterological Association: As of 3/11/2014 No guideline or position statement on the use of serum antibodies for the diagnosis of inflammatory bowel disease was found on their public website.

V. DEFINITIONS

TOP

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 contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital for benefit information.

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VII. DISCLAIMER

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Capital'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. Capital 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 when used for determination of anti-neutrophil cytoplasmic antibody (ANCA) and anti-Saccharomyces cerevisiae antibody (ASCA) in the workup and monitoring of patients with inflammatory bowel disease; therefore the following are not covered:

CPT Codes®								
84999								

ICD-9-CM Diagnosis Code*	Description
	Investigational for all diagnosis`

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

The following ICD-10 diagnosis codes will be effective October 1, 2015:

ICD-10-CM Diagnosis Code*	Description
	Investigational for all diagnosis`

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

IX. REFERENCES

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1. *1999 TEC Assessments; Tab 12.*
2. *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.*
3. *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.*
4. *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.*
5. *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.*
6. *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.*
7. *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.*
8. *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.*
9. *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.*
10. *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.*
11. *The Institute for Clinical Systems Improvement (ICSI) Technology Assessment. Serum Antibodies for the Diagnosis of Inflammatory Bowel Disease (IBD): pANCA for Ulcerative Colitis (UC) and ASCA for Crohn's Disease (CD). Released November 2002. No longer available on ICSI website*

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Other Sources

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 July 31, 2013. [Website]: www.uptodate.com . Accessed March 11, 2014.

Stone, J. Clinical Spectrum of anti-neutrophil cytoplasmic antibodies. In: UpToDate Online Journal [serial online]. Waltham, MA: UpToDate; updated January 2, 2013. [Website]: www.uptodate.com. Accessed March 11, 2013.

X. POLICY HISTORY

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wMP 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 complete--rsb
	CAC 9/24/13 Consensus, no change to policy statements, references updated
	3/25/14 Consensus, no change to policy statements. References updated.

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