Serum Antibodies for Diagnosis of Inflammatory Bowel Disease

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Developed By: Medical Necessity Criteria Committee

I. Description

Inflammatory bowel disease (IBD) is a chronic relapsing inflammatory intestinal condition that can be subdivided into ulcerative colitis (UC) and Crohn's disease (CD). Patients with IBD may have a wide variety of symptoms including diarrhea, abdominal pain, and rectal bleeding. Diagnosis is established by a combination of radiographic, endoscopic, and histologic work-up. However, in approximately 10% of patients with IBD, the distinction between ulcerative colitis and Crohn's disease cannot be made with certainty and the diagnosis becomes "indeterminate colitis." Two serum antibodies, anti-neutrophilic cytoplasmic antibody (ANCA) and anti-saccharomyces cerevisiae (ASCA) have been investigated as a technique to improve the efficiency and accuracy of diagnosing IBD. ANCA has been detected in UC patients 50-80%, and less frequently in CD patients, 10-40%. ASCA has been detected in 46-70% of patients with Crohn's disease and 6-12% of patient with ulcerative colitis. These non-invasive tests examine serological panels of antibodies, including ASCA and ANCA, to diagnose IBD and differentiate between UC and CD. However, research has determined that there is insufficient sensitivity to diagnose ulcerative colitis or Crohn's disease.

Genetic polymorphisms for thiopurine methyltransferase (TPMT), the primary enzyme-metabolizing azathiopurine and 6-mercaptopurine, have been identified to assist in regulating therapy according to the measurements of azathiopurine/6-mercaptopurine metabolites. Current recommendations from the FDA include determination of TPMT (either enzyme of genotype) prior to initiating treatment with azathiopurine or 6-mercaptopurine. Tests were developed by Prometheus® (and other labs have followed) in order to provide guidance in determining therapeutic direction and predicting therapeutic response in individual patients receiving treatment with Infliximab (IFX), vedolizumab (VDZ), or Adalimunab (ADA). The Thiopurine metabolite test is used during treatment for the ongoing evaluation of patient response to thiopurine therapies.

The tests may be performed by other laboratories besides Prometheus® but the medical criteria below apply regardless of the requesting laboratory.

II. Criteria: CWQI HCS-0061

A. Moda Health considers baseline TPMT genotype testing medically necessary in individuals with inflammatory bowel disease, for any of the following: ***<u>**Note – this test is covered for these indications one time during the patient's lifetime**</u>***
   a. To determine candidacy for thiopurine treatment prior to initiation of 6-Mercaptopurine (6-MP), or Azathiopurine (AZA), or thioguanine (6-TG)
   b. In patients on thiopurine therapy with abnormal CBC results that do not respond to dose reduction

B. Monitoring of thiopurine metabolite levels in individuals with inflammatory bowel disease is considered medically necessary for either of the following indications:
   a. To measure blood levels in individuals suspected of having toxic responses to AZA and/or 6-MP (e.g., hepatotoxicity or myelotoxicity)
   b. To measure drug levels in individuals who have not responded

C. TPMT gene mutation assays and TPMT phenotypic assays are considered experimental and investigational for all other indications because their effectiveness for indications other than the one listed above has not been established.

D. Analysis of the metabolite markers of azathioprine and 6-mercaptopurine, including 6-methylmercaptopurine ribonucleotides (6-MMRP) and 6-thioguanine nucleotides (6-TGN), is considered E and I in all other situations

E. The following tests are considered experimental, investigational, or unproven to diagnose IBD, to distinguish UC from Crohn's, to manage IBD, and for all other indications because their effectiveness has not been established:
   a. ASCA – anti-Saccharomyces cerevisiae antibodies
   b. ANCA – anti-neutrophil cytoplasmic antibodies
   c. ACCA – anti-chitobioside carbohydrate antibodies
   d. ALCA – anti-laminaribioside carbohydrate antibodies
   e. AMCA – anti-mannobioside carbohydrate antibodies
   f. Anti-C – anti-chitin IgA
   g. Anti-L – anti-laminarin IgA
   h. OmpC anti-outer membrane porin C antibodies
   i. anti-Cbir1 – anti-Cbir1 flagellin antibodies
   j. 12 antibodies

F. Anti-smooth muscle antibodies (ASMA) is considered experimental and investigational to diagnose inflammatory bowel disease or to distinguish ulcerative colitis from Crohn's disease because its effectiveness for these indications has not been established. ***Note: ASMA may be medically necessary to diagnose autoimmune hepatitis***

G. <u>Fecal measurement of calprotectin</u> is considered medically necessary for management of inflammatory bowel diseases and for distinguishing inflammatory bowel disease from irritable bowel syndrome

H. Fecal measurement of calprotectin is considered experimental or investigational for other indications because its clinical value has not been established

I. <u>Fecal lactoferrin</u> is medically necessary for distinguishing inflammatory bowel disease from irritable bowel syndrome

J. Fecal lactoferrin is considered experimental or investigational for evaluation of infectious diarrhea, Clostridium difficile infection, and all other indications
K. Measurement of antibodies to any/all of the following, either alone or as a combination test is considered experimental or investigational
    a. Infliximab (Remicade)
    b. Humira (adalimumab)
    c. Entyvio (vedolizumab)
    d. Stelara (ustekinumab)
L. In an individual receiving treatment with any medications, measurement of serum levels of any of the following, either alone or as a combination test is considered experimental or investigational
    a. Infliximab (Remicade)
    b. Humira (adalimumab)
    c. Entyvio (vedolizumab)
    d. Stelara (ustekinumab)
M. Tests that are considered experimental or investigational for measurement of antibodies and/or serum levels include, but are not limited to:
    a. Anser IFX (Remicade/infliximab),
    b. Anser ADA (Humira/adalimumab),
    c. Anser VDZ (Entyvio/vedolizumab),
    d. Anser UST (Stelara/ustekinumab)

III. Information Submitted with the Prior Authorization Request:

1. Chart notes and history and physical from ordering specialist
2. Results of colonoscopy and other diagnostic studies performed
3. Pathology report

IV. CPT or HCPC codes covered when criteria requirements are met:

Codes	Description
	TPMT
81401	TPMT genetics (Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81335	TPMT (thiopurine S-methyltransferase) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3)
82657	Enzyme activity in blood cells, cultured cells, or tissue, not elsewhere specified; nonradioactive substrate, each specimen
82542	Column chromatography, includes mass spectrometry, if performed (eg, HPLC, LC, LC/MS, LC/MS-MS, GC, GC/MS-MS, HPLC/MS), non-drug analyte(s) not elsewhere specified, qualitative or quantitative, each specimen
6-thioguanine nucleotide (6-TGN) and 6-methylmercaptopurine nucleotide (6-MMPN)	

Calprotectin, Fecal	
83993	Calprotectin, fecal
Lactoferrin, Fecal	
No specific code	Firmicutes and Bacteroidetes (F/B) ratio stool test, measurements of DNA, mRNA and protein biomarkers
83630	Lactoferrin, fecal; qualitative
83631	Lactoferrin, fecal; quantitative

V. CPT or HCPC codes NOT covered:

Codes	Description
TPMT	
83789	Mass spectrometry and tandem mass spectrometry (e.g., MS, MS/MS, MALDI, MS-TOF, QROF), non-drug analyst(s), not elsewhere specified, qualitative or quantitative, each specimen
86256	Fluorescent noninfectious agent antibody; titer, each antibody
6-thioguanine nucleotide (6-TGN) and 6-methylmercaptopurine nucleotide (6-MMPN)	
80299	Quantification of therapeutic drug, not elsewhere specified
ACCA, ALCA, AMCA, Anti-C, Anti-L, ANCA, ASCA, OmpC, anti-Cbir-1, 12 antibodies, and ASMA	
82397	Chemiluminescent assay
83516	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen, qualitative or semi-quantitative; multiple step method
83518	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, single step method (eg, reagent strip)
83519	quantitative, by radioimmunoassay (eg, RIA)
83520	Immunoassay, analyte, quantitative; not otherwise specified
86021	Antibody identification; leukocyte antibodies [ANCA antibodies]
86255	Fluorescent noninfectious agent antibody; screen, each antibody
86671	Antibody; fungus, not elsewhere specified
88350	Immunofluorescence, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)
ANSER IFX; ANSER ADA; ANSER VDZ; ANSER UST	
84999	Unlisted chemistry procedure
80299	Quantification of therapeutic drug, not elsewhere specified
83516	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen, qualitative or semi-quantitative; multiple step method
83520	Immunoassay, analyte, quantitative; not otherwise specified

86235	Extractable nuclear antigen, antibody to, any method (e.g., nRNP, SS-A, SS-B, Sm, RNP, Sc170, J01), each antibody [measurement of anti-histone antibodies for monitoring infliximab therapy]

VI. Annual Review History

Review Date	Revisions	Effective Date
05/2013	Annual Review: Added table with review date, revisions, and effective date. Revised criteria to include criteria for approval of TPMT testing.	05/2013
04/2014	Annual Review: Revised names of tests – added new tests from Prometheus considered E/I, added fecal calprotectin considered E/I	04/14
04/2015	Annual Review: Added test names from Prometheus and updated CPT codes covered and non-covered for each test.	04/25/2015
05/2016	Annual Review: Minor wording revisions – no change to criteria	05/25/2016
05/2017	Annual Review: Revised wording for the non-covered tests	05/24/2017
05/2018	Annual Review: Added language tests may be performed by labs other than Prometheus. Removed fecal calprotectin for children 12 and under – no literature to support	05/24/2018
04/2019	Annual review – no changes	05/01/2019
11/2019	Updates & review: Criteria reviewed and updated to reflect indications required for coverage of TPMT genetic testing for IBD. Updated the list of tests considered E&I, covered and non-covered codes	12/05/2019
07/2020	Annual Review: Fecal measurement of calprotectin is now considered for management of inflammatory bowel diseases in addition to distinguishing inflammatory bowel disease from inflammatory bowel syndrome. Removed deleted code 82491	08/01/2020
07/31/2020	Update: added code 82542	
07/28/2021	Annual Review: No content change	08/01/2021
06/22/2022	Annual Review: No content change	07/01/2022

VII. References

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27. Physician Advisors

Appendix 1 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD) and Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD):

Jurisdiction(s): 5, 8	NCD/LCD Document (s):

NCD/LCD Document (s):

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	Applicable State/US Territory	Contractor
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC