# Medical Coverage Policy

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# Serological Testing for Inflammatory Bowel Disease

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## Overview

This Coverage Policy addresses serological testing for the diagnosis and management of inflammatory bowel disease (IBD).

## Coverage Policy

**Testing for serological markers for the diagnosis or management of inflammatory bowel disease is considered experimental, investigational or unproven. Tests/test panels include, but are not limited to the following:**

- anti-neutrophilic cytoplasmic antibody (ANCA), perinuclear anti-neutrophilic cytoplasmic antibody (pANCA)
- anti-saccharomyces cerevisiae antibody (ASCA)
- anti-outer membrane porin C (anti-OmpC) antibody
- anti-CBir1 flagellin (anti-CBir1) antibody
- anti-I2
- antilaminaribioside carbohydrate IgG (ALCA)
- antichitobioside carbohydrate IgA (ACCA)

- anti-synthetic mannoside antibodies (AΣMA or AMCA).
- Pseudomonas-associated sequence I-2 (Anti-I2)
- Prometheus® IBD sgi Diagnostic®
- Prometheus® Crohn's Prognostic

**Testing for the measurement of serum drug levels and/or antibodies to monoclonal antibody (MAB) drugs, including anti-tumor necrosis factor (TNF) drugs (e.g., infliximab, adalimumab, golimumab, ustekinumab, vedolizumab) performed individually or as part of a test panel (e.g., Prometheus® Anser®, LabCorp DoseASSURE™) for the management of inflammatory bowel disease is considered experimental, investigational or unproven.**

## General Background

**Diagnosis of IBD and Prediction of Disease-Related Complications**

Perinuclear anti-neutrophilic cytoplasmic antibody (pANCA) and anti-saccharomyces cerevisiae antibody (ASCA) are serological markers that have been proposed as tools to assist in diagnosing inflammatory bowel disease, differentiating ulcerative colitis (UC) from Crohn's disease (CD) in patients with indeterminate colitis, and determining therapy and monitoring response to treatment. Anti-neutrophilic cytoplasmic antibody (ANCA) has been used in the diagnosis and classification of various vasculitis-associated and autoimmune disorders, and has been associated with renal manifestations of small vessel vasculitis with rapidly progressing glomerulonephritis. pANCA is an antibody directed against the cytoplasmic components of neutrophils with a perinuclear staining pattern. Serum pANCA has been reported to be present in 20–85% of patients with ulcerative colitis, and in 2–28% of patients with Crohn's disease. Elevated levels of serum pANCA in ulcerative colitis patients are believed to be caused by pANCA production in the colonic mucosa (Feldman: Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 2016; Iskandar, 2012).

Anti-saccharomyces cerevisiae antibody (ASCA) is an antibody that reacts to a component of yeast commonly found in food. ASCA has been detected in the serum of a majority of Crohn's disease patients, but fewer ulcerative colitis patients. The origin of ASCA is not clear, nor is it known why this antibody occurs in only a subset of patients with Crohn's disease. ASCA has been detected in approximately 39–76% of Crohn's disease patients, and up to 15% in ulcerative colitis patients (Feldman: Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 2016; Iskandar, 2012).

Several additional antibodies have been described as serological markers for IBD, including anti-outer membrane porin C (anti-OmpC) and anti-CBir1 flagellin (anti-CBir1). These antibodies are directed against luminal bacterial components seen in IBD. Anti-OmpC, directed against the outer membrane porin C of Escherichia coli, is reportedly seen more often in patients with a mixed family history of Crohn's disease (CD) and ulcerative colitis (UC) as opposed to those with a family history of only UC. The antigens CBir1, A4-Fla2, and Fla-X are flagellin subunit proteins linked to Clostridium cluster XIVa. Anti-CBir1 is an antibody to flagellin from Clostridium species and is reported to be found in approximately 6% of UC patients and 50% of patients with CD, and may be associated with more complicated disease. Pseudomonas-associated sequence I-2 (Anti-I2 is a bacterial DNA fragment, and has been identified in lamina propria mononuclear cells of active CD patients. Anticarbohydrate antibodies have also been used in inflammatory bowel disease management, including antilaminaribioside carbohydrate IgG (ALCA), antichitobioside carbohydrate IgA (ACCA), and anti-synthetic mannoside antibodies (AΣMA or AMCA). ALCA, ACCA, and AMCA are similar to ASCA in that they are antibodies to sugars on the surface of microorganisms. ALCA and ACCA are reported to be associated with CD, and are found in 17–28% of CD patients. AΣMA is an antibody against synthetic oligomannose epitopes, and is found to be positive in 24% of patients with CD who were negative for ASCA, and had a lower sensitivity but higher specificity compared to ASCA (Feldman: Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 2016; Iskandar, 2012; Bossuyt, 2006).

Combined serological testing has been proposed as a screening method for patients who present with signs and symptoms of inflammatory bowel disease, and as a method to differentiate CD from UC. The Prometheus® IBD Serology 7 was commercially available through Prometheus (San Diego, CA) as a diagnostic panel consisting of ASCA IgA, ASCA IgG, anti-CBir1, ANCA, anti-OmpC, pANCA, and DNAse-senstitive pANCA. The updated test

panel, Prometheus® IBD sgi Diagnostic, combines serologic, genetic and inflammation markers in a proprietary Smart Diagnostic Algorithm, and is intended to assist in differentiating IBD vs. non-IBD and CD vs. UC in one comprehensive test (Prometheus website). The clinical utility of this testing has not been established. Patients with negative results would still need to undergo the standard diagnostic testing for inflammatory bowel disease. Patients with a positive result would still need to undergo additional testing to distinguish Crohn's disease from ulcerative colitis and to determine the extent of disease.

Combined serological testing has also been proposed as a method of determining the risk for disease-related complications in patients with CD. Prometheus Crohn's Prognostic, combines proprietary serogenetic markers and serologic markers, including Anti-I2 and many of the assays included in the Prometheus® IBD sgi Diagnostic panel. The test employs a logistic regression model to provide probabilities for developing disease complications in patients diagnosed with Crohn's disease.

There is insufficient evidence in the published medical literature to determine the role of serological testing, (whether performed as individual assays or in test panels) in the diagnosis and management of inflammatory bowel disease. There is insufficient evidence to demonstrate that the use of these tests results in improved health outcomes.

**Literature Review: Diagnosis of IBD and Prediction of Disease-Related Complications**
A prospective study (n=169 patients/523 samples) by Hamilton et al. (2017) evaluated the role of serological antibodies in predicting recurrence after Crohn's disease resection. Subjects were prospectively tested for serologic antibody presence (e.g., pANCA, ASCA, IgA/IgG, anti-OmpC, anti-CBir1, anti-A4-Fla2, anti-Fla-X) and titer perioperatively, and at six, 12 and 18 months postoperatively. Colonoscopy was performed at 18 months postoperatively. Quartile sum score (range 6-24), logistic regression analysis, and correlation with phenotype, smoking status, and endoscopic outcome were assessed. Patients with ≥ 2 previous resections were found to be more likely to be anti-OmpC positive (p=0.001). Recurrence at 18 months was associated with anti-Fla-X positivity at baseline (p=0.033) and 12 months (p=0.04). Patients who were positive (n=28) for all four antibacterial antibodies (anti-CBir1, anti-OmpC, anti-A4-Fla2, and anti-Fla-X) at baseline were more likely to experience recurrence at 18 months than those who were negative (n=32) for all four antibodies (p=0.034). The baseline quartile sum score for all six antimicrobial antibodies was higher in patients with severe recurrence at 18 months, adjusted for clinical risk factors (p=0.039). It was concluded that pre-operative serologic screening may help to identify patients at increased risk for Crohn's disease recurrence.

A Hayes Medical Technology Directory report evaluated the evidence (22 studies/9130 patients) on serological assays for the diagnosis and treatment of IBD/CD. The review included systematic reviews (n=4) and primarily case-controlled studies. Of these studies, 19 evaluated the accuracy of serological assays for diagnosis of CD in various patient populations and three evaluated the accuracy of serological assays for predicting treatment response in patients with CD. The outcomes included measures of diagnostic performance (i.e., sensitivity, specificity, PPV, and NPV) for two individual serological markers, ASCA and anti-glycan-associated saccharomyces cerevisiae antibodies (gASCA). It also included a combination of ASCA or gASCA in combination with other antibodies. According to the report, the studies provided insufficient evidence to establish definitive patient selection criteria. Based on the body of low quality evidence, it was concluded that serological assays, particularly ASCA/gASCA and pANCA, have a specificity of generally ≥ 85% for diagnosis of CD, suggesting that a positive finding from such an assay may be useful for confirming this diagnosis. The sensitivity of assays with these serological antibodies was found to be too low (i.e., ≤ 65%) to be effective for identifying CD, indicating that the test is likely not useful for screening. The addition of other serological antibodies improved specificity to approximately 90%, but it was not clear which antibodies were responsible for the increased specificity and what constituted the most favorable combination of antibodies (Hayes, 2013; reviewed 2017).

Kaul et al. (2012) performed a systematic review (n=14 studies) and meta-analysis (n=9/14 studies) of the evidence evaluating the diagnostic ability of the anti-glycan antibodies (ASCA/gASCA, AMCA, ALCA, ACCA, Anti-L, Anti-C) to differentiate IBD from non-IBD and CD from UC, as well as their association with disease complications and/or need for surgery in IBD. Studies were primarily retrospective and were included if they compared the performance of at least two of the six anti-glycan antibody markers in at least one of the following outcomes: differentiating IBD from non-IBD; CD from UC; IBD-related complication; or need for IBD-related surgery. The mean age of the IBD patients ranged from 29 to 47 years, with mean duration of disease ranging

from five to 12 years. For individual antibodies, ASCA was reported to have the highest diagnostic performance in differentiating conditions:

- IBD versus healthy: Diagnostic odds ratio (DOR), 21.1; 95% CI, 1.8-247.3; sensitivity 44.0%; specificity 96.4%
- CD versus UC: DOR, 10.2; 95% CI, 7.7-13.7; sensitivity 56.6%; specificity 88.1%
- CD versus other gastrointestinal disorders: DOR, 10.3; 95% CI, 5.0-21.0; sensitivity 52.8%; specificity 90.0%
- CD versus healthy: DOR, 2.7; 95% CI, 0.3-21.6; sensitivity 53.0%; specificity 70.4%

ASCA had the highest sensitivity compared to the other anti-glycan markers for diagnosis of both CD (52.8-56.6% versus 15.0-27.8%) and CD related surgery (60.2% versus 43.9-47.3%) or complications (70.8% versus 42.3-54.5%). For specificity all individual markers performed similarly (88-95%). The authors noted that although individual studies suggested that the combination of at least two markers had a better diagnostic value, this meta-analysis indicated that the combination of markers performs only slightly better than any individual marker. Limitations of this review include the retrospective design of studies included and the lack of data demonstrating improved clinical outcomes. Although results indicated that the measurement of serological antibodies may have some value in differentiating IBD conditions, additional well designed controlled studies are needed to demonstrate clinical utility and impact on health outcomes.

Dubinsky et al. (2006) conducted a prospective case series to examine the association of immune responses to microbial antigens with disease behavior and to determine the influence of immune reactivity on disease progression in pediatric CD patients. Serological testing for expression of ASCA, anti-outer membrane protein C (anti-OmpC), anti-12, and anti-CBir1 flagellin was performed in a blinded fashion by ELISA. Associations between immune responses and clinical phenotypes were evaluated. A total of 58 patients developed internal penetrating and/or stricturing (IP/S) disease after a median follow-up of 18 months. Anti-OmpC ($p<0.0006$) and anti-12 ($p<0.003$) were associated with IP/S disease. The frequency of IP/S disease increased with increasing numbers of immune responses (p trend=0.002). The chance of developing IP/S disease was highest in patients who were positive for all four immune responses. The presence and/or magnitude of ASCA and CBir1 did not significantly influence disease behavior, however. The authors concluded that immune responses to an increasing number of microbial antigens are associated with complicating IP/S disease in pediatric CD patients, and serum immune responses predict a more rapid progression from uncomplicated to complicated disease. The authors stated that further studies in large independent cohorts will be important to validate the clinical applicability of these findings.

Reese at al. (2006) conducted a meta-analysis to assess the diagnostic precision of ASCA and pANCA in inflammatory bowel disease. Sensitivity, specificity and likelihood ratios (LR) were calculated for different test combinations for Crohn's disease, ulcerative colitis and for inflammatory bowel disease compared with controls. A total of 66 studies/4019 patients were included. The ASCA+ with pANCA– test offered the best sensitivity for Crohn's disease (54.6%) with 92.8% specificity and an area under the ROC (receiver operating characteristic) curve, area under the receiver operating characteristic curve (AUC) of 0.85 (LR + = 6.5; LR – = 0.5). Sensitivity and specificity of pANCA + tests for UC were 55.3% and 88.5%, respectively (AUC of 0.82; LR + = 4.5, LR – = 0.5). Sensitivity and specificity were improved to 70.3% and 93.4%, respectively, in a pediatric subgroup when combined with an ASCA test. The authors concluded that ASCA and pANCA testing are specific but not sensitive for CD and UC. The authors stated ASCA and pANCA testing may be useful for differentiating UC from CD in the pediatric population, but this needs to be the subject of further research.

A prospective multicenter study conducted by Joosens et al. (2002) evaluated the value of ASCA and pANCA to increase diagnostic accuracy in categorizing indeterminate colitis. A total of 97 patients with indeterminate colitis from three centers were analyzed for pANCA and ASCA and followed up prospectively. A definitive diagnosis was reached using conventional techniques for 31 of 97 patients. The authors reported that a positive ASCA and negative pANCA predicted Crohn's disease in 80% of patients with indeterminate colitis, and a negative ASCA and positive pANCA predicted ulcerative colitis in 63.3% of patients with indeterminate colitis. A total of 48.5% of patients did not show antibodies against ASCA or pANCA, and most remained diagnosed with indeterminate colitis. Because only 31 patients had a confirmed diagnosis and only 21 of these patients were included in an

evaluation of specificity and sensitivity, it is difficult to draw conclusions regarding the accuracy of serological testing in this study.

Dubinsky (2001) conducted a prospective study of pediatric patients to determine if accuracy of diagnosing IBD vs. functional childhood disorders was improved by the use of modified assays for pANCA and ASCA, with enzyme-linked immunosorbent assay test (ELISA) cut-off values maximized to increase sensitivity. ASCA, ANCA and pANCA profiles were obtained from 128 children undergoing diagnostic evaluation for IBD. Investigators were blinded to clinical diagnoses. Sensitivity of the modified assays for diagnosing IBD was 81% compared to 69% for the traditional tests, but specificity in terms of diagnosing IBD was lower, at 72% vs. 95%. The authors concluded that the incorporation of sequential noninvasive testing into a diagnostic strategy may avoid unnecessary and costly evaluations and facilitate clinical decision-making when the diagnosis of IBD in children is uncertain. The study was limited by small numbers in each group and a lack of distinction between UC and CD.

**Measurement of Serum Drug Levels and/or Antibodies (e.g., Infliximab)**

Biologics are monoclonal antibodies used to treat patients with moderate to severe IBD, as a monotherapy, or in combination with immunomodulators. Biologic therapies for IBD include tumor necrosis factor (TNF) antagonist therapy (e.g., infliximab, adalimumab, golimumab), anti-integrin antibodies (e.g., vedolizumab, natalizumab) and anti-IL-12/23 (e.g., ustekinumab) (Al Hashash and Regueiro, 2020; Ince and Elliott, 2019). TNF antagonists or blockers bind to the TNF-alpha, and block its interaction with the cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses.

Infliximab is an intravenously administered chimeric (i.e., combination of non-human and human genetic material) monoclonal antibody to tumor necrosis factor-alpha, and may be used in selected patients for the treatment of moderate to severe ulcerative colitis (UC) or Crohn's disease (CD). Some patients do not respond to initial therapy, and a percentage of patients who do respond to initial therapy become unresponsive over time. It has been suggested that this loss of response may be due to the production of antibodies to infliximab. Infusion reactions to infliximab may also occur, and are typically associated with antibodies to infliximab, also referred to as HACA (human antichimeric antibodies).

Antibodies to infliximab (ATI) are less likely to occur in patients treated with glucocorticoids or immune modulators. Delayed hypersensitivity reactions although unusual, may occur two to twelve days after an infusion, and high ATI appear after such reactions, but are not necessarily found before reinfusion. Long delays between infusions are considered to be a significant risk factor for delayed hypersensitivity. Delayed hypersensitivity is less common when a standard induction regime is used and an immune modulator is administered concurrently. Options for treatment of diminished response therefore include decreasing the interval between doses or increasing the dose, and if necessary, changing to a different anti-TNF agent.

Adalimumab is a fully human monoclonal antibody, administered subcutaneously, and may be used in the treatment of moderate to severe CD. Antibodies to the drug may also occur with adalimumab; with formation of antihuman antibodies (HAHAs). There is no consensus on the clinical significance of the presence of antidrug antibodies, but with episodic therapy there is an association between lower infliximab serum levels when ATI formation is highest, and a decreased response rate to adalimumab in patients with HAHAs (Feldman: Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 2016).

Golimumab is a fully human monoclonal TNF antibody for the treatment of moderate to severe ulcerative colitis. It should be considered as one of the treatment options when patients have begun failing therapy with mesalamine products or are at risk for developing steroid dependence. Golimumab is administered subcutaneously (SC) allowing for self-administration and patient independence. To date, little is known about anti-golimumab antibody development and its relation to clinical response in patients with UC. (Cunningham, et al., 2019; Swaroop, 2019).

Ustekinumab (UST) is a human monoclonal antibody that blocks the biologic activity of IL-12 and IL-23 by inhibiting receptors for these cytokines on T cells, natural killer cells and antigen presenting cells. The drug is used in patients with active moderate to severe Crohn's disease who had failed standard therapy (glucocorticoids, immunosuppressive agents, or anti-TNF-agents). Induction therapy with ustekinumab is given

intravenously with weight-based dosing. Maintenance dosing is 90 mg subcutaneously every eight weeks. (Al Hashash and Regueiro, 2020).

Vedolizumab (VDZ) is a humanized anti-alpha-4-beta-7 integrin monoclonal antibody used in patients with active moderate to severe Crohn's disease or ulcerative colitis. VDZ is administered intravenously and specifically targets the $\alpha_4\beta_7$ integrin that is selectively expressed on gut-homing T lymphocytes. The drug is used in patients with IBD who have had an inadequate response with, lost response to, or were intolerant to inhibitors of tumor necrosis factor-alpha (TNF-alpha) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids (Al Hashash and Regueiro, 2020).

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; however, laboratories offering such tests as a clinical service must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA) and must be licensed by CLIA for high-complexity testing (Hayes, 2015; reviewed 2017). The most common laboratory methods used to evaluate drug and anti-drug antibodies (ADAb) include enzyme-linked immunosorbent assay (ELISA), homogenous mobility shift assay (HMSA), and electrochemiluminescence immunoassay (ECLIA). Anti-drug antibody (ADAb) assays that are carried out in a fluid phase environment (HMSA, ECLIA, and radioimmunoassay [RIA]) are more sensitive to detect low affinity antibodies than solid-phase ADAb assays (ELISA). For measuring ADAbs, no international analytical standard is currently available and different assays report different ADAb titers. (Vande Casteele, et al., 2017; Marini, et al., 2017).

Prometheus® Laboratories offers non-radiolabeled, fluid phase HMSA tests for identifying serum antibodies. Prometheus® Anser IFX is a quantitative infliximab monitoring assay designed to measure infliximab (IFX) and antibodies to infliximab (ATI) levels. A similar test, Prometheus® Anser ADA, measures serum adalimumab (ADA) and antibodies to adalimumab (AMA) levels. The Prometheus® Anser UST measures serum concentration of ustekinumab (UST) and antibodies to ustekinumab. The Prometheus® Anser VDZ measures serum concentration of vedolizumab (VDZ) and antibodies to vedolizumab. LabCorp offers electrochemiluminescence immunoassay (ECLIA) testing for identifying serum and anti-drug antibodies. DoseASSURE™ IFX, ADL, GOL, VDZ, and UST provides drug concentration levels as well as antibody levels for infliximab, adalimumab, golimumab, vedolizumab and ustekinumab, respectively. The tests are intended to provide clarity on factors contributing to a patient's loss of response and to guide treatment decisions.

There is insufficient evidence in the published medical literature to determine the role of serum drug levels and/or antibodies to monoclonal antibody (MAB) drugs, including anti-tumor necrosis factor (TNF) drugs (e.g. infliximab, adalimumab, golimumab, ustekinumab, vedolizumab) in the management of inflammatory bowel disease. There is insufficient evidence to demonstrate that the use of these tests results in improved health outcomes compared to usual clinical management.

**Literature Review: Measurement of Serum Levels and Antidrug Antibodies (e.g., Infliximab)**
**Randomized Controlled Trials:** Adedokun et al. (2020) collected data from two phase III randomized controlled trials of patients with ulcerative colitis that evaluated the association between ustekinumab concentration and efficacy, serum based on clinical effects (Mayo score), histologic features, and inflammation (measurement of C-reactive protein, fecal calprotectin, and fecal lactoferrin), as well as safety (infections, serious infections, and serious adverse events), during induction and maintenance therapy. The 52-week trial (UNIFI trial) comprised an eight-week, randomized, placebo-controlled, induction study, and a 44-week, randomized-withdrawal, maintenance study. At induction week 0, patients (n=961) randomly (1:1:1) received the following: (1) ustekinumab 130 mg (n=320); (2) ustekinumab weight-range–based dose of approximately 6 mg/kg (n=322); or (3) placebo (n=319). Patients who had a response to induction therapy at eight weeks following administration of intravenous ustekinumab were randomly assigned to receive subcutaneous maintenance injections of 90 mg of ustekinumab (either every 12 weeks [n=172] or every eight weeks [n=176]) or placebo (n=175). Serum samples for ustekinumab drug concentration were collected at all visits during induction (weeks 0, two, four, eight, and 16) and during maintenance (every four weeks through week 44) using a drug-tolerant electrochemiluminescence assay (ECLIA). Anti-drug antibodies were collected during induction (weeks 0, four, eight, and 16) and during maintenance (weeks four, 12, 24, 36, and 44). In the analysis of data from two phase III trials of patients with ulcerative colitis, the authors reported that serum concentrations of ustekinumab were proportional to dose and unaffected by prior biologic or concomitant immunomodulator therapies. Serum concentrations of ustekinumab

were associated with clinical and histologic efficacy and markers of inflammation, and were not associated with safety events at the doses evaluated. The authors concluded that associations between serum ustekinumab concentration (SUC) and clinical efficacy do not prove cause and effect. A prospective, interventional, longitudinal study is required to address whether trough SUC optimization by TDM improves efficacy outcomes.

D'Haens et al. 2018 conducted a prospective randomized controlled trial to determine whether therapeutic drug monitoring (TDM) to maintain serum levels of infliximab above 3 mg/mL produced higher rates of clinical and endoscopic remission than adjusting the dose based on symptoms only. Patients (n=122) were randomized into three double-blind infliximab (IFX) maintenance regimens: dose intensification strategy 1 (DIS1) group (n=45) with dose increases (two maximum) in steps of 2.5 mg/kg based on clinical symptoms and biomarker analysis and/or serum infliximab concentrations; dose intensification strategy 2 (DIS2) group (n=37) with dose increase from five to 10 mg/kg based on the same criteria; control group (n=40) with dose increase to 10 mg/kg based on clinical symptoms alone. Adult patients with active luminal Crohn's Disease (CD) naïve to biologics with an indication to start anti-TNF therapy were included. The primary endpoint was sustained corticosteroid-free clinical remission (CD activity index <150) from weeks 22 through 54 with no ulcers at week 54 and no surgery for bowel resection or abscess and no new fistula. The secondary endpoints were the proportion of patients with no ulcers at weeks 12 and 54, clinical remission (CDAI < 150) at each visit, sustained remission from week 14 onward, endoscopic remission (CDEIS < 3) at weeks 12 and 54, endoscopic response (decrease of CDEIS score of at least 50%) at weeks 12 and 54, IFX dose increase during the study period, IFX TL> 3 mg/mL between weeks 14 and 54, adverse events, total use of infliximab, need for resection, and new fistula or abscesses. Thirty-five (29%) of the patients dropped out of the trial before week 54. The primary endpoint was reached by 15 patients (33%) in the DIS1 group, 10 patients (27%) in the DIS2 group, and 16 patients (40%) in the control group which was not statistically significant between the groups(p=0.50). Secondary endpoints for all groups did not reach statistical significance. The treatment was well tolerated and the incidence of adverse events and serious adverse events was similar across the three groups. The author noted limitation stated that the study was not designed or statistically powered to determine the superiority of therapeutic drug monitoring (TDM). The authors concluded that increasing dose of infliximab based on a combination of symptoms, biomarkers and serum drug concentrations does not lead to corticosteroid-free clinical remission in a larger proportion of patients than increasing dose based on symptoms alone.

Vande Casteele et al. (2015) conducted a randomized controlled trial that aimed to determine whether dosing based on therapeutic drug monitoring increases the rate of remission and whether continued concentration based dosing is superior to clinically based dosing of infliximab for maintaining remission in patients with CD and UC. Adults (n=263) were included in the study had a confirmed diagnosis of moderate-to-severe CD (n=178) or UC (n=85). Included patients had a stable clinical response to infliximab therapy for at least 14 weeks. Before randomization, doses were adjusted using an algorithm to reach a target trough concentration (TC) of 3–7 mg/mL in all patients (optimization phase). Patients were then randomized to infliximab dosing based on clinical symptoms and C-reactive protein (CRP) (n=123), or to continue dosing based on infliximab TC (n=128). The primary end point measured clinical and biochemical remission at one year following the optimization phase. At screening, 115 of 263 patients had a TC of infliximab of 3–7 mg/mL (43.7%). Seventy-two patients had TCs > 7 mg/mL requiring a dose reduction. Following the dose reduction, 67 patients (93%) achieved TCs of 3–7 mg/mL. At the 12 month follow-up, 66% percent of patients whose dosing was based on clinical features and 69% whose dosing was based on TC achieved remission, which did not reach clinical significance (p=0.686). Disease relapsed occurred in 21 patients who received clinically based dosing (17%) and in nine patients who received concentration-based dosing (7%), which was clinically significant in favor of the concentration based dosing (p=0.018). The authors concluded that targeting patients' infliximab TCs to 3–7 mg/mL results in a more efficient use of the drug. Additionally, after dose optimization, continued concentration-based dosing was not superior to clinically based dosing for achieving remission after one year, but was associated with fewer flares during the course of treatment. Additional randomized controlled trials with dose optimization during the induction phase and with longer follow-up are warranted.

Steenholdt et al. (2014) conducted a randomized, controlled, single-blind, multicenter study that assessed if the combination of serum drug and serum antibody (Ab) measurements optimized treatment in patients with secondary loss of response to infliximab (IFX) maintenance therapy when compared to dose intensification. Patients (n=69) were randomized into the infliximab (IFX) dose intensification group (n=36) (5 mg/kg every four weeks) or the algorithm group (n=33) with interventions based on serum IFX and IFX antibody levels. Adult

patients were included if they had Crohn's disease, a previous beneficial clinical response to standard IFX maintenance therapy with regular infusions of 5 mg/kg and secondary IFX treatment failure. A primary outcome measured at week 12 was the proportion of patients responding (Crohn's Disease Activity Index (CDAI) decrease ≥ 70, or ≥ 50% reduction in active fistulas) to treatment. Serum samples for IFX and IFX Ab testing were collected at the time of reported IFX treatment failure. The majority (70%) of patients with secondary IFX treatment failure had therapeutic serum IFX levels and undetectable IFX Abs at the time of therapeutic failure. Response rates at the end of the trial in the intention-to-treat population and in the per-protocol population were not clinically significant in the algorithm group and in the IFX intensification group (p=0.810; p=0.781, respectively). An author noted limitation included the cut off values in the study originate from a single retrospective study and there is not a gold standard for measuring assays of IFX and IFX Abs. The study concluded that interventions based on the algorithm achieved similar clinical, biological and life quality outcomes to dose intensification.

**Systematic Reviews:** Freeman et al. (2017) conducted a systematic review and meta-analysis on the accuracy of antitumor necrosis factor (anti-TNF) and antibodies to anti-TNF to predict loss of response or lack of regaining response in patients with anti-TNF managed Crohn's disease (n=31). The included studies consisted of patients with Crohn's disease treated with infliximab or adalimumab. Studies with mixed Crohn's and ulcerative colitis populations were included if the proportion of Crohn's patients was at least 70%. Studies reporting clinical status (i.e., response or lack of response) as an outcome were eligible for inclusion. Studies were heterogeneous with respect to the type of test used, criteria for establishing response/lack of response, population examined and results. Meta-analytic summary point estimated for sensitivity and specificity were 65.7% and 80.6% for infliximab trough levels and 56% and 79% for antibodies to infliximab, respectively. Pooled positive and negative predictive values ranged between 70% and 80% implying that between 20% and 30% of both positive and negative test results may have been incorrect in predicting loss of response. Author-noted limitations were insufficient data for subgroup analyses and many of the studies had a high risk of bias. The review concluded that these tests have modest predictive accuracy for clinical status. Additional studies are required before the clinical utility of the tests can be reliably evaluated.

A Hayes published a Search and Summary on Anser ADA (Prometheus Laboratories Inc.) for monitoring adalimumab treatment of inflammatory bowel disease. The review included six abstracts (a prospective comparative study, a validation study, a technical review and prospective uncontrolled studies). Hayes concluded there is insufficient published evidence to assess the safety and/or impact on health outcomes or patient management for the use of Anser ADA for monitoring adalimumab treatment in patients with IBD (Hayes, 2017).

A Hayes Technology Brief evaluated the evidence (n=13 studies) on the utility of antidrug antibodies for monitoring patients treated receiving infliximab for IBD. The report included RCTs (n=2), prospective and retrospective cohort studies (n=9), and retrospective cross-sectional studies (n=2). Most of the studies were found to be of poor quality. Sample sizes in studies ranged from 69-573 patients with follow-up periods of 12 weeks to 48 months. Outcomes included concentrations, titers, or presence of ATI or infliximab at trough using ELISA, RIA, or HMSA and ATI-free survival. It was determined that the overall low to very-low-quality body of evidence was insufficient to support a conclusion as to whether or not assessment of ATI is warranted to guide infliximab treatment of patients with IBD. Although some evidence was from RCTs, only a single poor-quality RCT was specifically designed to determine whether knowledge of ATI is helpful in guiding patient management. Most of the evidence reviewed originated from observational studies. Many of these studies did not assess patients using objective criteria such as clinical activity index scores or endoscopic evaluation. According to the Hayes Technology Brief, the evidence is equivocal on whether ATI are associated with clinical outcomes in patients with IBD who are treated with infliximab (Hayes 2015; reviewed 2017).

Moore et al. (2016) performed a systematic review and meta-analysis of the evidence (n=22 studies/3483 patients) evaluating the association between serum levels of infliximab at various thresholds and clinical outcomes in IBD. Controlled trials and observational studies were included that reported outcomes [clinical, mucosal, CRP, colectomy] in patients who were treated with IFX for UC or CD, and grouped these outcomes according to mean/median IFX levels, or according to a cut-off threshold level of IFX. Studies that only measured TNF-binding capacity, not serum drug levels or did not report clinical outcomes of IFX therapy or serum IFX levels were excluded. The primary outcome measure was clinical remission defined as absence of clinical

symptoms in patients who had responded to IFX. Secondary outcomes were relative risk of remission, endoscopic remission, or colectomy, according to a threshold serum IFX level. Mean levels of serum CRP above and below a specified level of serum IFX were also compared. Meta-analysis of five studies demonstrated a significant difference in mean serum IFX levels between remission and non-remission patients ($p<0.001$). Comparisons were made from pooled remission rates (n=7 studies) between patients with an IFX level < 2 µg/ml, and those with a level > 2 µg/ml. Analysis of remission rates from raw data in these studies showed that patients with an IFX level greater than 2 µg/ml were more likely to be in remission than those with an IFX level < 2 µg/ml ($p<0.001$). Patients with an IFX level > 2 µg/ml were also more likely to achieve endoscopic remission ($p=0.004$) than patients with levels < 2 µg/ml. The authors noted that cumulatively these data may imply that patients with low trough IFX levels experience worse outcomes than patients with higher levels, and thus interventions to identify and address this are warranted. However a considerable overlap in the range of drug levels in 'remitters/relapsers' was observed, suggesting that serum IFX levels alone do not explain clinical status in most patients. Acknowledged limitations include the heterogeneity of patient populations, assays, and outcome measures and the retrospective, uncontrolled design of studies. Further prospective studies analyzing the clinical effectiveness of adjustments of IFX dosing to trough levels are needed to support the use of routine evaluations of serum IFX levels in practice.

A systematic review and meta-analysis was conducted by O'Meara et al. (2014) to provide a pooled estimate of the risk of infusion reactions according to patients' ATI status and to analyze the relationship of immunomodulators (e.g., methotrexate) to this risk. Eight studies (1351 patients) met the inclusion criteria; seven of the eight studies had a high risk of bias in at least one quality domain. The cumulative data indicated that in patients with ATI compared to those without ATI, there was a higher risk ratio (RR) of any acute infusion reaction (RR 2.4; 95% CI 1.5-3.8, $p<0.001$) and severe infusion reactions (RR 5.8, 95% CI 1.7-19), $p=0.004$). The authors noted that there was statistical heterogeneity among the studies that implies that the summary RR should be interpreted with caution. Patients who were prescribed immunomodulators during maintenance therapy had a reduction in the risk of ATI development (RR 0.6, 95% CI 0.4-0.9, $p=0.02$) and infusion reactions (RR 0.6, 95% CI 0.4-0.8, $p<0.001$).

Nanda et al. (2013) conducted a meta-analysis of studies that reported clinical outcomes and infliximab levels according to the antibodies to infliximab (ATI) status in patients treated for ulcerative colitis (UC) or Crohn's disease (CD) (13 studies, 1378 patients). Included studies consisted of controlled trials, observational studies, and cohort studies. The pooled risk ratio of loss of clinical response to infliximab in patients with IBD who had ATI was 3.2 (95% confidence internal [CI: 2.0-4.9, $p<0.0001$) when compared to patients without ATI. This effect estimate was primarily based on CD patients (n=494). In patients with UC (n=86) with ATI, there was a non-significant risk ratio of loss of response of 2.2 (95% CI: 0.5-9.0, $p=0.3$). The authors noted limitations of the analysis, including heterogeneity among the studies in methods of ATI detection and clinical outcomes reported, a high risk of bias in at least one quality domain in each study, and the fact that a funnel plot suggested publication bias.

Lee et al. (2012) conducted a meta-analysis to determine the prevalence of ATI in patients receiving infliximab, the effect of immunosuppressants on the prevalence of ATI, the effect of ATI on the prevalence of infusion reactions and the effect of ATI on the rates of remission (18 studies/3326 patients). The prevalence of ATI was 45.8% when episodic infusion of infliximab was given and 12.4% when maintenance infliximab was given. Infusion reaction rates were significantly higher in patients with ATI (relative risk: 2.07; 95% CI, 1.61-2.67). Immunosuppressants resulted in a 50% reduction in the risk of developing ATI ($p<0.00001$). The presence or absence of ATI did not affect the rates of clinical remission. The authors stated that further analysis is required to determine whether loss of response is dependent on the titer of ATI.

Cassinotti and Travis (2009) conducted a systematic review to evaluate the incidence of ATI in CD and their impact on the efficacy and safety of infliximab. The authors stated that the observation that Infliximab use is associated over time with loss of response and infusion reactions has led to the presumption that this is due to immunogenicity, and that ATI are the principal cause. The authors stated that the mechanisms for ATI development are poorly understood, and the incidence depends on multiple patient-specific and treatment-related analytical and clinical factors. The review demonstrated that the presence of ATI is weakly and variably associated with clinical response or infusion reactions, but not with reactions relevant to clinical decision making. The authors stated that enormous variation in the methods of reporting ATI and immunogenicity of infliximab

make almost any interpretation possible from different studies, but few have clinical relevance. The authors concluded that there is no clear evidence that ATI have an impact on efficacy or safety, nor is there a need to measure them in clinical practice.

**Non-Comparative Studies:** Gomes et al. (2020) conducted a prospective study to evaluate the quantitative serum level of infliximab (IFX) as well as the detection of anti-infliximab antibodies (ATIs) in patients with Crohn's disease (CD). The study included adults (n=40) aged 18–70 years in the maintenance phase of IFX therapy. All patients had already received induction therapy (0, two, six weeks), followed by maintenance therapy (5 mg/kg). IFX and ATI levels were analyzed and compared between the patients with active CD (CDA) and those with CD in remission (CDR). Peripheral blood samples were collected just before the new maintenance infusion. The IFX and ATI serum levels were detected using a quantitative ELISA from Promonitors. The study reported no difference in the IFX level between active CD (CDA) and those in remission (CDR) groups ($p>0.05$). Eighty percent of all patients had IFX levels above the therapeutic concentration (6–10 mg/mL). Two (9%) of the 22 patients with active disease and four (22.2%) of the 18 patients in remission had undetectable levels of IFX. Four (66.6%) of the six patients with undetectable levels of IFX had positive ATI levels; three of these patients were in remission, and one had active disease. In addition, the other two patients with undetectable levels of IFX presented with ATI levels close to the positivity threshold. An author noted limitation of this study was the lack of longitudinal data for the measurement of the IFX and ATI levels over time and over the course of the disease. The authors concluded that the undetectable levels of IFX correlated with the detection of ATIs, which was independent of disease activity. Immunogenicity was not the main factor for the loss of response to IFX in our study, and the majority of patients in both groups (CDA and CDR) had supratherapeutic levels of IFX.

Grinman et al., (2020) conducted an observational cross sectional study that measured serum levels of anti-TNF-α biological drugs and their respective antibodies to identify correlations with sustained clinical response, nonresponse, and loss of drug response in IBD patients. Patients (n=95) with Crohn's disease (n=85) or ulcerative colitis (n=10) in maintenance therapy with infliximab (n=63) or adalimumab (n=32) were included. Venous blood samples were harvested in serum tubes immediately before infliximab and adalimumab infusion. Drug trough levels and anti-drug levels were determined using Lisa Tracker Duo Infliximab and Lisa Tracker Duo Adalimumab enzyme-linked immunosorbent assay (ELISA)-based techniques. The authors reported that among the patients with CD, 56 (65.9%) were responders (sustained response), 11 (12.9%) were primary nonresponders (primary failure), and 18 (21.2%) were secondary nonresponders (secondary failure). Among the patients with UC, 7 (70%) were responders, and 3 (30.0%) were secondary nonresponders; there were no reports of patients with UC who were primary nonresponders. Patients with higher C-reactive protein (CRP) levels had significantly lower levels of serum infliximab ($p=0.028$). Higher concentrations of anti-IFX antibodies were detected among the patients who were not using immunomodulators concomitantly, who had more side effects related to biologicals and who had high levels of CRP ($p=0.022$, $p=0.001$, $p=0.042$; respectively). Lower body mass index (BMI) was significantly associated with higher levels of anti-ADA antibodies ($p=0.036$), with no significant difference between BMI and anti-IFX antibodies. Patients with adequate serum levels of infliximab present a therapeutic response with decreased levels of inflammatory markers including serum CRP ($p=0.033$). In contrast, patients with low serum levels of infliximab had high CRP, and anti-infliximab antibodies were present. Patients who had higher serum albumin concentrations also had higher serum levels of infliximab and adalimumab. The results obtained in this IBD cohort study do not show a clear correlation between anti-TNF-α trough levels and immunogenicity (loss of response) with disease outcomes. The authors concluded that the results do not show a clear correlation between anti-TNF-α trough levels and immunogenicity with disease outcomes. However, there were significant associations with BMI, the concomitant use of immunomodulators, the rate of side effects, and laboratory markers, including serum albumin, and CRP. Prospective controlled trials will be necessary to further investigate the most appropriate approaches to monitor patients under biologic therapy, particularly individuals who lose the response.

Chaparro et al. (2019) conducted a multicenter, prospective study that evaluated the diagnostic accuracy of anti-TNF trough levels and aimed to define the best cut-off point to predict mucosal healing in inflammatory bowel disease (IBD). The primary outcome measured the correlation between anti-TNF drug levels and mucosal healing. The secondary outcome defined the optimal drug level required to have the highest probability of achieving mucosal healing. The study included IBD patients (n=182) under anti-TNF treatment using adalimumab (n=94) or infliximab (n=88) for at least six months that had to undergo an endoscopy. Clinical and endoscopic activity was assessed within a month following the endoscopy and blood samples were obtained

before the administration of the drug. Anti-TNF concentrations were measured using SMART ELISAs assay at trough. Among the 182 included patients, 93 (51.1%) had mucosal healing. Median IFX and ADA trough levels were significantly higher in patients with mucosal healing than in those without mucosal healing (p=0.03; p=0.04, respectively). Trough levels were significantly higher in patients on escalated dosages of IFX or ADA. There was an association between anti-TNF trough levels and mucosal healing in IBD patients. However, the accuracy of anti-TNF serum concentrations ability to predict mucosal healing is poor (AUC < 0.7), meaning that a high proportion of patients would be misclassified based on anti-TNF serum levels. The study reported that the best cutoff values for predicting mucosal healing was 3.4 and 7.2 µg/mL for infliximab and adalimumab, respectively. Author noted limitations were that the study only included patients with luminal CD and there was a lack of centralized reading of endoscopic images. However, all examinations were performed by endoscopists with wide experience in IBD, who were responsible for those procedures in their centers. The authors concluded that there is a relationship between infliximab and adalimumab trough levels, and mucosal healing in IBD patients. Additionally, several factors were associated with a lower probability of mucosal healing and included smoking, having CD (vs. UC), and the need to be treated with an escalated dosage of anti-TNF. However, due to the low accuracy of the test, the results should be interpreted with caution in clinical practice.

Paul et al. (2013) conducted a prospective case series to evaluate the relationship between infliximab (IFX) trough levels and antibodies to infliximab (ATI) and mucosal healing in 52 patients with IBD (34 with CD and 18 with UC). According to the authors, accumulating evidence indicates that mucosal healing may change the natural course of the disease by decreasing the need for surgery and reducing hospitalization. Consecutive patients receiving IFX (5mg/kg) treatment who were developing secondary failure to IFX were included. IFX trough levels, antibodies to IFX concentrations, C-reactive protein levels, and fecal calprotectin were measured prior to IFX optimization and at week eight. On the day of the first IFX optimization, a proctrosigmoidoscopy was performed and was repeated at week eight in patients with UC. After IFX dose intensification, half of the CD and UC patients achieved mucosal healing. Increase in IFX trough levels (called “delta IFX” in micrograms per milliliter) was associated with mucosal healing in both groups (p=0.001). A delta IFX >0.5 ug/ml was associated with mucosal healing (sensitivity 0.88; specificity 0.77; p=0.0001, area under the receiver operating characteristic curve, 0.89). The only factor associated with mucosal healing after IFX optimization was a delta IFX > 0.5 ug/ml (likelihood ratio=2.02, 95% confidence internal, 1.01–4.08, p=0.48) the authors stated that because of small sample size, these results need to be confirmed in studies including a higher number of patients.

There is currently a paucity of evidence in the published peer-reviewed medical literature evaluating the effectiveness of measuring serum drug levels and/or antibodies to monoclonal antibody (MAB) drugs, including anti-tumor necrosis factor (TNF) drugs (e.g. infliximab, adalimumab, golimumab, ustekinumab, vedolizumab) for the management of inflammatory bowel disease. Studies primarily include small patient populations, short-term follow-ups and conflicting outcomes. Further long-term studies with large patient populations are needed to help identify the exact concentration ranges predictive of clinical and endoscopic remission. Additionally, studies are needed to confirm that dose optimization based on therapeutic drug monitoring improves clinical outcomes (Kennedy, et al., 2019; Hanžel, et al., 2019; Papamichael, et al., 2019; Restellini, et al, 2019; Ricciuto, et al., 2018; Detrez, et al., 2016; Roblin, et al., 2014).

**Professional Societies/Organizations**

**American College of Gastroenterology (ACG):** The 2019 ACG clinical guideline on ulcerative colitis in adults, recommended against serologic antibody testing to establish or rule out a diagnosis of UC. Perinuclear anti-neutrophilic cytoplasmic antibody (pANCA) has been identified in up to 70% of UC patients. It has been proposed that using a combination of negative anti–saccharomyces cerevisiae antibodies (ASCA) with elevated pANCA levels facilitates 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. The guideline also stated that patients with moderately to severely active UC who are responders to anti-TNF therapy and now losing response, suggested measuring serum drug levels and antibodies (if there is not a therapeutic level) to assess the reason for loss of response. This is a conditional recommendation based on very low quality of evidence (Rubin, et al., 2019).

The ACG clinical guideline on the management of Crohn’s disease in adults stated that the routine use of serologic markers of IBD to diagnose Crohn’s disease is not indicated. Anti-glycan antibodies are more prevalent

in Crohn's disease, however they have a low sensitivity which makes their use in diagnosis less helpful (Lichtenstein, et al., 2018).

**North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the Crohn's and Colitis Foundation of America (CCFA):** The NASPGHAN and CCFA jointly developed a consensus conference report on differentiating UC from CD in children and young adults (Bousvaros, et al., 2007). The report stated 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.

Recommendations for testing for the measurement of antibodies to infliximab or adalimumab are not included in any of the above guidelines.

**American Gastroenterological Association (AGA):** The AGA Institute guideline on therapeutic drug monitoring in inflammatory bowel disease suggested that reactive therapeutic drug monitoring can be used to guide treatment changes in adults with active IBD being treated with anti-TNF agents. This is a conditional recommendation based on very low quality of evidence with very little confidence in the effect estimate (Feuerstein et al., 2017).

**Use Outside the U.S.**
The European Crohn's and Colitis Organization (ECCO) and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) published a joint guideline for the diagnostic assessment in IBD. The guideline stated that genetic and serological testing is not recommended for the routine diagnosis of CD or UC. The accuracy of serologic markers (pANCA, ASCAs) is rather limited and therefore ineffective at differentiating colonic CD from UC. According to the guideline, therapeutic drug monitoring may be beneficial in CD and UC patients that do not respond to thiopurines or anti-TNF therapy (Maaser, et al., 2019).

A 2016 National Institute for Health and Clinical Excellence (NICE) guidance evaluated the efficacy of ELISA kits for the therapeutic monitoring of TNF-alpha inhibitors in Crohn's disease. The assessment included patients who lost response to initial treatment as well as those who maintained treatment response, as this subset of patients may continue to receive the same of TNF-alpha inhibitor dosage when decreased dosing might be equally effective. Patients who did not respond to treatment during the induction phase were not considered in the analysis. It was concluded that although the testing shows promise, there is insufficient evidence to recommend routine adoption (NICE, 2016).

The third European evidence-based consensus on the diagnosis and management of ulcerative colitis, part 1, definitions and diagnosis includes the following statement:

- The routine clinical use of genetic or serological molecular markers is not recommended for the classification of ulcerative colitis

The authors noted that the most studied serological markers associated with UC, include the pANCA and ASCA. Positive pANCA serology is found in up to 65% of patients with UC and in less than 10% of patients with CD. Due to the sensitivity of these markers, their routine use is not justified (Magro et al., 2017).

The third European evidence-based consensus on the diagnosis and management of Crohn's disease, stated that genetic or serological testing is currently not recommended for routine diagnosis of CD. In a discussion of initial laboratory investigations, the authors state that currently available serologic testing may be used as an adjunct to diagnosis, but the accuracy of the available tests (ASCA, ANCA) is such that they are unlikely to be useful in routine diagnosis, and are ineffective at differentiating colonic Crohn's disease from ulcerative colitis. Other serologic markers, including anti-OmpC and CBir1 have not yet been shown to help in differentiating CD from UC. The authors also note that despite advances in Crohn's disease genetics, there are currently no genetic tests which are recommended routinely for diagnoses. In regards to the loss of response to an anti-TNF agent, it was recommended to use dose optimization. If dose optimization is not successful, switching to a

different anti-TNF was recommended. Where available, measurement of anti-TNF trough levels and anti-drug antibodies could be used to guide therapy (Gomollón et al., 2017).

## Medicare Coverage Determinations

| | Contractor | Policy Name/Number | Revision Effective Date |
|---|---|---|---|
| NCD | | No National Coverage Determination found | |
| LCD | Cigna Government Services | Prometheus IBD sgi Diagnostic Policy (L37352) | 11/14/2019 |
| LCD | Palmetto GBA | MolDX: Prometheus IBD Sgi Diagnostic Policy (L37260) | 11/07/2019 |
| LCD | Noridian Healthcare Solutions, LLC | MolDX: Prometheus IBD sgi Diagnostic Policy (L37299) | 12/01/2019 |
| LCD | Noridian Healthcare Solutions, LLC | MolDX: Prometheus IBD sgi Diagnostic Policy (L37313) | 12/01/2019 |
| LCD | Wisconsin Physicians Service Insurance Corporation | MolDX: Prometheus IBD sgi Diagnostic Policy (L37539) | 12/01/2019 |

Note: Please review the current Medicare Policy for the most up-to-date information.

## Coding/Billing Information

**Note:** 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

**Considered Experimental/Investigational/Unproven when used to report testing for serological markers for the diagnosis or management of inflammatory bowel disease:**

| **CPT®* Codes** | **Description** |
|---|---|
| 81401 | 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) NOD2 (nucleotide-binding oligomerization domain containing 2) (eg, Crohn's disease, Blau syndrome), common variants (eg, SNP 8, SNP 12, SNP 13) |
| 81479 | Unlisted molecular pathology procedure |
| 82397 | Chemiluminescent assay |
| 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 |
| 84999 | Unlisted chemistry procedure |
| 86021 | Antibody identification; leukocyte antibodies |
| 86255 | Fluorescent noninfectious agent antibody; screen, each antibody |
| 86256 | Fluorescent noninfectious agent antibody; titer, each antibody |
| 86671 | Antibody; fungus, not elsewhere specified |
| 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) |

**Considered Experimental/Investigational/Unproven when used to report testing for the measurement of serum drug levels and/or antibodies to monoclonal antibody (MAB) drugs, including anti-tumor necrosis**

**factor (TNF) drugs (e.g. infliximab, adalimumab, golimumab, ustekinumab, vedolizumab) individually or as part of a test panel:**

| CPT®* Codes | Description |
|---|---|
| 80145 | Adalimumab |
| 80230 | Infliximab |
| 80280 | Vedolizumab |
| 80299 | Quantitation of therapeutic drug, not elsewhere specified |
| 82397 | Chemiluminescent assay |
| 83520 | Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified |
| 84999 | Unlisted chemistry procedure |

| ICD-10-CM Diagnosis Codes | Description |
|---|---|
| K50.00 | Crohn's disease of small intestine without complications |
| K50.011 | Crohn's disease of small intestine with rectal bleeding |
| K50.012 | Crohn's disease of small intestine with intestinal obstruction |
| K50.013 | Crohn's disease of small intestine with fistula |
| K50.014 | Crohn's disease of small intestine with abscess |
| K50.018 | Crohn's disease of small intestine with other complication |
| K50.019 | Crohn's disease of small intestine with unspecified complications |
| K50.10 | Crohn's disease of large intestine without complications |
| K50.111 | Crohn's disease of large intestine with rectal bleeding |
| K50.112 | Crohn's disease of large intestine with intestinal obstruction |
| K50.113 | Crohn's disease of large intestine with fistula |
| K50.114 | Crohn's disease of large intestine with abscess |
| K50.118 | Crohn's disease of large intestine with other complication |
| K50.119 | Crohn's disease of large intestine with unspecified complications |
| K50.80 | Crohn's disease of both small and large intestine without complications |
| K50.811 | Crohn's disease of both small and large intestine with rectal bleeding |
| K50.812 | Crohn's disease of both small and large intestine with intestinal obstruction |
| K50.813 | Crohn's disease of both small and large intestine with fistula |
| K50.814 | Crohn's disease of both small and large intestine with abscess |
| K50.818 | Crohn's disease of both small and large intestine with other complication |
| K50.819 | Crohn's disease of both small and large intestine with unspecified complications |
| K50.90 | Crohn's disease, unspecified, without complications |
| K50.911 | Crohn's disease, unspecified, with rectal bleeding |
| K50.912 | Crohn's disease, unspecified, with intestinal obstruction |
| K50.913 | Crohn's disease, unspecified, with fistula |
| K50.914 | Crohn's disease, unspecified, with abscess |
| K50.918 | Crohn's disease, unspecified, with other complication |
| K50.919 | Crohn's disease, unspecified, with unspecified complications |
| K51.00 | Ulcerative (chronic) pancolitis without complications |
| K51.011 | Ulcerative (chronic) pancolitis with rectal bleeding |
| K51.012 | Ulcerative (chronic) pancolitis with intestinal obstruction |
| K51.013 | Ulcerative (chronic) pancolitis with fistula |

| ICD-10-CM Diagnosis Codes | Description |
|---|---|
| K51.014 | Ulcerative (chronic) pancolitis with abscess |
| K51.018 | Ulcerative (chronic) pancolitis with other complication |
| K51.019 | Ulcerative (chronic) pancolitis with unspecified complications |
| K51.20 | Ulcerative (chronic) proctitis without complications |
| K51.211 | Ulcerative (chronic) proctitis with rectal bleeding |
| K51.212 | Ulcerative (chronic) proctitis with intestinal obstruction |
| K51.213 | Ulcerative (chronic) proctitis with fistula |
| K51.214 | Ulcerative (chronic) proctitis with abscess |
| K51.218 | Ulcerative (chronic) proctitis with other complication |
| K51.219 | Ulcerative (chronic) proctitis with unspecified complications |
| K51.30 | Ulcerative (chronic) rectosigmoiditis without complications |
| K51.311 | Ulcerative (chronic) rectosigmoiditis with rectal bleeding |
| K51.312 | Ulcerative (chronic) rectosigmoiditis with intestinal obstruction |
| K51.313 | Ulcerative (chronic) rectosigmoiditis with fistula |
| K51.314 | Ulcerative (chronic) rectosigmoiditis with abscess |
| K51.318 | Ulcerative (chronic) rectosigmoiditis with other complication |
| K51.319 | Ulcerative (chronic) rectosigmoiditis with unspecified complications |
| K51.40 | Inflammatory polyps of colon without complications |
| K51.411 | Inflammatory polyps of colon with rectal bleeding |
| K51.412 | Inflammatory polyps of colon with intestinal obstruction |
| K51.413 | Inflammatory polyps of colon with fistula |
| K51.414 | Inflammatory polyps of colon with abscess |
| K51.418 | Inflammatory polyps of colon with other complication |
| K51.419 | Inflammatory polyps of colon with unspecified complications |
| K51.50 | Left sided colitis without complications |
| K51.511 | Left sided colitis with rectal bleeding |
| K51.512 | Left sided colitis with intestinal obstruction |
| K51.513 | Left sided colitis with fistula |
| K51.514 | Left sided colitis with abscess |
| K51.518 | Left sided colitis with other complication |
| K51.519 | Left sided colitis with unspecified complications |
| K51.80 | Other ulcerative colitis without complications |
| K51.811 | Other ulcerative colitis with rectal bleeding |
| K51.812 | Other ulcerative colitis with intestinal obstruction |
| K51.813 | Other ulcerative colitis with fistula |
| K51.814 | Other ulcerative colitis with abscess |
| K51.818 | Other ulcerative colitis with other complication |
| K51.819 | Other ulcerative colitis with unspecified complications |
| K51.90 | Ulcerative colitis, unspecified, without complications |
| K51.911 | Ulcerative colitis, unspecified with rectal bleeding |
| K51.912 | Ulcerative colitis, unspecified with intestinal obstruction |
| K51.913 | Ulcerative colitis, unspecified with fistula |
| K51.914 | Ulcerative colitis, unspecified with abscess |
| K51.918 | Ulcerative colitis, unspecified with other complication |

| ICD-10-CM Diagnosis Codes | Description |
|---|---|
| K51.919 | Ulcerative colitis, unspecified with unspecified complications |
| K58.0 | Irritable bowel syndrome with diarrhea |
| K58.1 | Irritable bowel syndrome with constipation |
| K58.2 | Mixed irritable bowel syndrome |
| K58.8 | Other irritable bowel syndrome |
| K58.9 | Irritable bowel syndrome without diarrhea |
| K59.31 | Toxic megacolon |



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