

## Medical Policy Reference Manual Medical Policy

### 11.01.029 Serum Antibody Marker Testing for Inflammatory Bowel Disease

Original MPC Approval: 06/23/2004  
Last Review Date: 11/01/2022  
Last Revision Date: 11/01/2022

#### **Description**

Blood serum tests have been proposed to provide a mechanism for diagnosing IBD rapidly and definitively. By testing blood samples for biomarkers, an objective diagnosis of IBD may be possible. The serum antibodies known as anti-neutrophilic cytoplasmic antibody (ANCA) and anti-Saccaromyces cerevisiae antibody (ASCA) are associated with the presence of inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC). Testing for the presence of these antibodies has been proposed as a diagnostic aid for the physician in a case of a patient presenting with symptoms suggestive of IBD. The rationale is that antibody testing could be used as a first step to conceivably rule out the need for more invasive studies such as endoscopic examination or imaging of the bowel. Other suggested uses for ANCA and ASCA testing include confirmatory testing for CD or UC, differentiation of UC and CD, and as a predictor of response to certain therapies.

Prometheus® Laboratories of San Diego, California markets a proprietary product dedicated to serum antibody testing for inflammatory bowel disease.

Cytolethal distending toxin B and vinculin IgG are biomarkers included in diagnostic blood tests for irritable bowel syndrome. Cytolethal distending toxin B (CdtB) is commonly produced by bacterial pathogens that cause gastroenteritis. It has an ability to disrupt tight junction proteins. The levels of circulating host antibodies to CdtB are correlated with levels of small intestine bacterial overgrowth, and these anti-CdtB antibodies cross-react with the enteric neuronal protein, vinculin, likely through molecular mimicry (where the similarities between foreign and self-peptides are sufficient to elicit cross-reactivity). ELISA testing for anti-CdtB and anti-vinculin can discriminate patients with irritable bowel syndrome with diarrhea (IBS-D) from those with inflammatory bowel disease (IBD). Blood tests for IBS are able to distinguish IBS from inflammatory bowel disease (IBD) and reduce the need for unnecessary testing to rule out more serious conditions.

The IBSDetex™ test is offered by Quest Diagnostics. The ibs-smart™ is offered by Gemelli Biotech. Both tests detect anti-CdtB and anti-vinculin antibodies for the purpose of distinguishing IBS from IBD.

#### **Policy**

Testing for anti-neutrophilic cytoplasmic antibody (ANCA) and anti-Saccaromyces cerevisiae antibody (ASCA) is considered **not medically necessary** in the diagnosis and monitoring of patients with inflammatory bowel disease.

Testing for anti-CdtB and anti-vinculin antibody is considered **not medically necessary** in the diagnosis and monitoring of patients with inflammatory bowel disease.

#### **Policy Guidelines**

##### **Rationale:**

Serum antibody marker testing for inflammatory bowel disease is considered not medically necessary because the value this testing adds to conventional diagnostic techniques is unclear.

##### **Update 2022:**

A review of the literature was performed from April 2021 through April 2022. Findings in the literature do not change the current policy statement.

#### Update 2021:

A review of the peer-reviewed literature was performed from the period of February 2019 through January 2021. Findings in the recent literature do not change the conclusions regarding anti-neutrophilic cytoplasmic antibody (ANCA) and anti-Saccaromyces cerevisiae antibody (ASCA) testing in the diagnosis and monitoring of patients with inflammatory bowel disease. Therefore, the policy statements are not medically necessary.

#### Update 2019:

A review of the peer-reviewed literature was performed from December 2016 through January 2019. Findings in the recent literature do not change the conclusion on anti-neutrophilic cytoplasmic antibody (ANCA) and anti-Saccaromyces cerevisiae antibody (ASCA) testing in the diagnosis and monitoring of patients with inflammatory bowel disease. Therefore, the policy remains experimental / investigational.

#### Update 2016:

A review of the peer-reviewed literature was performed for October 2014 through November 2016. A Hayes Directory review (2016) assigned a C rating for serological assays using a combination of antibodies (including ASCA and ANCA) as an adjunct to conventional diagnostic techniques. According to the Hayes review although these assays may be beneficial in confirming a diagnosis of Crohn's disease, the quality of the evidence is low, there is uncertainty regarding the optimal combination of antibodies, and there is a lack of evidence demonstrating a positive impact on patient management or outcomes. A D1 rating was assigned for population screening of Crohn's disease in asymptomatic individuals due to the evidence of low sensitivity. A D2 rating was assigned for serological assays using a combination of antibodies to predict disease phenotype, disease progression, or response to treatment due to low-quality and/or limited evidence as well as lack of studies evaluating the impact on patient management or outcomes. Findings in the literature do not change the indication for ANCA or ASCA antibody testing. Therefore, the policy remains unchanged.

#### Update 2014:

A review of the peer-reviewed literature was performed for October 2012 through September 2014. A Hayes Directory review (2013) assigned a C rating for serological assays using a combination of antibodies (including ASCA and ANCA) as an adjunct to conventional diagnostic techniques. According to the Hayes review although these assays may be beneficial in confirming a diagnosis of Crohn's disease, the quality of the evidence is low, there is uncertainty regarding the optimal combination of antibodies, and there is a lack of evidence demonstrating a positive impact on patient management or outcomes. A D1 rating was assigned for population screening of Crohn's disease in asymptomatic individuals due to the evidence of low sensitivity. A D2 rating was assigned for serological assays using a combination of antibodies to predict disease phenotype, disease progression, or response to treatment due to low-quality and/or limited evidence as well as lack of studies evaluating the impact on patient management or outcomes. Findings in the literature do not change the indication for ANCA or ASCA antibody testing. Therefore, the policy remains unchanged.

#### Update 2012:

A review of the peer-reviewed literature was performed for June 2010 through September 2012. Findings in the literature do not change the indication for ANCA or ASCA antibody testing. Therefore, the policy remains unchanged.

#### Update 2010:

In July of 2006 Prometheus Laboratories made available an expanded panel of markers. Called IBD Serology 7, the panel is composed of five markers: ASCA IgA, ASCA IgG, anti-OmpC IgA, anti-CBir1, and IBD-specific pANCA. The results of the component tests are analyzed using a proprietary computer algorithm, which Prometheus maintains is able to predict the presence of IBD. Most of the available evidence published in the peer-reviewed literature is focused on testing of ANCA and ASCA antibodies. There is insufficient published evidence to permit conclusions on diagnostic capability or patient outcomes for the IBD Serology 7 panel. Furthermore, a review by Sabery and Bass (2007) evaluated an earlier generation serology test by Prometheus called IBD First Step and determined an overall 60% sensitivity and 92% specificity. A positive test for anemia and erythrocyte sedimentation rate (ESR) however showed an 83% sensitivity and 96% specificity. The authors concluded that a combination of ESR and hemoglobin has a higher positive predictive value for IBD and is more sensitive and specific than commercial serologic testing. Criteria 2-5 are not met for the IBD Serology 7 panel; therefore, the policy statement is unchanged.

#### Update 2008:

A review of the peer-reviewed literature was performed from June 2006 through June 2008. Findings in the literature do not change the indications for ANCA or ASCA antibody testing in the current policy. Therefore, the policy remains unchanged.

#### Update 2006:

A review of the peer-reviewed literature from June 2004 to June 2006 did not demonstrate any clinical advantage with the use of the above markers. It does not appear that the use of ANCA and ASCA antibodies is likely to alter the diagnostic work-up, the final diagnosis, or the treatment provided for patients with suspected IBD.

## **Benefit Applications**

There are no Benefit Applications for this Medical Policy.

## **Provider Guidelines**

There are no Provider Guidelines for this Medical Policy.

## **Cross References to Related Policies and Procedures**

7.01.076	Wireless Capsule Endoscopy (Enteral Camera), Policy
11.01.031	Pharmacogenomic and Serologic Metabolite Markers for Inflammatory Bowel Disease Patients Treated with Azathioprine, Policy (archived)
11.01.075	Serologic Metabolite Markers for Inflammatory Bowel Disease Patients Treated with Azathioprine, Policy

## **References**

**The following were among the resources reviewed and considered in developing this policy. By reviewing and considering the resources, CareFirst does not in any way endorse the contents thereof nor assume any liability or responsibility in connection therewith. The opinions and conclusions of the authors of these resources are their own and may or may not be in agreement with those of CareFirst.**

Abbasian, J., Martin, T., Patel, S., et al. (2012, July). Immunologic and genetic markers in patients with idiopathic ocular inflammation and a family history of inflammatory bowel disease. *Am J Ophthalmol.* 154(1):72-7.

Annese V., Piepoli, A., Perri, F., Lombardi, G., et al. (2004, November). Anti-Saccharomyces cerevisiae mannan antibodies in inflammatory bowel disease: comparison of different assays and correlation with clinical features. *Alimentary Pharmacology & Therapeutics.* 15; 20(10): 1143 - 1152.

Binder, H.J. (1999). Is antibody testing for inflammatory bowel disease clinically useful? *Gastroenterology* 116, 1001-1008.

Elitsur, Y., Lawrence Z., Tolaymat, N. (2005, September). The diagnostic accuracy of serologic markers in children with IBD: the West Virginia experience. *Journal of Clinical Gastroenterology* 39(8): 670 - 3.

Forcione, DG., Rosen, MJ., Kisiel, JB., Sands, BE. (2004, August). Anti-Saccharomyces cerevisiae antibody (ASCA) positivity is associated with increased risk for early surgery in Crohn's disease. *Gut*; 53(8): 1117-22.

Gupta SK., Fitzgerald, JF., Croffie, JM., Pfefferkorn, MD, Molleston, JP, Corkins, MR. (2004, May). Comparison of serological markers of inflammatory bowel disease with clinical diagnosis in children. *Inflammatory Bowel Disease*; 10(3): 240-4.

Halfvarson, J., Standaert-Vitse, A., Jarnerot, G., Sendid, B., Jouault, T., Bodin, L., Duhamel, A., Colombel, JF., Tysk, C., Poulain, D. (2005, September). Anti-Saccharomyces cerevisiae antibodies in twins with inflammatory bowel disease. *Gut*; 54 (9): 1237 - 43. Epub 2005 April 29.

Halme, L., Turunen, U., Helio, T. et al (2002). Familial and sporadic inflammatory bowel disease: comparison of clinical features and serological markers in a genetically homogeneous population. *Scandinavian Journal of Gastroenterology* 37, 692-8.

Hayes Directory (2013, March 12). Serological assays for the diagnosis and management of inflammatory bowel disease: Crohn's disease. Lansdale PA: Hayes, Inc.

Hayes GTE Report. (2017, March; 2018, March- annual review; 2020, October- annual review). Prometheus IBD sgi Diagnostic (Prometheus Laboratories Inc.) Lansdale PA: Hayes, Inc.

Hayes Inc. Hayes Search and Summary (2015, July). Anser ADA (Prometheus Laboratories Inc.) for monitoring adalimumab treatment of inflammatory bowel disease. Lansdale PA: Hayes, Inc.

Hayes Inc. Medical Technology Directory. (published 2013, March; reviewed 2016, January; 2017, January- annual review; 2018, April- archived). Serological assays for diagnosis and management if inflammatory bowel disease: ulcerative crohn's disease. Lansdale PA: Hayes, Inc.

Hayes Inc. Medical Technology Directory. (published 2013, April; reviewed 2016, March; 2017, March- annual review; 2018, May-archived). Serological assays for diagnosis and management if inflammatory bowel disease: ulcerative colitis. Lansdale PA: Hayes, Inc.

Hayes Search & Summary. (2017, December). Anser ADA (Prometheus Laboratories Inc.) for monitoring adalimumab treatment of inflammatory bowel disease. Lansdale, PA: Hayes, Inc.

He, Z., Gharaibeh, R.Z., Newsome, R.C., Pope, J.L., Daugherty, M.W., Tomkovich, S., ..., Jobin, C. (2019) Campylobacter jejuni promotes colorectal tumorigenesis through the action of cytolethal distending toxin, *Gut*, 68(2): 289-300.

Iskandar, H., Ciorba, M. (2012, April). Biomarkers in inflammatory bowel disease: current practices and recent advances. *Transl Res*. 159(4):313-25.

Joossens, S., Reinisch, W., Vermeire, S. et al (2002). The value of serologic markers in indeterminate colitis: a prospective follow-up study. *Gastroenterology* 122, 1242-7.

Kaul, A., Hutfless, S., Liu, L. et al. (2012, January). Serum anti-glycan antibody biomarkers for inflammatory bowel disease diagnosis and progression: A systematic review and meta-analysis. *Inflamm Bowel Dis*. [Epub ahead of print].

Kim, J.H., Lin, E., Pimentel, M. (2017) Biomarkers of irritable bowel syndrome, *J Neuroastroenterol Motil*, 23(1): 20-26.

Klutts, J.S., Korzenik, J.R. et al (2003). The use of serologic markers in inflammatory bowel disease. *Laboratory Medicine Newsletter* 9 (3), 1-4.

Kornbluth, A., Sachar, David. (2004). Ulcerative Colitis Practice Guidelines in Adults (Update): American College of Gastroenterology, Practice Parameters Committee. *American College of Gastroenterology*; 10.1111/j.1572-0241

Lecis, P., Germana, B., Papa, N. et al (2002). p-ANCA and ASCA antibodies in the differential diagnosis between ulcerative rectocolitis and Crohn's disease. *Recenti Prog Med*. 93(5):308-13.

Lewis, James. (2011, May). The Utility of Biomarkers in the Diagnosis and Therapy of Inflammatory Bowel Disease. *Gastroenterology*. 140(6):1817-1826.

Linskens, R.K., Mallant-Hent, R.C., Groothuismink, Z.M. et al (2002). Evaluation of serological markers to differentiate between ulcerative colitis and Crohn's disease: pANCA, ASCA and agglutinating antibodies to anaerobic coccoid rods. *European Journal of Gastroenterology and Hepatology* 14, 1013-8.

MacDermott, R.P. (1999). Lack of current clinical value of serological testing in the evaluation of patients with IBD. *Inflammatory Bowel Diseases* 5, 64-65.

Morales, W., Rezaie, A., Barlow, G., Pimentel, M. (2019) Second-generation biomarker testing for irritable bowel syndrome using plasma anti-CdtB and anti-vinculin levels, *Dig Dis Sci*, 64(11): 3115-3121.

Papadakis, K.A., Targan, S.R. (1999). Serologic testing in inflammatory bowel disease: its value in indeterminate colitis. *Current Gastroenterology Reports* 1, 482-5.

Papp, M., Norman, G.L., Altorjay, I., Lakatos, P.L. (2007). Utility of serological markers in inflammatory bowel diseases: gadget or magic? *World Journal of Gastroenterology* 13, 2028-36.

Peyrin-Biroulet, L., Standaert-Vitse, A., Branche, J., Chamaillard, M. (2007). IBD serological panels: facts and perspectives. *Inflammatory Bowel Disease* 13, 1561-6.

Prideaux, L., De Cruz, P., Ng, S.C., & Kamm, M.A. (2012, November 8). Serologic antibodies in inflammatory bowel disease: a systematic review. *Inflammatory Bowel Diseases* 18(7): 1340-1355. doi: 10.1002/ibd.21903

Quinton, J.F., Sendid, B., Reumaux, D., et al (1998). Anti-*Saccharomyces cerevisiae* mannan antibodies combined with antineutrophil cytoplasmic autoantibodies in inflammatory bowel disease: prevalence and diagnostic role. *Gut* 42, 788-91.

Reese, George E., Constantinides, V.A., Simillis, C., Darzi, A.W., et al. (2006, October). Diagnostic Precision of Anti-*Saccaromyces cerevisiae* Antibodies and Perinuclear Antineutrophil Cytoplasmic Antibodies in Inflammatory Bowel Disease. *The American Journal of Gastroenterology* 2006; 101(10):2410-2422.

Sabery, N., Bass, D. (2007). Use of serologic markers as a screening tool in inflammatory bowel disease compared with elevated erythrocyte sedimentation rate and anemia. *Pediatrics* 119, e193-9.

Sellin, J., Shah, R. (2012, June). The promise and pitfalls of serologic testing in inflammatory bowel disease. *Gastroenterol Clin North Am.* 41(2):463-82.

Sheikh, S., Uno, J., Matsuoka, K., Plevy, S. (2008). Abnormal mucosal immune response to altered bacterial flora following restorative proctocolectomy in patients with ulcerative colitis: serologic measures, immunogenetics, and clinical correlations. *Clinical Immunology* 127, 270-9.

Sandborn, W.J., Loftus, E.V., Colombel, J.F. et al (2001). Evaluation of serologic disease markers in a population-based cohort of patients with ulcerative colitis and Crohn's disease. *Inflammatory Bowel Diseases* 7, 192-201.

Targan, S.R. (1999). The utility of ASCA and ASCA in inflammatory bowel disease. *Inflammatory Bowel Diseases* 5, 61-63.

Vasiliauskas, E.A., Kam, L.Y., et al (2000). Marker antibody expression stratifies Crohn's disease into immunologically homogeneous subgroups with distinct clinical characteristics. *Gut* 47, 487-496.

Vernier, G., Sendid, B., Poulain, D., Colombel, JF. (2004, December). Relevance of serologic studies in inflammatory bowel disease. *Current Gastroenterology Report*; 6(6): 482 - 7.

Vojdani, A., Vojdani, E. (2019) Reaction of antibodies to *Campylobacter jejuni* and cytolethal distending toxin B with tissues and food antigens, *World J Gastroenterol*, 25(9): 1050-1066.

Wang, Z. Z., Shi, K., Peng, J. (2017, April). Serologic testing of a panel of five antibodies in inflammatory bowel diseases: Diagnostic value and correlation with disease phenotype. *Biomedical Report*. doi: 10.3892/br.2017.860.

**This policy statement relates only to the services or supplies described herein. Coverage will vary from contract to contract and by line of business and should be verified before applying the terms of the policy.**