

MARKERS FOR DIGESTIVE DISORDERS**Effective Date: January 1, 2019****Review Dates: 2/11, 2/12, 2/13, 2/14, 2/15, 2/16,
11/16, 8/17, 11/17,11/18****Date Of Origin: February 9, 2011****Status: Current****Summary of Changes**

Additions:

- Pg.1, Section I, A, 2, criteria updated to reflect that the measurements of anti-drug antibody of infliximab, adalimumab, vedolizumab, and ustekinumab are considered experimental and investigational.
- Pg. 1, Section I, A, 3, criteria updated to include TMPT phenotyping and genotyping for thiopurine drug response as covered according to eviCore guidelines.

I. POLICY/CRITERIA**A. Inflammatory digestive disorders**

1. Measurements of serum concentration of infliximab (IFX) or adalimumab (ADA) or vedolizumab (VDZ) or ustekinumab (UST) for reactive therapeutic drug monitoring of members with active inflammatory bowel disease (IBD) treated with anti- tumor necrosis factor (TNF) agents are considered medically necessary.
2. Measurements of anti-drug antibody to infliximab or adalimumab or vedolizumab or ustekinumab (e.g. PROMETHEUS® Anser™IFX / Anser ADA/Anser VDZ/Anser UST) are considered experimental & investigational.
3. Thiopurine methyltransferase (TMPT) phenotype (analysis of enzyme activity) and genotype (identification of specific variants) testing for thiopurine drug response may be covered according to eviCore guidelines.
4. 6-thioguanine nucleotide (6-TGN) and 6-methylmercaptopurine nucleotide (6-MMPN) measurements (e.g. PRO-PredictR 6MP / azathioprine, PRO-Predict Metabolites) are medically necessary to monitor compliance in those not responding to 6-MP or azathioprine and to assess suspected toxicity.
5. Fecal measurement of calprotectin is a covered benefit for the management of inflammatory bowel diseases (e.g. Crohn's disease, ulcerative colitis). It is not a covered benefit for other indications because its clinical value has not been established.
6. The following tests are experimental and investigational because their clinical value has not been established.
 - Crohn's disease peptide antibody testing
 - ECM1 and Stat-3 testing for ulcerative colitis
 - Measurement of serum mannose-binding lectin
 - Myeloperoxidase antibody testing for inflammatory bowel disease,

- Proteinase-3 antibody testing,
- Raman spectroscopy for inflammatory bowel disease.

B. Celiac Disease

1. Serological testing of anti-gliadin antibodies (AGA), anti-reticulin antibodies (ARA), IgA anti-human tissue transglutaminase (TTG) antibodies (TGA), and IgA anti-endomysial antibodies (EMA) are medically necessary for any of the following indications:
 - a. As a preliminary diagnostic test for persons with symptoms suggestive of celiac disease; *or*
 - b. To monitor response to a gluten-free diet; *or*
 - c. To screen first-degree relatives of individuals with celiac disease; *or*
 - d. To screen persons with type 1 diabetes for celiac disease.
2. IgG-TTG and IgG-EMA are considered to be medically necessary for persons with symptoms suggestive of celiac disease and a serum IgA deficiency.
3. Deamidated gliadin antibodies (DGP) are experimental and investigational as serological markers for celiac disease.
4. Serological tests individually or as part of a panel for celiac disease (IgA-AGA, IgG-AGA, IgA-TTG, and IgA-EMAt) are experimental and investigational as an alternative to biopsy for assessing mucosal damage in individuals with celiac disease, and for all other indications (i.e. PROMETHEUS® Celiac PLUS, PROMETHEUS® Celiac Serology).
5. Genetic testing for HLA-DQ2 and HLA-DQ8 haplotypes is medically necessary ONLY for members with symptoms suggestive of celiac disease and indeterminate serology results. Genetic testing as initial screening in symptomatic or in asymptomatic individuals is considered to be experimental and investigational (i.e. MyCeliacID, PROMETHEUS® Celiac Genetics).
6. The following tests are experimental and investigational for the diagnosis of celiac disease: (not an all-inclusive list):
 - D-xylose and/or lactulose absorption test
 - Intestinal permeability tests
 - Salivary tests
 - Small-bowel follow-through (barium follow-through examination)
 - Stool studies.

II. MEDICAL NECESSITY REVIEW

- All tests performed at non-participating laboratories will require prior authorization; and as indicated.

III. APPLICATION TO PRODUCTS

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

- ❖ **HMO/EPO:** *This policy applies to insured HMO/EPO plans.*
- ❖ **POS:** *This policy applies to insured POS plans.*
- ❖ **PPO:** *This policy applies to insured PPO plans. Consult individual plan documents as state mandated benefits may apply. If there is a conflict between this policy and a plan document, the provisions of the plan document will govern.*
- ❖ **ASO:** *For self-funded plans, consult individual plan documents. If there is a conflict between this policy and a self-funded plan document, the provisions of the plan document will govern.*
- ❖ **INDIVIDUAL:** *For individual policies, consult the individual insurance policy. If there is a conflict between this medical policy and the individual insurance policy document, the provisions of the individual insurance policy will govern.*
- ❖ **MEDICARE:** *Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, this policy applies.*
- ❖ **MEDICAID/HEALTHY MICHIGAN PLAN:** *For Medicaid/Healthy Michigan Plan members, this policy will apply. Coverage is based on medical necessity criteria being met and the appropriate code(s) from the coding section of this policy being included on the Michigan Medicaid Fee Schedule located at: http://www.michigan.gov/mdch/0,1607,7-132-2945_42542_42543_42546_42551-159815--,00.html. If there is a discrepancy between this policy and the Michigan Medicaid Provider Manual located at: http://www.michigan.gov/mdch/0,1607,7-132-2945_5100-87572--,00.html, the Michigan Medicaid Provider Manual will govern. For Medical Supplies/DME/Prosthetics and Orthotics, please refer to the Michigan Medicaid Fee Schedule to verify coverage.*

IV. DESCRIPTION

The American College of Gastroenterology (AGA) Practice Guidelines for Management of Crohn's disease in adults (Lichtenstein et al., 2009) state that serological studies evaluating antibodies against *Saccharomyces cerevisiae*, antineutrophil cytoplasmic antibodies, antibodies directed against CBir1, OmpC are evolving to provide adjunctive support for the diagnosis of Crohn's disease, but are not sufficiently sensitive or specific to be recommended for use as a screening tools.

The American College of Gastroenterology Ulcerative Colitis Practice Guidelines in Adults, updated in 2010, states that pANCA have been identified in 60–70% of ulcerative colitis (UC) patients but are also found in up to 40% of patients with CD. These pANCA-positive CD patients typically have a clinical phenotype resembling left-sided UC patients, so ANCA detection alone is of little value in distinguishing between UC and CD. The low sensitivity of pANCA for the diagnosis of UC prevents it from serving as a useful diagnostic tool. These assays may be useful, however, in the occasional patient in whom no other clinical or pathologic features allow a differential diagnosis between UC and Crohn's colitis.

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the Crohn's and Colitis Foundation of America consensus conference report on differentiating UC from CD in children and young adults (Bousvaros, et al., 2007) states that the value of serology in a patient with IC remains a topic of study, and further research should examine, among other areas, the role of surrogate laboratory markers (genetics, serology, microbiology) in distinguishing these entities. A proposed algorithm to assist clinicians in differentiating UC from CD does not include serological testing.

The American Gastroenterological Association Clinical Guidelines for Therapeutic Drug Monitoring in Inflammatory Bowel Disease (Feuerstein et al, 2017) suggests reactive therapeutic drug monitoring to guide treatment changes in adults with active IBD treated with anti-TNF agents. However, the AGA does not recommend the use of routine proactive therapeutic drug monitoring in adult patients with inactive IBD treated with anti-TNF agents. The evidence is currently insufficient to support the use of Anser IFX, Anser ADA, Anser UST, and Anser VDZ for the treatment management for adult or pediatric patients with IBD.

V. CODING INFORMATION

ICD-10 Codes that may apply:

D50.0	Iron deficiency anemia secondary to blood loss (chronic)
D63.8	Anemia in other chronic diseases classified elsewhere
K50.00 – K50.919	Crohn's disease
K51.00 – K51.919	Ulcerative colitis
K52.2	Allergic and dietetic gastroenteritis and colitis
K52.89	Other specified noninfective gastroenteritis and colitis
K52.9	Noninfective gastroenteritis and colitis, unspecified
K58.0 – K58.9	Irritable bowel syndrome
K59.8	Other specified functional intestinal disorders
K59.9	Functional intestinal disorder, unspecified
K90.0	Celiac disease
K90.1	Tropical sprue
K90.41	Non-celiac gluten sensitivity
K90.49	Malabsorption due to intolerance, not elsewhere classified
K90.89	Other intestinal malabsorption
K90.9	Intestinal malabsorption, unspecified
K92.1	Melena
K92.2	Gastrointestinal hemorrhage, unspecified
P78.9	Perinatal digestive system disorder, unspecified
R11.0 – R11.2	Nausea and vomiting
R19.4	Change in bowel habit
R19.5	Other fecal abnormalities
R19.7	Diarrhea, unspecified
R19.8	Other specified symptoms and signs involving the digestive system and abdomen

- R63.8 Other symptoms and signs concerning food and fluid intake
R93.5 Abnormal findings on diagnostic imaging of other abdominal regions, including retroperitoneum

CPT/HCPCS Codes:

- Codes are covered or not covered based on indications in this policy:* 81382 HLA Class II typing, high resolution (i.e., alleles or allele groups); one locus (eg, HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each
- 81335 TPMT (thiopurine S-methyltransferase) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3) **PA through eviCore** *Not covered for Medicaid*
- 82397 Chemiluminescent assay
- 82491 Chromatography, quantitative, column (e.g., gas liquid or HPLC); single analyte not elsewhere specified, single stationary and mobile phase *Not covered for Medicaid*
- 82542 Column chromatography, includes mass spectrometry, if performed (eg, HPLC, LC, LC/MS, LC/MS-MS, GC, GC/MS-MS, GC/MS, HPLC/MS), non-drug analyte(s) not elsewhere specified, qualitative or quantitative, each specimen *(Not Covered for Medicaid)*
- 82657 Enzyme activity in blood cells, cultured cells, or tissue, not elsewhere specified; nonradioactive substrate, each specimen *Not covered for Medicaid*
- 82784 Gammaglobulin (immunoglobulin); IgA, IgD, IgG, IgM, each
- 83516 Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method
- 83519 Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, by radioimmunoassay (e.g., RIA)
- 83520 Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
- 83993 Calprotectin, fecal
- 84620 Xylose absorption test, blood and/or urine
- 84999 Unlisted chemistry procedure
- 81599 Unlisted multianalyte assay with algorithmic analysis
(Explanatory notes must accompany claims billed with unlisted codes.) Not covered when billed for Anser® tests
- 86021 Antibody identification; leukocyte antibodies
- 86140 C-reactive protein
- 86255 Fluorescent noninfectious agent antibody; screen, each antibody
- 86256 Fluorescent noninfectious agent antibody; titer, each antibody
- 88344 Immunohistochemistry or immunocytochemistry, per specimen; each multiplex antibody stain procedure
- 88346 Immunofluorescence, per specimen; initial single antibody stain procedure
- 88350 Immunofluorescence, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)

Not Covered for any indication:

0034U TPMT (thiopurine S-methyltransferase), NUDT15 (nudix hydroxylase 15) (e.g., thiopurine metabolism), gene analysis, common variants (i.e., TPMT *2, *3A, *3B, *3C, *4, *5, *6, *8, *12; NUDT15 *3, *4, *5)

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