Serum Antibodies for Diagnosis of Inflammatory Bowel Disease

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 azathioprine and 6-mercaptopurine, have been identified to assist in regulating therapy according to the measurements of azathioprine/6-mercaptopurine metabolites. Current recommendations from the FDA include determination of TPMT (either enzyme of genotype) prior to initiating treatment with azathioprine 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 Adalimumab (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: ***Note – this test is covered for these indications one time during the patient’s lifetime***
   a. To determine candidacy for thiopurine treatment prior to initiation of 6-Mercaptopurine (6-MP), or Azathioprine (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. Fecal measurement of calprotectin 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. Fecal lactoferrin 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:

<table>
<thead>
<tr>
<th>Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPMT</td>
<td></td>
</tr>
<tr>
<td>81401</td>
<td>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)</td>
</tr>
<tr>
<td>81335</td>
<td>TPMT (thiopurine S-methyltransferase) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3)</td>
</tr>
<tr>
<td>82657</td>
<td>Enzyme activity in blood cells, cultured cells, or tissue, not elsewhere specified; nonradioactive substrate, each specimen</td>
</tr>
<tr>
<td>82542</td>
<td>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</td>
</tr>
</tbody>
</table>

6-thioguanine nucleotide (6-TGN) and 6-methylmercaptopurine nucleotide (6-MMPN)
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>83993</td>
<td>Calprotectin, fecal</td>
</tr>
<tr>
<td></td>
<td><strong>Calprotectin, Fecal</strong></td>
</tr>
<tr>
<td>83630</td>
<td>Lactoferrin, fecal; qualitative</td>
</tr>
<tr>
<td>83631</td>
<td>Lactoferrin, fecal; quantitative</td>
</tr>
<tr>
<td></td>
<td><strong>Lactoferrin, Fecal</strong></td>
</tr>
<tr>
<td></td>
<td>No specific code</td>
</tr>
<tr>
<td></td>
<td>Firmicutes and Bacteroidetes (F/B) ratio stool test, measurements of DNA, mRNA and protein biomarkers</td>
</tr>
<tr>
<td></td>
<td><strong>V. CPT or HCPC codes NOT covered:</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPMT</td>
<td><strong>TPMT</strong></td>
</tr>
<tr>
<td>83789</td>
<td>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</td>
</tr>
<tr>
<td>86256</td>
<td>Fluorescent noninfectious agent antibody; titer, each antibody</td>
</tr>
<tr>
<td>6-thiouguanine nucleotide (6-TGN) and 6-methylmercapturine nucleotide (6-MMPN)</td>
<td><strong>6-thiouguanine nucleotide (6-TGN) and 6-methylmercapturine nucleotide (6-MMPN)</strong></td>
</tr>
<tr>
<td>80299</td>
<td>Quantification of therapeutic drug, not elsewhere specified</td>
</tr>
<tr>
<td>ACCA, ALCA, AMCA, Anti-C, Anti-L, ANCA, ASCA, OmpC, anti-Cbir-1, 12 antibodies, and ASMA</td>
<td><strong>ACCA, ALCA, AMCA, Anti-C, Anti-L, ANCA, ASCA, OmpC, anti-Cbir-1, 12 antibodies, and ASMA</strong></td>
</tr>
<tr>
<td>82397</td>
<td>Chemiluminescent assay</td>
</tr>
<tr>
<td>83516</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen, qualitative or semi-quantitative; multiple step method</td>
</tr>
<tr>
<td>83518</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semi-quantitative, single step method (eg, reagent strip)</td>
</tr>
<tr>
<td>83519</td>
<td><strong>quantitative, by radioimmunoassay (eg, RIA)</strong></td>
</tr>
<tr>
<td>83520</td>
<td>Immunoassay, analyte, quantitative; not otherwise specified</td>
</tr>
<tr>
<td>86021</td>
<td>Antibody identification; leukocyte antibodies [ANCA antibodies]</td>
</tr>
<tr>
<td>86255</td>
<td>Fluorescent noninfectious agent antibody; screen, each antibody</td>
</tr>
<tr>
<td>86671</td>
<td>Antibody; fungus, not elsewhere specified</td>
</tr>
<tr>
<td>88350</td>
<td>Immunofluorescence, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ANSER IFX; ANSER ADA; ANSER VDZ; ANSER UST</th>
<th><strong>ANSER IFX; ANSER ADA; ANSER VDZ; ANSER UST</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>84999</td>
<td>Unlisted chemistry procedure</td>
</tr>
<tr>
<td>80299</td>
<td>Quantification of therapeutic drug, not elsewhere specified</td>
</tr>
<tr>
<td>83516</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen, qualitative or semi-quantitative; multiple step method</td>
</tr>
<tr>
<td>83520</td>
<td>Immunoassay, analyte, quantitative; not otherwise specified</td>
</tr>
</tbody>
</table>
VI. Annual Review History

<table>
<thead>
<tr>
<th>Review Date</th>
<th>Revisions</th>
<th>Effective Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>05/2013</td>
<td>Annual Review: Added table with review date, revisions, and effective date. Revised criteria to include criteria for approval of TPMT testing.</td>
<td>05/2013</td>
</tr>
<tr>
<td>04/2014</td>
<td>Annual Review: Revised names of tests – added new tests from Prometheus considered E/I, added fecal calprotectin considered E/I.</td>
<td>04/14</td>
</tr>
<tr>
<td>04/2015</td>
<td>Annual Review: Added test names from Prometheus and updated CPT codes covered and non-covered for each test.</td>
<td>04/25/2015</td>
</tr>
<tr>
<td>05/2016</td>
<td>Annual Review: Minor wording revisions – no change to criteria</td>
<td>05/25/2016</td>
</tr>
<tr>
<td>05/2017</td>
<td>Annual Review: Revised wording for the non-covered tests</td>
<td>05/24/2017</td>
</tr>
<tr>
<td>05/2018</td>
<td>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</td>
<td>05/24/2018</td>
</tr>
<tr>
<td>04/2019</td>
<td>Annual review – no changes</td>
<td>05/01/2019</td>
</tr>
<tr>
<td>11/2019</td>
<td>Updates &amp; 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</td>
<td>12/05/2019</td>
</tr>
<tr>
<td>07/2020</td>
<td>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.</td>
<td>08/01/2020</td>
</tr>
<tr>
<td>07/31/2020</td>
<td>Update: added code 82542</td>
<td></td>
</tr>
<tr>
<td>07/28/2021</td>
<td>Annual Review: No content change</td>
<td>08/01/2021</td>
</tr>
<tr>
<td>06/22/2022</td>
<td>Annual Review: No content change</td>
<td>07/01/2022</td>
</tr>
</tbody>
</table>

VII. References


10. Information provided by Prometheus Laboratories-IBD First Step, IBD Diagnostic System, Comparison of ANCA.


13. Kornbluth and Sachar. The practice parameters committee of the American College of


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):

<table>
<thead>
<tr>
<th>Jurisdiction(s): 5, 8</th>
<th>NCD/LCD Document (s):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NCD/LCD Document (s):

<table>
<thead>
<tr>
<th>Medicare Part B Administrative Contractor (MAC) Jurisdictions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jurisdiction</td>
</tr>
<tr>
<td>F (2 &amp; 3)</td>
</tr>
</tbody>
</table>