Serological and Fecal Testing for Inflammatory Bowel Disease

INDEPENDENT CARE HEALTH PLAN

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Medicare Advantage Medical Coverage Policy

Table of Contents

Related Medicare Advantage Medical/Pharmacy Coverage Policies

None

Related Documents

Please refer to CMS website for the most current applicable National Coverage Determination (NCD)/ Local Coverage Determination (LCD)/Local Coverage Article (LCA)/CMS Online Manual System/Transmittals.

Type	Title	ID Number	Jurisdiction Medicare Administrative Contractors (MACs)	Applicable States/Territories
LCD	MolDX: Molecular Diagnostic Tests (MDT)	L36807		IA, KS, MO, NE

LCD	MolDX: Prometheus IBD sgi Diagnostic® Policy	L37539	J5 - Wisconsin Physicians Service Insurance Corporation	
LCD LCD	MolDX: Molecular Diagnostic Tests (MDT) MolDX: Prometheus IBD sgi Diagnostic® Policy	L36021 L37352	J15 - CGS Administrators, LLC	KY, OH
LCD LCD	MolDX: Molecular Diagnostic Tests (MDT) MolDX: Prometheus IBD sgi Diagnostic® Policy	L35160 L37299	JE - Noridian Healthcare Solutions, LLC	CA, HI, NV, American Samoa, Guam, Northern Mariana Islands
LCD LCD	MolDX: Molecular Diagnostic Tests (MDT) MolDX: Prometheus IBD sgi Diagnostic® Policy	L36256 L37313	JF - Noridian Healthcare Solutions, LLC	AK, AZ, ID, MT, ND, OR, SD, UT, WA, WY
LCD LCD	MolDX: Molecular Diagnostic Tests (MDT) MolDX: Prometheus IBD sgi Diagnostic® Policy	L35025 L37260	JJ - Palmetto GBA	AL, GA, TN

Description

Inflammatory bowel disease (IBD) is comprised of two major disorders: ulcerative colitis (UC) and Crohn disease (CD). UC affects the colon and is characterized by inflammation of the mucosal layer. CD can involve any component of the gastrointestinal tract from the oral cavity to the anus and is characterized by transmural inflammation.

Serological testing is proposed as an adjunctive test for the diagnosis and management of IBD and involves obtaining a blood sample. Serological testing can analyze the presence of autoantibodies not limited to the following:

- Antibodies directed against the porin protein C of Escherichia coli (AntiOmp C)
- Antisaccharomyces cerevisiae antibodies (ASCA)
- Perinuclear antineutrophil cytoplasmic antibodies (pANCA)

Antiglycan antibodies are other serological markers that are reportedly being utilized for testing in IBD. Antiglycan antibodies include, but may not be limited to the following:

- Antichitin (AntiC)

- Antichitobioside (ACCA)
- Antilaminaribioside (ALCA)
- Antilaminarin (AntiL)
- Antimannobioside (AMCA)
- Antismooth muscle antibody (ASMA)

Bile acid malabsorption (BAM) has been suggested as a test to determine the cause of chronic diarrhea in an individual with IBD. Excess bile acids entering the colon may cause symptoms such as watery stool, urgency and fecal incontinence. An example of this test includes, but may not be limited to, PROMETHEUS 7C4 Diagnostic test.

Combined serological testing has been proposed to diagnose and assist in treatment planning. Examples of these tests include, but may not be limited to, IBSDetex, IBSchek, Ibs-smart, PredictSURE IBD, PROMETHEUS tests for IBD.

The measurement of antibodies of commonly used drugs to treat IBD eg, adalimumab, infliximab, infliximab biosimilar, ustekinumab or vedolizumab have been proposed to determine whether an individual with IBD/Crohn's have antibodies and/or sufficient drug concentrations. Examples of these tests include, but may not be limited to, the following:

- Anser ADA
- Anser IFX
- Anser UST
- Anser VDZ
- Electrochemiluminescence immunoassay (ECLIA)

Fecal testing analyses stool samples for markers of intestinal inflammation. This type of testing has been utilized to differentiate CD from UC. Another method of fecal testing includes screening for multiple biomarkers in a single test which includes but may not be limited to, GI Effects Comprehensive Profile.

Coverage Determination

iCare follows the CMS requirement that only allows coverage and payment for services that are reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member except as specifically allowed by Medicare.

Genetic tests must demonstrate clinical utility, analytical and clinical validity and fulfill the CMS "reasonable and necessary" criteria. Analytic validity (test accurately identifies the gene variant), clinical validity (test identifies or predicts the clinically defined disorder) and clinical utility (test measurably improves clinical outcomes) of the genetic test is supported by generally accepted standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, specialty society recommendations, and views of physicians practicing in relevant clinical areas. The test must be ordered by a physician who is treating the beneficiary and the results will be used in the management of a beneficiary's specific medical problem.

For jurisdictions with no Medicare guidance for a particular test, iCare will utilize the MolDX program and Technical Assessments for molecular assays as the standard to evaluate clinical utility, analytical and clinical validity in conjunction with adhering to Medicare's reasonable and necessary requirement.

In interpreting or supplementing the criteria above and in order to determine medical necessity consistently, iCare may consider the following criteria:

Fecal calprotectin testing (83993) will be considered medically reasonable and necessary when all the following requirements are met:

- Testing is performed to assist in the detection of IBD; **AND**
- Individual has chronic diarrhea (eg, loose or watery stools that last for greater than 4 weeks) of unknown etiology

The use of the criteria in this Medicare Advantage Medical Coverage Policy provides clinical benefits highly likely to outweigh any clinical harms. Services that do not meet the criteria above are not medically necessary and thus do not provide a clinical benefit. Medically unnecessary services carry risks of adverse outcomes and may interfere with the pursuit of other treatments which have demonstrated efficacy.

Coverage Limitations

US Government Publishing Office. Electronic code of federal regulations: part 411 – 42 CFR § 411.15 - Particular services excluded from coverage

The following tests may not be considered a benefit (statutory exclusion)[45]:

- Tests considered screening in the absence of clinical signs and symptoms of disease that are not specifically identified by the law; **OR**
- Tests that confirm a diagnosis or known information; **OR**
- Tests to determine risk for developing a disease or condition; **OR**
- Tests performed to measure the quality of a process; **OR**
- Tests without diagnosis specific indications; **OR**
- Tests identified as investigational by available literature and/or the literature supplied by the developer and are not a part of a clinical trial

These treatments and services fall within the Medicare program's statutory exclusion that prohibits payment for items and services that have not been demonstrated to be reasonable and necessary for the diagnosis and treatment of illness or injury (§1862(a)(1) of the Act). Other services/items fall within the Medicare program's statutory exclusion at 1862(a)(12), which prohibits payment.

The following **serological and fecal testing for IBD** will not be considered medically reasonable and necessary:

- Genetic tests that have not demonstrated clinical utility, analytical and clinical validity via the MolDX Program; **OR**
- Serological testing for autoantibodies and/or antiglycan antibodies including, but not limited to:
    - ACCA; **OR**
    - ALCA; **OR**
    - AMCA; **OR**
    - ANCA; **OR**
    - AntiA4-Fla2; **OR**
    - AntiCBir1; **OR**
    - AntiFlaX; **OR**
    - AntiL; **OR**
    - AntiOmpC; **OR**
    - ASCA; **OR**
    - ASMA; **OR**
    - DNAse-sensitive pANCA; **OR**
    - pANCA; **OR**
- Fecal lactoferrin testing (83630, 83631); **OR**
- GI Effects Comprehensive Profile; **OR**
- Measurement of antibodies to adalimumab, infliximab, infliximab biosimilar, ustekinumab or vedolizumab when performed individually or as part of a panel (eg, Anser ADA, Anser IFX, Anser UST and Anser VDZ, ECLIA); **OR**
- Measurement of biomarkers CdtB and antivinculin (eg, IBSchek [0176U], IBDetex, Ibs-smart [0164U]) to aid in the diagnosis of diarrhea-predominate IBS; **OR**
- NOD2 (CARD15) gene testing to determine susceptibility, disease severity or response to treatment of CD; **OR**
- PredictSURE IBD (0203U); **OR**
- PROMETHEUS 7C4 Diagnostic Test for BAM; **OR**

- PROMETHEUS Crohn's Prognostic; **OR**
- PROMETHEUS IBD sgi Diagnostic; **OR**
- PROMETHEUS Monitr Crohn's Disease

A review of the current medical literature shows that the evidence is insufficient to determine that these services are standard medical treatments. There remains an absence of randomized, blinded clinical studies examining benefit and long-term clinical outcomes establishing the value of these services in clinical management.

Summary of Evidence

Autoantibodies and Antiglycan antibodies

Findings from a large body of low-quality evidence indicate that serological assays, specifically those incorporating ASCA (or anti-glycan saccharomyces cerevisiae antibodies [gASCA]) and pANCA, have high specificity (typically ≥ 85%) for diagnosis of CD, suggesting that a positive finding from such an assay may be useful for confirming a diagnosis of the disease. In contrast, the sensitivity of assays with these serological antibodies is too low (typically ≤ 65%) to be effective for identifying the disease in question, indicating that the test is likely not useful for screening. The addition of other serological antibodies, including anti-OmpC and anti-glycan antibodies (ACCA, ALCA, AMCA, anti-C, antiL) to assays with ASCA, gASCA, or pANCA modestly improves specificity (typically > 90%), but it is unclear which antibodies contribute to the enhanced specificity and what constitutes the optimal combination of antibodies. There is also low-quality evidence that serological antibodies (individually or in combination) can predict disease phenotype or progression. Furthermore, there is limited evidence regarding the use of serological antibodies for predicting response to treatment. Although there is currently no evidence from prospective studies that serological testing improves patient management or health outcomes for patients with CD, if cross-sectional studies confirm the high specificity for CD, such improvements are likely.[35]
The American College of Gastroenterology recommends against serologic antibody testing to establish/rule out a diagnosis or prognosis of UC (strong recommendation, very low quality of evidence).[3] Findings from a large body of low-quality evidence indicate that serological assays, specifically those incorporating pANCA and ASCA, have high specificity (typically ≥ 85%) for diagnosis of UC, suggesting that a positive finding from such an assay may be useful for confirming a diagnosis of the disease. In contrast, the sensitivity of assays with these serological antibodies is too low (typically ≤ 50%) to be effective for identifying the disease in question, indicating that the test is likely not useful for screening. There is also limited, low-quality evidence that the presence of pANCA can predict disease phenotype or progression of UC. Furthermore, there is limited evidence regarding the use of serological antibodies for predicting response to treatment. Although there is currently no evidence from prospective studies that serological testing improves patient management or health outcomes for patients with UC, such improvements are likely if cross-sectional

studies confirm the high specificity for UC. Due to the lack of prospective studies in asymptomatic individuals at risk, there is no evidence at this time regarding the usefulness of these markers in population screening for UC.[36]

Fecal lactoferrin testing

Studies have demonstrated comparable sensitivity and specificity between fecal lactoferrin and fecal calprotectin. However, this biomarker is less commonly used clinically, perhaps because of fewer publications on its utility [51]

A meta-analysis of 7 eligible small studies in adults and pediatric patients who underwent fecal lactoferrin testing showed a pooled accuracy of 88% (standard error = 0.01), sensitivity of 78%, and specificity of 94% for differentiating IBD (active and inactive) from irritable bowel syndrome (IBS). Fecal rapid tests are available for both fecal lactoferrin and fecal calprotectin. Rapid testing may be even more accurate than enzyme-linked immunosorbent assay for both fecal tests, although they are not widely available. Importantly, significant heterogeneity is seen between cutoff values for both fecal lactoferrin and fecal calprotectin with higher levels of fecal lactoferrin being more predictive of IBS and thus less helpful in distinguishing between the 2 diseases as compared to fecal calprotectin.[2]

Levels of antibodies or drug concentration in drugs to treat IBD

Therapeutic drug monitoring involves measuring serum drug trough concentrations and anti-drug antibodies to optimize the use of anti-TNF agents for patients with IBD. Some patients who initially achieve remission will develop secondary loss of response during the first year of therapy. Reactive drug monitoring in this setting can help the clinician decide whether dose escalation is needed or if switching to a different drug is preferred.[57]

Available studies provide only low quality to no data on clinical validity of Anser assays which are intended to help clinicians optimize treatment of IBD by monitoring serum drug levels and antibody levels in patients receiving immunotherapy. There is no data to assess the test's clinical utility.[29-32]

In a conditional recommendation based on a very low quality of evidence the American College of Gastroenterology stance is in patients with moderately to severely active UC who are responders to anti-TNF therapy and now losing response, we suggest measuring serum drug levels and antibodies (if there is not a therapeutic level) to assess the reason for loss of response.[3]

NOD2 (CARD15) gene testing

No peer-reviewed studies demonstrated clinical utility for genetic testing for IBD in symptomatic individuals with known/suspected IBD or in asymptomatic individuals with a family history of IBD. Studies are needed that demonstrate improved health outcomes for individuals with known or suspected IBD when genetic testing is performed.[33]

PROMETHEUS 7C4 Diagnostic Test for BAM

Testing for BAM in the United States remains limited and incompletely validated. No study has evaluated the utility of testing and compared it with empiric therapy using a bile acid sequestrant, which is a reasonable course of action if BAM is suspected. In the absence of widely accessible, reliable testing, and

given the lack of controlled trials of bile acid sequestrants in patients with IBS with diarrhea, the use of these therapies should be at the discretion of the clinician.[2]

Coding Information

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
80145	Adalimumab	
80230	Infliximab	
80280	Vedolizumab	
80299	Quantitation of therapeutic drug, not elsewhere specified	
81401	MOLECULAR PATHOLOGY PROCEDURE LEVEL 2	
82239	Bile acids; total	
82240	Bile acids; cholylglycine	
82271	Blood, occult, by peroxidase activity (eg, guaiac), qualitative; other sources	
82272	Blood, occult, by peroxidase activity (eg, guaiac), qualitative, feces, 1-3 simultaneous determinations, performed for other than colorectal neoplasm screening	
82274	Blood, occult, by fecal hemoglobin determination by immunoassay, qualitative, feces, 1-3 simultaneous determinations	
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	
82656	Elastase, pancreatic (EL-1), fecal; qualitative or semi-quantitative	
82710	Fat or lipids, feces; quantitative	
82715	Fat differential, feces, quantitative	
82725	Fatty acids, nonesterified	
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	

83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified	
83630	Lactoferrin, fecal; qualitative	
83631	Lactoferrin, fecal; quantitative	
83986	pH; body fluid, not otherwise specified	
83993	Calprotectin, fecal	
84311	Spectrophotometry, analyte not elsewhere specified	
84999	Unlisted chemistry procedure	
86021	Antibody identification; leukocyte antibodies	
86140	C-reactive protein;	
86141	C-reactive protein; high sensitivity (hsCRP)	
86255	Fluorescent noninfectious agent antibody; screen, each antibody	
86256	Fluorescent noninfectious agent antibody; titer, each antibody	
86625	Antibody; Campylobacter	
86671	Antibody; fungus, not elsewhere specified	
87045	Culture, bacterial; stool, aerobic, with isolation and preliminary examination (eg, KIA, LIA), Salmonella and Shigella species	
87046	Culture, bacterial; stool, aerobic, additional pathogens, isolation and presumptive identification of isolates, each plate	
87075	Culture, bacterial; any source, except blood, anaerobic with isolation and presumptive identification of isolates	
87102	Culture, fungi (mold or yeast) isolation, with presumptive identification of isolates; other source (except blood)	
87177	Ova and parasites, direct smears, concentration and identification	
87209	Smear, primary source with interpretation; complex special stain (eg, trichrome, iron hemotoxylin) for ova and parasites	
87324	Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative; Clostridium difficile toxin(s)	
87328	Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative; cryptosporidium	

87329	Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative; giardia	
87336	Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative; Entamoeba histolytica dispar group	
87338	Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative; Helicobacter pylori, stool	
87427	Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative; Shiga-like toxin	
87449	Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative; not otherwise specified, each organism	
87505	Infectious agent detection by nucleic acid (DNA or RNA); gastrointestinal pathogen (eg, Clostridium difficile, E. coli, Salmonella, Shigella, norovirus, Giardia), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 3-5 targets	
87507	Infectious agent detection by nucleic acid (DNA or RNA); gastrointestinal pathogen (eg, Clostridium difficile, E. coli, Salmonella, Shigella, norovirus, Giardia), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 12-25 targets	
87798	Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; amplified probe technique, each organism	
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)	

89160	Meat fibers, feces	
0164U	Gastroenterology (irritable bowel syndrome [IBS]), immunoassay for anti-CdtB and anti-vinculin antibodies, utilizing plasma, algorithm for elevated or not elevated qualitative results	
0176U	Cytolethal distending toxin B (CdtB) and vinculin IgG antibodies by immunoassay (ie, ELISA)	
0203U	Autoimmune (inflammatory bowel disease), mRNA, gene expression profiling by quantitative RT-PCR, 17 genes (15 target and 2 reference genes), whole blood, reported as a continuous risk score and classification of inflammatory bowel disease aggressiveness	
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		
HCPCS Code(s)	**Description**	**Comments**
No code(s) identified		

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