

MARKERS FOR DIGESTIVE DISORDERS

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Status: Current

Summary of Changes

- Deletion: Removed anti-gliadin antibodies (AGA) and anti-reticulin antibodies (ARA) from list of medically necessary serological tests for Celiac disease
- Addition/Clarification: Deamidated gliadin antibodies (DGP) is no longer considered experimental and investigational for Celiac disease. DGP testing is medically necessary if IgA deficiency is present.

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 are medically necessary to assess therapy response (i.e., dose escalation) when the biologic agent drug level is below the therapeutic range and limited to 1 test per 6 months. Routine or serial testing is not medically necessary due to insufficient evidence demonstrating improvement in clinical outcomes or management.
3. Thiopurine methyltransferase (TMPT) phenotype (analysis of enzyme activity) and genotype (identification of specific variants) testing for thiopurine drug response may be medically necessary 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 medically necessary for the management of inflammatory bowel diseases (e.g., Crohn's disease, ulcerative colitis). It is not medically necessary for other indications because its clinical utility has not been established.

6. The following tests are experimental and investigational because their clinical utility 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 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 medically necessary for persons with symptoms suggestive of celiac disease and a serum IgA deficiency.
3. Deamidated gliadin antibodies (DGP) testing is medically necessary if IgA deficiency is present.
4. Serological tests individually or as part of a panel (IgA-AGA, IgG-AGA, IgA-TTG, and IgA-EMAt) for celiac disease (i.e. PROMETHEUS® Celiac PLUS, PROMETHEUS® Celiac Serology) are experimental and investigational as an alternative to biopsy for assessing mucosal damage in individuals with celiac disease, and for all other indications.
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 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

Prior authorization for certain drug, services, and procedures may or may not be required. In cases where prior authorization is required, providers will submit a request demonstrating that a drug, service, or procedure is medically necessary. For more information, please refer to the [Priority Health Provider Manual](#).

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) and/or the Evidence of Coverage (EOC); 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

Inflammatory bowel disease (IBD) includes two major disorders: ulcerative colitis (UC) and Crohn disease (CD). UC affects the colon and is characterized by inflammation of the mucosal layer. CD is characterized by transmural inflammation and may involve any portion of luminal gastrointestinal tract, from the oral cavity to the perianal area.

Crohn's disease has an unknown etiology that may be influenced by genetic, immunologic, and environmental factors. The American College of

Gastroenterology (AGA) Practice Guidelines for Management of Crohn's disease in adults (Lichtenstein et al., 2018) states that the diagnosis of Crohn's disease (CD) is based on a combination of clinical presentation and endoscopic, radiologic, histologic, and pathologic findings that demonstrate some degree of focal, asymmetric, and transmural granulomatous inflammation of the luminal GI tract. Laboratory testing is complementary in assessing disease severity and complications of disease. There is no single laboratory test that can make an unequivocal diagnosis of CD. The sequence of testing is dependent on presenting clinical features. Routine use of serologic markers of IBD to establish the diagnosis of Crohn's disease is not indicated.

Ulcerative colitis is a chronic immune-mediated inflammatory disease in which abnormal reactions of the immune system cause inflammation and ulcers on the inner lining of the large intestine (NIDDK, 2020). The American College of Gastroenterology Ulcerative Colitis Practice Guidelines in Adults (2019) states that serologic markers such as perinuclear antineutrophil cytoplasmic antibodies (pANCA) may be found in up to 70% of patients with UC, and combination of negative anti-Saccharomyces cerevisiae antibodies with elevated pANCA levels has been proposed to facilitate establishing a diagnosis of UC. However, the pooled sensitivity of antibody testing for diagnosis of UC is low, and such markers are not used for establishing or ruling out a diagnosis of UC. Although pANCA positivity has also been associated with treatment refractory UC, the evidence supporting this is limited, and there is currently no role for such testing to determine the likelihood of disease evolution and prognosis. (

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 (TDM) 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. Defined as the assessment of drug concentrations and anti-drug antibodies, TDM, is an important tool for optimizing biologic therapy. Anti-drug antibody testing in patients who are undergoing treatment for IBD has been proposed to help determine whether ongoing treatment is safe and effective and whether changes are needed. Many patients who initially benefit from treatment experience a gradual decline or loss of treatment efficacy, which is often attributable to

formation of anti-drug antibody that inactivate or accelerate the clearance of the drugs from the bloodstream. Anti-drug antibody levels are usually measured with an enzyme-linked immunosorbent assay (ELISA), but in patients who are undergoing treatment with ADA, IFX, UST, VDZ, detecting ATI with a conventional ELISA is often not possible because of interference by the drugs in the blood sample. This interference can be overcome, but it requires specialized sample processing or a more complex assay technique. Prometheus Anser tests (Anser ADA, IFX, UST, and VDZ) are novel laboratory-developed tests that measure both serum drug and anti-drug antibodies. An Expert Consensus Development Meeting consisting of members of the BRIDGe group and TDM specialists reached consensus statements on the application of TDM in clinical practice (Papamichael, 2019) including when it would be appropriate to order drug/antibody concentration testing.

Celiac disease is an autoimmune disease of the small intestine caused by sensitivity to dietary gluten and related proteins that occurs in genetically predisposed people. Celiac disease has a wide spectrum of clinical manifestations that resemble a multisystemic disorder rather than an isolated intestinal disease and is characterized by small bowel injury and the presence of specific antibodies (Rubio-Tapia, 2023). In patients with celiac disease, immune responses to gliadin fractions promote an inflammatory reaction, characterized by infiltration of the lamina propria and the epithelium with chronic inflammatory cells and villous atrophy. Serologic evaluation of tissue transglutaminase (tTG)-immunoglobulin A (IgA) antibody is the preferred test for detection of celiac disease in adults. Serologic testing of serum tissue transglutaminase (tTG)-immunoglobulin A (IgA) and endomysial (EMA)-IgA antibody tests have high sensitivities. Intestinal biopsy is required in most patients to confirm the diagnosis.

According to the American College of Gastroenterology Guidelines Update: Diagnosis and Management of Celiac Disease (2023), genetic testing for CD-compatible human leukocyte antigen (HLA) haplotype is not required for diagnosis in all cases but may be helpful in selected situations such as in the context of serology-histology discrepancy. In a change from their previous guidelines, ACG no longer recommends the use of AGA antibodies to test for celiac disease (Rubio-Tapia, 2023). Assays for deamidated gliadin peptide (DGP) antibodies have been shown to have reasonably high accuracy. The use of anti-reticulín antibodies (ARA) in the diagnosis of celiac disease has fallen out of favor. While IgA antibodies to reticulín connective tissue did see some use, primarily in pediatric celiac disease evaluation, and appeared to have test performance equal to or better than AGA, ARA was largely supplanted first by AGA for technical reasons and later on by EMA and tTG which had markedly better test performance (Adriaanse et al, 2015). In a review of literature and recommendations for serologic evaluation for celiac disease by Nandiwata and colleagues (2013), it was concluded that ARA assays lack optimal sensitivities and specificities for routine diagnostic use.

The USPSTF (2017) found inadequate evidence regarding the accuracy of screening tests for celiac disease in asymptomatic populations. The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for celiac disease in asymptomatic persons. Evidence is lacking, and the balance of benefits and harms cannot be determined.

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
K52.2X	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
K59.8X	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:

81375	HLA Class II typing, low resolution (eg, antigen equivalents); HLA-DRB1/3/4/5 and -DQB1
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
81383	HLA Class II typing, high resolution (ie, alleles or allele groups); 1 allele or allele group (eg, HLA-DQB1*06:02P), 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

- 81479 Unlisted molecular pathology procedure (*Explanatory note must accompany claim*)
- 81596 Infectious disease, chronic hepatitis C virus (HCV) infection, six biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, and haptoglobin) utilizing serum, prognostic algorithm reported as scores for fibrosis and necroinflammatory activity in liver
- 82397 Chemiluminescent assay
- 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*)
- 82552 Creatine kinase (CK), (CPK); isoenzymes
- 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
- 84433 Thiopurine S-methyltransferase (TPMT)
- 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.*)
- 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)
- 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)
- 0286U CEP72 (centrosomal protein, 72-KDa), NUDT15 (nudix hydrolase 15) and TPMT (thiopurine S-methyltransferase) (eg, drug metabolism) gene analysis, common variants
- 0430U Gastroenterology, malabsorption evaluation of alpha-1-antitrypsin, calprotectin, pancreatic elastase and reducing substances, feces, quantitative (*Not Covered*)
- 0514U Gastroenterology (irritable bowel disease [IBD]), immunoassay for quantitative determination of adalimumab (ADL) levels in venous serum in patients

- undergoing adalimumab therapy, results reported as a numerical value as micrograms per milliliter ($\mu\text{g/mL}$)
- 0515U Gastroenterology (irritable bowel disease [IBD]), immunoassay for quantitative determination of infliximab (IFX) levels in venous serum in patients undergoing infliximab therapy, results reported as a numerical value as micrograms per milliliter ($\mu\text{g/mL}$)

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