Medical Coverage Policy

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Inflammatory Bowel Disease - Testing for the Diagnosis and Management

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INSTRUCTIONS FOR USE

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for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

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

Coverage Policy

Fecal calprotectin is considered medically necessary when EITHER of the following criteria is met:

- for the purpose of distinguishing irritable bowel syndrome (IBS) from inflammatory bowel disease (IBD) in individuals with chronic diarrhea
- for the management of inflammatory bowel disease

Fecal calprotectin for ANY other indication is not covered or reimbursable.

Testing for serological and/or genetic 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
- antilaminaribioside carbohydrate IgG (ALCA)
- antichitobioside carbohydrate IgA (ACCA)
- anti-synthetic mannoside antibodies (AΣMA or AMCA)
- Pseudomonas-associated sequence I-2 (Anti-I2)
- Prometheus® Crohn's Prognostic
- IBDX Tool
- PredictSURE IBD™
- Prometheus Monitr® Crohn's Disease
- Prometheus® RiskImmune™

Therapeutic drug monitoring (TDM) used for the management of inflammatory bowel disease, including serum drug levels and/or antibodies, performed individually or as part of a test panel (e.g., Prometheus® Anser®, LabCorp DoseASSURE™), is considered experimental, investigational or unproven for the following agents:

- Certolizumab (Cimzia)
- Etanercept (Enbrel)
- Golimumab (Simponi)
- Natalizumab (Tysabri)

- Risankizumab (Skyrizi)
- Tofacitinib (Xeljanz)
- Upadacitinib (Rinvoq)
- Ustekinumab (Stelara)
- Vedolizumab (Entyvio)

General Background

Inflammatory bowel disease (IBD) is a condition, not a specific disease, which is characterized by chronic or relapsing immune activation and inflammation within the GI tract. Ulcerative colitis (UC) and Crohn's disease (CD) are the two main forms of IBD. CD is a chronic inflammatory disorder that can involve any part of the gastrointestinal tract from the mouth to the anus. UC is characterized by recurrent episodes of inflammation that is limited to the mucosal layer of the colon. The clinical characteristics of these disorders have substantial overlap. The symptoms of CD usually include diarrhea and abdominal pain which can be accompanied by weight loss. The symptoms of UC include bloody diarrhea with urgency. CD may manifest unique complications such as strictures and fistulas, which often necessitate surgery (Kaplan and Ng, 2021).

The prevalence of IBD has been increasing globally with variations by geographic region. The amount of individuals affected by IBD across the globe increased from 3.7 million in 1990 to 6.8 million in 2017. Asia and the Middle East have a lower incidence and prevalence of Crohn disease and ulcerative colitis; however, in some newly industrialized countries in Africa, Asia, and South America, the incidence of IBD has been rising. In a large systematic review of population-based studies on the incidence of Crohn disease and ulcerative colitis, the following trends were noted: in Brazil, the annual percentage change (APC) increased for Crohn disease by 11.1 percent and for ulcerative colitis by 14.9 percent, and in Taiwan, the APC increased for Crohn disease by 4 percent and for ulcerative colitis by 4.8 percent. Ulcerative colitis and Crohn disease are more common in Jewish compared to non-Jewish populations. Hispanic and Black populations have a lower incidence of IBD compared to White populations (Peppercorn and Cheifetz, 2021).

There are significant differences in IBD phenotype and outcomes based on race and ethnicity. This difference is likely due to a multitude of factors that includes both social and biologic differences. Minority and lower socioeconomic status groups are more likely to use the emergency department, be hospitalized, experience a complicated disease course and have IBD-related disability. Genes implicated in IBD risk differ in non-White compared with White patients with IBD. The data are increasing on the sex-based differences in IBD phenotype and outcomes, which may be related to differences in pathogenic pathways and progression. Females are more likely to experience consistent extraintestinal manifestations (EIMs). Additionally, girls are more likely to have EIMs and less likely to have growth impairment compared to boys, this could be related to lower insulin like growth factor-1 level in boys. CD and UC severity can vary from mild disease with few symptoms to complicated disease with strictures and fistulas. In a French population-based study, the cumulative probability of perianal CD varied between 11% and 19% at 1–10 years after diagnosis. In an Asian study of 983 patients with CD, stricturing or penetrating CD occurred in 41% and perianal disease in 25% of patients (Agrawal et al., 2021).

The diagnosis of IBD is established through a complete assessment of the clinical presentation with confirmatory evidence from radiologic, endoscopic, and, in most cases, pathologic findings. Endoscopic biopsies are helpful in the diagnosis of IBD and the differentiation of UC from CD through the recognition of microscopic changes suggestive of UC, CD, or both. Laboratory testing using stool and serological biomarkers are proposed to help predict ongoing intestinal inflammation, which could help decrease the repeated use of invasive and expensive testing in patients with non-specific symptoms. In the absence of biomarkers that are strongly predictive for

disease activity, clinicians rely on endoscopy to monitor these patients. There are no available biomarkers with adequate sensitivity or specificity to directly diagnose IBD, rule out disease expression or that can distinguish hard to differentiate CD from UC. Fecal biomarkers are more specific for luminal inflammation than serologic biomarkers. Fecal calprotectin and lactoferrin concentrations often increase in the stool of patients with active IBD. They have been used to distinguish IBD from irritable bowel syndrome, which can have similar presentations and overlapping symptoms. Stool markers have been evaluated for use in the diagnosis and surveillance of disease activity in IBD, however none are clinically validated for replacement of endoscopy with biopsy (Winter and Weinstock, 2020).

In general chronic diarrhea is defined as three or more loose or watery stools daily lasting for four or more weeks (Bonis and Lamont, 2022). Common causes include irritable bowel syndrome (IBS), inflammatory bowel disease, malabsorption syndromes (such as lactose intolerance and celiac disease), and chronic infections (particularly in patients who are immunocompromised). When the diarrhea is thought to be caused by inflammation, calprotectin testing is recommended. If there is a positive FC test, an ileocolonoscopy and biopsy to confirm the diagnosis of IBD is indicated. If fecal calprotectin is normal, a diagnosis of IBD is unlikely (Bonis and Lamont, 2022).

U.S. Food and Drug Administration (FDA)
PhiCal™ Fecal Calprotectin Immunoassay (Genova Diagnostics, Inc., Ashville, NC) received 510 (k) device approval in 2006. The immunoassay is a lab test that measures the amount of fecal calprotectin in a patient's stool sample. The PhiCal test is indicated for use as an in vitro diagnostic to aid in the diagnosis of inflammatory bowel diseases (IBD) (Crohn's disease and ulcerative colitis), and to differentiate IBD from irritable bowel syndrome (IBS) when used in conjunction with other diagnostic testing and the total clinical picture.

BUHLMANN fCAL® ELISA (BUHLMANN Laboratories AG, Lexington, Kentucky) received 510 (k) approval 2018. It is an in vitro diagnostic assay that is intended for the quantitative measurement of fecal calprotectin in human stool. The test aids in the diagnosis of inflammatory bowel disease (IBD), specifically Crohn's disease (CD) and ulcerative colitis (UC) and aids in the differentiation of IBD from irritable bowel syndrome (IBS) in conjunction with other laboratory and clinical findings.

Literature Review - Fecal calprotectin: Chen et al. (2021) conducted a prospective study that evaluated the clinical significance of fecal calprotectin (FC) in the assessment of ulcerative colitis (UC) clinical activity and mucosal healing (MH). Patients (n=143) referred for a colonoscopy with a previously confirmed diagnosis of UC included in the study. Patients were diagnosed on the basis of clinical, endoscopic, and histologic criteria. A second cohort of 108 healthy volunteers served as controls. After providing stool samples, patients underwent total colonoscopy. FC was measured by an enzyme-linked immunosorbent assay (ELISA). Clinical activity was based on the Mayo score. Endoscopic findings was scored by the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). The median of FC levels was 211 μg/g in UC and 87.5 μg/g in the control group. According to Mayo scores, 49 (34.27%) UC patients were in remission, 46 (32.17%) UC patients had mild, 41 (28.67%) UC patients had moderate, and 7 (4.90%) UC patients had severe disease activity. Overall, mucosal healing, defined as UCEIS score 0 or 1, was observed in 48 ulcerative colitis patients (33.57%). The measured FC concentrations were 38 μg/g, 220.5 μg/g, 1,138 μg/g, and 2,481 μg/g, respectively with each stage (remission, mild, moderate and severe) classified by Mayo scores. There was a significant difference in FC levels between patients with mild disease and moderate disease ($p<0.05$) as well as between moderate disease and severe disease ($p<0.05$). Fecal calprotectin correlated significantly with both Mayo and UCEIS scores ($p<0.01$). With a cut-off value of 164μg/g for fecal calprotectin concentration, sensitivity was 85.42%, specificity was 73.68%, positive predictive value (PPV) was 62.12%, and negative predictive value (NPV) was 9.10% in predicting clinical active disease. Similarly, the power of FC to predict mucosal healing (MH) was modest. With a cut-off value of 154.5μg/g, the AUC was 0.839,

sensitivity was 72.34%, and specificity was 85.71%. Author noted limitations included: small patient population, using FC as a predictive tool for MH requires analysis from patients in clinical remission and FC levels are variable. An additional limitation was that the study occurred in China and the results may not be applicable to other races or ethnic groups. The study concluded that FC is a clinically relevant biomarker for both clinically active disease and MH in patients with UC. However, the appropriate cut-off value needs to be determined.

Engström et al. (2019) conducted a cross-sectional study with longitudinal follow-up that assessed how fecal calprotectin (FC) and serum C-reactive protein (CRP) can be implemented in the clinical routine for monitoring sustained treatment response and the need of therapy adjustments or surgery over 48 weeks. The study included adults (n=123) aged 18–75 years of age that were diagnosed with CD (n=76) or UC (n=47) at least one year prior to study with a maximum dosage of mesalazine up to 4.8 grams per day. Patients received infliximab (IFX) induction therapy according to the standard protocol at weeks 0, two and six at a dose of 5 mg/kg followed by maintenance therapy every eight weeks. All patients underwent ileocolonoscopic examination prior to IFX administration. Fecal calprotectin, CRP and clinical assessments (Harvey–Bradshaw index (HBi) for CD and the partial Mayo Clinic score (pMCS) for UC) were evaluated at baseline and at 12 weeks. Responders were monitored 48 weeks for an 'incident' (dosage increase, shortened dosage interval, surgery). Clinical response was defined as a decrease of ≥ 3 points of either HBi or pMCS, and clinical remission as < 5 and ≤ 1 in HBi and pMCS, respectively. Following infliximab, FC and CRP significantly declined ($p<0.0001$) along with HBi for CD and pMCS for UC. Optimal FC ROC cutoff was 221 mg/g (sensitivity 66%, specificity 67%, AUC 0.71) and CRP ROC cutoff 2.1mg/L (sensitivity 54%, specificity 60%, AUC 0.58). In CD, FC > 221 mg/g ($p<0.0001$), but not CRP > 2.1 mg/L predicted an incident (an increase of infliximab dosage, shortening of infliximab dosage interval, or surgery). However, combined FC and CRP also predicted an 'incident' ($p<0.042$). In UC, both FC > 221 mg/g ($p<0.0005$) and CRP > 2.1mg/L ($p=0.0334$) predicted 'incident', as did combined biomarkers ($p<0.005$). Limitations to the study include the small patient population, short term follow-up and that the study occurred in Sweden and the results may not be applicable to other races or ethnic groups. The authors concluded that a treatment 'incident' in CD while receiving infliximab treatment (dose adjustment, surgery) was predicted by high FC but not CRP values, whereas high values in FC and CRP in UC were predictive of a treatment incidence.

Brand et al. (2019) investigated whether published non-invasive models (including fecal calprotectin) (based on symptoms and biomarkers) to evaluate Crohn's disease (CD) activity have sufficient accuracy to replace ileocolonoscopy. The study found two of the 7 models (but not the FC or C-reactive protein [CRP] values) identified patients without endoscopic activity with a negative predictive value (NPV) of 90% or more, leading to correct prediction of endoscopic healing in 3.2% to 11.3% of all patients which lead to correct predicted endoscopic healing in a small proportion of patients. The authors concluded that Ileocolonoscopy must therefore be used to evaluate CD mucosal disease activity and healing.

Yamamoto et al. (2018) conducted a prospective study that compared the clinical relevance of endoscopic scoring to fecal biomarkers for predicting relapse after clinical remission and mucosal healing (MH). Adults (n=164) aged 20–75 years were included in the study if the following criteria were met: confirmed diagnosis of UC; clinical remission achieved (normal stool frequency and no rectal bleeding) with medical treatment; mucosal healing (MH) achieved (Mayo endoscopic subscore [MES] 0 or 1) at endoscopy that was performed when they went into clinical remission; and scheduled to receive mesalamine maintenance therapy after achieving clinical remission and MH. At study entry, fecal samples were collected and measured for calprotectin, lactoferrin and hemoglobin. Following the fecal samples, patients received mesalamine maintenance therapy, and followed in the clinic every two or three months up to 12 months. When a patient developed symptoms suggestive of a flare-up, an endoscopic examination was done. Endoscopic score was

measured according to the MES. Forty-six patients (28%) relapsed. The relapse rate was not significantly different in patients with MES 1 or MES 0 (p=0.16). The median fecal calprotectin, lactoferrin, and hemoglobin were significantly higher in patients with relapse than those in remission (calprotectin, 182 vs. 94 μg/g; lactoferrin, 185.5 vs. 111 μg/g; hemoglobin, 168 vs. 104 ng/mL; all p<0.0001). A cutoff value of 115 μg/g calprotectin had 83% sensitivity and 81% specificity to predict relapse. There was a significant relationship between the MES and the fecal biomarkers. The median calprotectin, lactoferrin, and hemoglobin levels were significantly higher in patients with MES 1 than those with MES 0 (calprotectin, 112 vs. 96 μg/g, p=0.01; lactoferrin, 130 vs. 113 μg/g, p=0.02; hemoglobin, 128 vs. 112.5 ng/mL, p=0.04). There was a significant relationship between the occurrence of relapse and the levels of fecal biomarkers. The median calprotectin, lactoferrin, and hemoglobin levels were significantly higher in patients (n=46) with relapse than those (n=118) in remission (calprotectin, 182 vs. 94 μg/g, p<0.0001; lactoferrin, 185.5 vs. 111 μg/g, p<0.0001; hemoglobin, 168 vs. 104 ng/mL, p<0.0001). The cumulative relapse-free rate was significantly higher in patients with low fecal calprotectin (< 115 μg/g) compared with those with higher level (≥ 115 μg/g, p<0.0001). Likewise, the cumulative relapse-free rate was significantly higher in patients with low fecal lactoferrin (< 145 μg/g) compared with those with higher level (≥ 145 μg/g, p<0.0001). Endoscopic examination was not performed for all patients during the follow-up; however the levels of fecal biomarkers were not elevated in symptomatic patients without endoscopic activity. Author noted limitations included: (1) the different induction treatments used before entry and the change in therapy after remission induction, could have limited the accuracy of our findings; (2) histological evaluation was not done in our patients who achieved clinical and endoscopic remission; (3) the measurement of fecal biomarkers was only performed at baseline, consecutive monitoring was not done in predicting future relapse. An additional limitation is that the study occurred in Japan and the results may not be applicable to other races or ethnic groups. The authors concluded that additional large scale studies are needed to confirm the results of this study. Additionally, future studies should investigate whether or not early medical intervention is beneficial for the prevention of relapse in patients with elevated fecal biomarkers. The study concluded that fecal calprotectin, lactoferrin, and fecal hemoglobin (although to a lesser degree) appeared to be objective biomarkers for predicting patient relapse after achieving clinical remission and MH.

Columbel et al. (2017) conducted a multicenter, open label, phase 3 randomized controlled trial (CALM) that evaluated the safety and efficacy of two treatment algorithms, tight control and clinical management, in patients with moderate to severe Crohn's disease. The study included adults aged 18–75 years with active endoscopic Crohn's disease, a Crohn's Disease Activity Index (CDAI) of 150–450 depending on dose of prednisone at baseline, and no previous use of immunomodulators or biologics. Patients (n=244) were randomly assigned 1:1 to tight control (n=122) or clinical management (n=122), stratified by smoking status, weight (< 70 kg or ≥ 70 kg), and disease duration (≤ 2 years or > 2 years) after eight weeks of prednisone induction therapy, or earlier if they had active disease. The primary endpoint assessed mucosal healing which was defined as a Crohn's Disease Endoscopic Index of Severity (CDEIS) score of less than four and no deep ulcers 48 weeks after randomization. In both groups, Adalimumab treatment was escalated in a stepwise manner at 12, 24, and 36 weeks if patients met the treatment failure criteria, including laboratory assessments of serum concentrations of CRP and stool concentrations of FC at 11, 23, and 35 weeks. Treatment failure criteria was different between groups. Failure criteria in the tight control group included fecal calprotectin ≥ 250 μg/g, C-reactive protein ≥ 5mg/L, CDAI ≥ 150, or prednisone use in the previous week. Failure in the clinical management group included a CDAI ≥ 200 or a CDAI decrease of < 100 points compared with baseline or prednisone use in the previous week. De-escalation was possible for patients receiving weekly adalimumab and azathioprine or weekly adalimumab alone if failure criteria were not met. Ileocolonoscopies to assess CDEIS were done at study sites during screening and at 48 weeks after randomization or early termination. Twenty-nine (24%) patients in the clinical management group and 32 (26%) patients in the tight control group discontinued the study. At week 48, the

primary endpoint was met in significantly more patients in the tight control group than the clinical management group (46% vs 30%, respectively; p=0.010). Treatment emergent adverse events occurred in 86% of patients in the tight control group and 82% of patients in the clinical management group; no treatment-related deaths occurred. The most common adverse events were nausea, nasopharyngitis, and headache in the tight control group, and worsening Crohn's disease, arthralgia, and nasopharyngitis in the clinical management group. Author noted limitations included: the open-label design, and short term follow-up (48 weeks). The authors concluded that timely escalation with an anti-tumor necrosis factor therapy on the basis of clinical symptoms combined with biomarkers in patients with early Crohn's disease results in better clinical and endoscopic outcomes than symptom-driven decisions alone. Future studies should assess the effects of such a strategy on long-term outcomes such as bowel damage, surgeries, hospital admissions, and disability. No health disparities were identified by the investigators.

Verdejo et al. (2018) conducted a prospective study of 86 patients at five centers with the aim to evaluate the predictive value of a rapid test of FC for the presence and severity of postoperative endoscopic recurrence in patients with Crohn's disease (CD), compared with C-reactive protein (CRP) and the clinical evaluation of disease activity. Blood and fecal samples were collected in consecutively recruited patients with CD who had undergone ileocolonic resection and required a colonoscopy to assess postoperative recurrence, as defined by the Rutgeerts score (RS). Overall, 49 (57%) had CD recurrence. FC concentrations trended to increase with RS severity; FC median (interquartile range) was significantly higher in patients with endoscopic recurrence than those in endoscopic remission. The same occurred for C-reactive protein and the Harvey-Bradshaw index (HBI) [4 (2-7) vs. 1 (0-3.5)]. The three variables significantly correlated. The area under the curve to discriminate between patients in endoscopic remission and recurrence was 0.698 for FC, with 62 μg/g being the optimal cut-off point. This indicated FC would have 85.7% sensitivity and 45.9% specificity in detecting any recurrence, having positive predictive value and negative predictive value of 67.7 and 70.8%, respectively. Area under the curve for CRP and HBI were both 0.710. The combination of CRP and HBI provided a positive predictive value 95.7 and a diagnostic odds ratio of 30.8. The authors concluded that FC is not better than CRP combined with HBI to predict endoscopic postoperative recurrence of CD.

El-Matary et al. (2017) reported on a retrospective cohort study that examined the impact of fecal calprotectin (FCal) measurements on decision-making and clinical care of children with IBD. FCal, clinical activity indices, and blood markers were measured in 77 (115 fecal samples) children with diagnoses of IBD. Pearson correlation coefficient analysis was performed to examine association between FCal and other markers. Then decisions based on FCal measurements were prospectively documented and participants were evaluated three to six months later. FCal positively correlated with clinical activity indices ($r = 0.481$, $P < 0.05$) and erythrocyte sedimentation rate ($r = 0.40$, $P < 0.05$) and negatively correlated with hemoglobin ($r = -0.40$, $P < 0.05$). Sixty-four out of 74 (86%) positive FCal measurements (≥250 μg/g of stools) resulted in treatment escalation with subsequent significant clinical improvement while in the FCal negative group, 34 out of 41 (83%) measurements resulted in no change in treatment and were associated with remission on follow-up. The study was limited by lack of randomization, retrospective design, and small sample size in particular for those for those who had colonoscopy.

Abej et al. (2016) reported on a prospective cohort study performed to determine the relationship between fecal calprotectin (FCAL) and imaging studies and other biochemical inflammatory markers and the impact of FCAL measurements on decision-making in IBD patient management in usual clinical practice. The study included 240 persons with IBD. The correlation between FCAL values and other markers for disease activity such as serum albumin (alb), hemoglobin (Hg), and C-reactive protein (CRP) and diagnostic imaging or colonoscopy were examined. FCAL ≥ 250 mcg/g of stool was considered a positive result indicating active IBD. The results of 183 stool samples (76.3%) were returned. The return rate in the pediatric and adult cohorts was 91%

(n=82) and 67.3% (n=101), respectively (p<0.0001). Positive FCAL was associated with colonoscopy findings of active IBD (p<0.05), low albumin (p<0.05), anemia (p<0.01), and elevated CRP (p<0.01). There was no significant difference for FCAL results by outcomes on small bowel evaluation among the 21 persons with small bowel CD. Most persons (87.5%) with normal FCAL and no change in therapy remained in remission during subsequent three months. Of 11 subjects with a positive FCAL who underwent imaging, only six had active disease on imaging; a positive FCAL was not significantly associated with radiologic evidence of active disease (p=0.31).this study was limited by lack of controls, and the small number who underwent imaging and endoscopy.

Bar-Gil Shitrit et al. (2016) reported on a study that prospectively assessed the value of fecal calprotectin and lactoferrin in 68 patients with Crohn's disease (CD) to predict capsule endoscopy (CE) findings. Stool samples for calprotectin and lactoferrin and blood samples were collected for relevant parameters. Correlation between fecal markers and CE findings was assessed and receiver operating characteristic (ROC) curves were built to determine the predictive values of fecal markers for the diagnosis of CD. Fecal calprotectin data was available for all the patients and lactoferrin data for 38. CE findings compatible with CD were found in 23 (33%) patients and 45 (67%) were negative for CD. The average age of the CD group was 34 compared to 46 in the non-CD group (p=0.048). Median calprotectin and lactoferrin in the CD group and control group were 169 mg/kg vs. 40 (p=0.004) and 6.6 mg/kg versus 1 (p=0.051), respectively. The area under the ROC curve was 0.767 for calprotectin and 0.70 for lactoferrin. A fecal calprotectin concentration of 95 mg/kg and fecal lactoferrin of 1.05 mg/kg had a sensitivity, specificity, positive predictive value and negative predictive value of 77 and 73%, 60 and 65%, 50 and 50%, and 84 and 84% in predicting CE findings compatible with CD. The study is limited by small number of participants and lack of controls.

Professional Societies/Organizations

American College of Gastroenterology (ACG): The ACG clinical guideline on the management of Crohn's disease in adults included the following recommendation for the use of fecal calprotectin (Lichtenstein, et al., 2018):

- Fecal calprotectin is a helpful test that should be considered to help differentiate the presence of IBD from irritable bowel syndrome (IBS) (strong recommendation, moderate level of evidence).
- In patients who have symptoms of active Crohn's disease, stool testing should include fecal pathogens, Clostridium difficile testing and may include studies that identify gut inflammation such as a fecal calprotectin.(summary statement, no level of evidence)
- Fecal calprotectin and fecal lactoferrin measurements may have an adjunctive role in monitoring disease activity.(summary statement, no level of evidence)

  Level of evidence:
  Moderate: (further research would be likely to have an impact on the confidence in the estimate of effect)

  Recommendation grading:
  Strength of a recommendation graded as "strong" when the desirable effects of an intervention clearly outweigh the undesirable effects.

Summary statements are descriptive and do not have associated evidence-based ratings.

Serological and/or genetic markers for the diagnosis or management of inflammatory bowel disease

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, an antibody to flagellin from Clostridium species, is reported to be found in approximately 6% of UC patients, 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, an antibody against synthetic oligomannose epitopes, was 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-sensitive 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. The IBDX (Crohn's disease Prognosis Test; Glycominds Ltd, Lod, Israel) tool detects serum levels of specific anti-glycan antibodies, which are a set of serological biomarkers proposed to be highly specific to CD with a potential predictive value for severe course of disease. PredictSURE-IBD (PredictImmune Ltd, Cambridge, UK) facilitates the stratification of people with IBD into high and low risk of a frequently relapsing course of disease through the detection of a gene sequence associated with CD8+ (cluster of differentiation 8) T-cell exhaustion (Edwards et al., 2021).

The Monitr® Crohn's Disease Test (Prometheus Laboratories Inc, San Diego, CA) evaluates multiple markers of mucosal damage and repair processes, regardless of disease location. The test applies a proprietary algorithm to 13 biomarkers to produce a quantitative Endoscopic Healing Index (EHI) Score which ranges from 0–100. The test is proposed to aid in distinguishing endoscopic remission from active disease in adult CD patients (Prometheus).

The Prometheus® RiskImmune™ is blood-based genetic test that identifies if an IBD patient is a variant carrier of HLADQA1*05 (rs2097432), a single nucleotide polymorphism. The test is proposed to help identify patients at greater risk of anti-TNF antibody (ADAb) formation to assist with therapeutic decision making.

There is insufficient evidence in the published medical literature to determine the role of serological testing and/or genetic markers (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 - Serological and/or genetic markers: Spencer et al. (2022) conducted a post-hoc analysis of Precision infliximab that analyzed study participants for the HLA-DQA1*05 risk variant identified in the PANTS study using the RiskImmune test (Prometheus Laboratories). The proportion of participants (90% on monotherapy) with immunogenicity in Precision infliximab was low, with 12% of patients (23/186) with antidrug antibodies (ADAs) by 1 year; 83% (19/23) of these occurred in the setting of a nontherapeutic drug concentration. HLA-DQA1*05 variant carriage in the entire cohort was 46%. Risk variant carriage was not associated with immunogenicity (p=0.50) with 9 of 23 patients (39%) with the risk variant with ADAs as compared to 14 of 23 (61%) in the absence of the variant. Only 10 patients discontinued infliximab because of high-level ADAs, and 50% of these were risk variant carriers (p=0.78). Hispanic ethnicity was the only demographic variable associated with immunogenicity in the cohort (p=0.02), with 47% of those of Hispanic ethnicity carrying the risk variant. Rate of ADA formation and infliximab durability were not significantly different between carriers and noncarriers. However, when comparing those who did and did not achieve the infusion 3 target trough level, the rate of ADA formation was significantly faster in those not achieving the target level, but durability was not different between these groups. Author noted limitations were the post-hoc design and short-term follow-up. Further investigation into the impact of risk variant carriage in the setting of early proactive dose optimization is needed. The study concluded that HLA-DQA1*05 risk variant carriage does not impact development of ADAs or durability.

Nowak et al. (2021) conducted an observational cohort study which assessed if the presence of HLA-DQA1*05 correlates with characteristics of pediatric IBD. The HLA-DQA1*05 was present in 221 (55.1%) out of 401 children with IBD (UC n=188, Crohn's disease n=213). The study

reported that the HLA-DQA1*05 correlates with a greater extent of colonic inflammation at diagnosis in children with UC. The authors concluded that future research focusing on explaining and preventing anti-TNF immunogenicity should take into account that ADA may develop not only as an isolated reaction to anti-TNF exposure but as a consequence of intrinsic differences in the early course of UC. No health disparities were identified by the investigators.

Edwards et al. (2021) conducted a health technology assessment on prognostic accuracy and clinical impact of the IBDX® (Crohn's disease Prognosis Test; Glycominds Ltd, Lod, Israel) biomarker stratification tool and the PredictSURE-IBD™ (PredictImmune Ltd, Cambridge, UK) tool. The systematic review included sixteen publications, including eight original studies (n=1478 patients). Additional documents reviewed were supplied by the company's marketing the prognostic tools. No study meeting the eligibility criteria reported on the sensitivity or specificity of the IBDX biomarker stratification tool, whereas one study provided estimates of sensitivity, specificity and negative predictive value for the PredictSURE-IBD tool. The studies identified were observational and provided weak evidence on the effectiveness of the tools. The author noted limitation included that the lack of robust evidence on the prognostic accuracy of the biomarker stratification tools IBDX and PredictSURE-IBD. The health technology assessment concluded that there is limited evidence on the efficacy that the tools worked in identifying people who were more likely to develop complications of Crohn's disease. No health disparities were identified by the investigators.

Halligan et al. (2021) conducted a health technology assessment on the prognostic biomarkers to identify patients who are likely to develop severe Crohn's disease. The systematic review included 71 individual studies with 56 non-overlapping cohorts. Five clinical biomarkers (Montreal behavior, age, disease duration, disease location and smoking), two serological biomarkers (anti-Saccharomyces cerevisiae antibodies and anti-flagellin antibodies) and one genetic biomarker (nucleotide-binding oligomerisation domain-containing protein 2) displayed statistically significant prognostic potential. Overall, the strongest association with subsequent severe disease was identified for Montreal B2 and B3 categories. Author noted limitations included that the definitions of severe disease varied widely, and some studies confused diagnosis and prognosis. The risk of bias was high in 92% of the studies. Lastly, some biomarkers that are used regularly in daily practice, (e.g., C-reactive protein) were studied too infrequently for meta-analysis. The authors concluded that the research for individual biomarkers to predict severe Crohn's disease is limited, heterogeneous with a high risk of bias. Despite a large amount of potential research, there was relatively few biomarkers with data sufficient for meta-analysis. No health disparities were identified by the investigators.

D'Haens et al. (2020) aimed to develop and validate a multimarker, serologic, algorithm-based diagnostic test that reliably reflects the severity of endoscopic inflammation in CD. The test measures 13 proteins in blood (ANG1, ANG2, CRP, SAA1, IL7, EMMPRIN, MMP1, MMP2, MMP3, MMP9, TGFA, CEACAM1, and VCAM1), called the endoscopic healing index (EHI; Monitr®, Prometheus Laboratories Inc, San Diego, CA). Patients (n=278) were included in the study if they were age ≥ 18 years with a confirmed diagnosis of CD, documented endoscopic disease activity and enough volume of serum for testing. There were three independent cohorts of prospectively collected, retrospectively analyzed samples for training and validation. The training cohort (n=278) included samples obtained from a prospectively recruited convenience sampling biobanks. The test was validated using two independent cohorts of patients with CD: biologic-naïve patients with early-stage CD (n=116; validation cohort 1) and biologic-exposed patients with chronic CD (n=195; validation cohort 2). The ability of the test to identify patients with active disease vs patients in remission was assessed by using area under receiver operating characteristic curve (AUROC) analysis. The diagnostic accuracy of the test was compared with that of measurement of serum C-reactive protein (CRP) and fecal calprotectin. The primary outcome was to assess the sensitivity and specificity of the EHI at various cutoffs for identifying the

presence of endoscopic inflammation. Secondary outcomes measured the diagnostic accuracy of the EHI at various cutoffs for identifying the presence of endohistopathologic inflammation and compare the diagnostic accuracy of the EHI to CRP and FC. Additionally the responsiveness of the EHI was compared to endoscopy, CRP, and FC, to assess its utility as a tool for monitoring endoscopic disease activity in patients with CD. The EHI scores range from 0–100 units; the higher scores indicated more severe CD activity, based on endoscopy findings. The EHI identified patients in remission with an AUROC of 0.962 in validation cohort 1 and an AUROC of 0.693 in validation cohort 2, regardless of CD location or phenotype. A cutoff value of 20 points identified patients in remission with the highest level of sensitivity (97.1% in validation cohort 1 and 83.2% in validation cohort 2), with specificity values of 69.0% and 36.6%, respectively. A cutoff value of 50 points identified patients in remission with the highest level of specificity (100% in validation cohort 1 and 87.8% in validation cohort 2), with sensitivity values of 37.3% and 30.0%, respectively. The EHI identified patients in remission with a significantly higher AUROC value than the test for CRP ($p<0.001$ in validation cohort 1 and $p=0.109$ in validation cohort 2). In analysis of patients with available FC measurements, the AUROC value for the EHI did not differ significantly from that of measurement of FC ($p=0.147$ in validation cohort 1 and $p=0.298$ in validation cohort 2). Author noted limitations included: 1) the observed diagnostic accuracy of EHI for identifying histologic inflammation was exploratory and is only available in a subset of patients from validation cohort; 2) the test is associated with endoscopic MH, and further work is needed to understand how the EHI performs for identifying the evolving definition of MH; 3) further analyses are required to understand how the EHI compares against cross-sectional imaging–based assessments of disease activity; 4) the investigators were unable to assess the prognostic value of the EHI for predicting future endoscopic recurrence or disease relapse; 5) the differences in performance of the EHI in various CD populations need to be further explored; 6) continued validation of the EHI will be needed to ensure generalizability across all populations. The authors also acknowledged that future studies should assess the cost effectiveness of the EHI, relative to both colonoscopy and to other available biomarker tests, such as CRP and FC. No health disparities were identified by the investigators. However, the majority of patients were of the white race and the results may not be applicable to other races or ethnic groups.

Sazonovs et al. (2020) performed a prospective observational study that assessed the treatment failure rates of the anti-TNF drugs infliximab and biosimilar, CTP13 and adalimumab in anti-TNF-naïve patients with Crohn's disease. The Personalising Anti-TNF Therapy in Crohn's Disease (PANTS) study used genomewide association to identify variants associated with time to development of anti-drug antibodies. The study enrolled biologic-naïve patients (n=1240) with Crohn's disease starting infliximab or adalimumab therapy. Pretreatment blood samples were collected and DNA was extracted for genotyping using the Illumina CoreExome microarray (Illumina, San Diego, CA). Follow-up occurred at first dose, post-induction (weeks 12–14), weeks 30 and 54, and at treatment failure. At each visit, serum infliximab or adalimumab drug and anti-drug antibody levels were analyzed using total antibody enzyme linked immunosorbent assays. For infliximab treated patients, additional visits occurred at each infusion. After 12 months, patients were invited to continue follow-up for an additional two years. Immunogenicity was defined as an anti-drug antibody titer 10 AU/mL using a drug-tolerant enzyme-linked immunosorbent assay. Within the first 12 months, 44% of patients developed anti-drug antibodies, and 62% of patients did so within 36 months. The rate of immunogenicity was greater in patients treated with infliximab (n=742) than adalimumab (n=498) ($p<0.05$). In a model including drug type as a covariate, rates of immunogenicity were greater in patients treated with anti-TNF monotherapy (n=544) compared to combination therapy with immunomodulators (n=696) ($p<0.05$). At the HLA allele group level, only HLA-DQA1*05 achieved genome-wide significance ($p<0.05$). The HLA-DQA1*05 which is carried by approximately 40% of Europeans, significantly increased the rate of immunogenicity ($p<0.05$). The highest rates of immunogenicity, 92% at 1 year, were observed in patients treated with infliximab monotherapy who carried HLA-DQA1*05; conversely the lowest rates of immunogenicity, 10% at 1 year, were observed in

patients treated with adalimumab combination therapy who did not carry HLA-DQA1*05. The findings were confirmed in a replication cohort (n=178) that comprised 107 Crohn's disease, 64 ulcerative colitis, and 7 inflammatory bowel disease (IBD) type unclassified patients. Cross-sectional drug and anti-drug antibody levels were measured as part of routine clinical practice. This association was consistent for patients treated with adalimumab or infliximab, and for patients treated with anti-TNF therapy alone or in combination with an immunomodulatory ($p<0.05$). An author noted limitation included that the study was limited to patients of European descent, 40% of whom carry the risk allele. The results of the study may not be applicable to other races or ethnic groups. The authors concluded that the study found a significant genomewide association between HLA-DQA1*05 and the development of antibodies against anti-TNF agents. However, a randomized controlled biomarker trial is required to determine whether pretreatment testing for HLA-DQA1*05 improves patient outcomes by helping physicians select anti-TNF and combination therapies.

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.

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.

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. Additionally, the guideline stated that genetic or serologic markers in predicting severity and course of UC has been limited, and their use cannot be recommended in routine clinical practice based on available data (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 and/or genetic testing 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.

Therapeutic Drug Monitoring (TDM)

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 (certolizumab, etanercept, golimumab), anti-integrin antibodies (vedolizumab, natalizumab) and anti-IL-12/23 (risankizumab, ustekinumab) (Al Hashash and Regueiro, 2022b; 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.

Certolizumab (Cimzia) is human monoclonal antibody Fab fragment linked to polyethylene glycol that neutralizes TNF for the treatment of moderate to severe Crohn's disease. The polyethylene glycol increases its plasma half-life and reduces the requirement for frequent dosing, possibly reducing loss of response. It can be considered as a second or third-line anti-TNF agent in patients who responded to infliximab or adalimumab and then lost response or became intolerant. It is administered subcutaneously every four weeks (Al Hashash and Regueiro, 2022b).

Etanercept (Enbrel) is not listed as a treatment option for ulcerative colitis or Crohn's disease. In a double-blind, placebo-controlled trial etanercept (Enbrel) was not effective for the treatment of moderate to severe Crohn's disease (Sandborn, et al., 2001).

Golimumab (Simponi) 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).

Natalizumab (Tysabri) is a human monoclonal antibody that blocks leukocyte migration to sites of inflammation. It is rarely used for Crohn disease because of its association with serious adverse events, including progressive multifocal leukoencephalopathy (PML). However, it can be used to induce and maintain clinical response and remission in adults with moderately to severely active disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional Crohn's disease therapies and inhibitors of tumor necrosis factor (TNF)-α.

Risankizumab (Skyrizi) is a human monoclonal antibody that blocks the p19 subunit of IL-23. The drug is used in patients with moderate to severe Crohn's disease. The induction dose of risankizumab is 600 mg intravenously at zero, four, and eight weeks. Maintenance dosing is 360 mg administered by subcutaneous injection at week 12 and every eight weeks thereafter Al Hashash and Regueiro, 2022b).

Ustekinumab (UST) (Stelara) 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, 2022b).

Vedolizumab (VDZ) (Entyvio) 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, 2022b).

Janus kinase (JAK) inhibitors are small, orally active drugs, also known as small molecules. Several JAK inhibitors are commercially available for clinical use as oral and topical agents for immune-mediated and inflammatory diseases. Two oral Janus kinase (JAK) inhibitors (tofacitinib and upadacitinib) are approved in the United States for treating adults with moderate to severe UC who have not responded or are intolerant to anti-TNF agent-based therapy. The onset of action of JAK inhibitors varies greatly. There are some patients that respond rapidly (within one week) and for other patients, response may take longer (up to 16 weeks) (Cohen and Reddy, 2022; Cohen and Stein, 2022).

Available small-molecule treatments for IBD are unlikely to induce the formation ADAs, in contrast with biologic agents. Additionally, these drugs are not used in combination with thiopurines, TPMT, and metabolite monitoring are not necessary, and the toxicity concerns are not present. Therefore, TDM is not likely to be necessary to optimize the treatment of IBD with small-molecule therapies. However, TDM remains a key recommendation for many IBD treatments (Mukherjee, et al., 2022; Lee, et al., 2021).

Tofacitinib (Xeljanz®) is used for treating moderately to severely active UC. The drug is available as immediate-release and extended-release tablets, as well as an oral solution. The induction dose is 5 mg twice daily. Patients with active UC who do not achieve remission with the induction dose and who are at low risk for thromboembolism or cardiovascular disease, tofacitinib can be increased to 10 mg twice daily for a maximum of 16 weeks before decreasing the dose to 5 mg twice daily. Obtaining biomarkers of inflammation including fecal calprotectin and C-reactive protein are recommended to guide therapy to achieve endoscopic and clinical remission (A-Rahim and Farrell, 2022; Cohen and Reddy, 2022; Cohen and Stein, 2022).

Upadacitinib (Rinvoq) is used for inducing remission in patients with UC who are non-responders to biologic therapy. The drug is administered as an oral tablet in a 24-hour extended-release formulation (Cohen and Reddy, 2022; Cohen and Stein, 2022).

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. 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 CTZ, ETN, GOL, VDZ, and UST provides drug concentration levels as well as antibody levels for certolizumab, etanercept, 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. Natalizumab serum drug and antibody level is not addressed by Prometheus or LabCorp.

There is insufficient evidence in the published medical literature to determine the role of serum drug levels and/or antibodies to the following monoclonal antibody (MAB) drugs (including anti-TNF) and JAK inhibitors: certolizumab, etanercept golimumab, natalizumab, risankizumab, ustekinumab, vedolizumab, tofacitinib and upadacitinib 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 (Nguyen, et al., 2022).

Literature Review - Therapeutic Drug Monitoring: Danese et al. (2022) conducted an open-label, multicenter, phase 3b randomized controlled trial (STARDUST trial) that evaluated whether a treat-to-target strategy was more effective in achieving endoscopic improvement compared to the standard of care in patients with ulcerative colitis (UC). The study was performed 12 European countries and enrolled adults, aged 18 years or older with active, moderate-to-severe Crohn's disease (Crohn's Disease Activity Index [CDAI] 220–450 and Simple Endoscopic Score in Crohn's Disease [SES-CD] ≥ 3) for whom conventional therapy and/or biologic therapy had failed. Patients (n=498) received intravenous ustekinumab 6 mg/kg at baseline and subcutaneous ustekinumab 90 mg at week eight. At week 16, patients (n=440) with a CDAI improvement of 70 or more points from baseline were randomly assigned (1:1) to receive standard-of-care (n=221) or treat-to-target maintenance treatment (n=219) through week 48. Patients assigned to the treat-to-target group received ustekinumab every 12 weeks or every eight weeks based on SES-CD improvement from baseline and could escalate to every four weeks through week 48 based on symptoms and biomarkers. The treat-to-target group had an endoscopy at week 16 to determine their initial dose of subcutaneous ustekinumab 90 mg according to their SES-CD improvement from baseline and to identify patients not responding to induction. Patients assigned to the standard-of-care group received ustekinumab every 12 weeks or every eight weeks. Dose adjustments were based solely on disease flare (loss of response) as confirmed by physician.

The primary outcome measured endoscopic response (defined as ≥50% reduction from baseline in SES-CD score) at week 48. The SES-CD score is an endoscopic scoring system for Crohn's disease, by which endoscopic parameters (ulcer size, ulcerated and affected surfaces, stenosis) are scored from 0–3. Secondary outcomes measured: endoscopic response at week 48, endoscopic remission (defined as an SES-CD score ≤2) and mucosal healing (defined as complete absence of mucosal ulcerations in any ileocolonic segment) at week 48. Further secondary endpoints assessed at week 48 included clinical remission (defined as a CDAI score <150 points), clinical response (defined by a ≥100-point CDAI score reduction from the baseline, or a CDAI score <150); corticosteroid-free clinical remission (defined as a CDAI score <150 points and not receiving corticosteroids at week 48) and corticosteroid free endoscopic response (defined as ≥50% reduction from baseline in SES-CD score and not receiving corticosteroids at week 48). Serum CRP, fecal calprotectin, and safety were also measured. All patients were evaluated during induction (baseline and week eight), at randomization (week 16) and during maintenance at each scheduled ustekinumab administration visit (weeks 16 through 48). CDAI scores were assessed at each visit for patients receiving the treat-to-target regimen and were assessed only at weeks 0, 16, and 48 for patients receiving the standard of-care regimen. The treat-to-target group had blood samples collected at weeks 0, eight, and 16, at all assessment visits, and at week 48, or early termination for pharmacokinetic and immunogenicity assessments. One-hundred seventy-nine (79%) patients in the treat-to-target group and 193 (87%) in the standard-of-care group completed week 48. At week 48, there was no significant difference in endoscopic response, endoscopic remission, mucosal healing, and clinical remission (p=0.087, p=0.334, p=0.449, p=0.072, respectively). However, clinical response was significantly lower in the treat-to-target group compared to the standard-of-care group (p=0·020). Other endoscopic, clinical, and biomarker outcomes were generally not significantly different between groups. Author acknowledged limitations included: the open-label design, only CDAI-70 responders were randomized at week 16, the treat-to-target regimen used protocol-defined criteria whereas the standard-of-care regimen used pragmatic criteria for dose escalations, dose escalation could have happened too fast and the rules for treatment discontinuation might have been too strict. An additional limitation of the study population was the inclusion of patients from European countries only; therefore, results may not be applicable to other races or ethnic groups. The study concluded that timely escalation of ustekinumab therapy for patients with Crohn's disease, based on early endoscopic response, clinical symptoms, and biomarkers, did not result in significantly better endoscopic outcomes at week 48 than symptom-driven decisions alone. Future studies need to confirm if a treat-to-target strategy is beneficial for those patients using ustekinumab.

Taxonera et al. (2022) conducted a multicenter, cross-sectional study that evaluated the association of golimumab trough concentrations during maintenance therapy with treatment outcomes, including endoscopic healing and histologic remission, in patients with ulcerative colitis. The study included patients (n=52), aged 18 years or older with an established diagnosis of UC who had received at least five maintenance doses of golimumab prior to inclusion. Patients underwent colonoscopy either for surveillance of dysplasia, for assessment of disease activity in patients with IBD-related symptoms or to evaluate mucosal healing based on a treat-to-target strategy for patients in clinical remission. All patients received induction with SC golimumab 200 mg at week 0 and 100 mg at week two. The median duration of golimumab exposure was 23 months. Samples for golimumab trough concentrations and anti-golimumab antibodies (AGA), C-reactive protein (CRP) and faecal calprotectin (FC) were obtained the day of the scheduled subcutaneous golimumab administration closest to the colonoscopy. Median golimumab trough concentrations were significantly higher in patients who had clinical remission (p=0.047), combined clinical-biochemical remission (p=0.041), endoscopic healing (p=0.003), histologic remission (p=0.02) and disease clearance (clinical remission endoscopic healing + histologic remission) (p=0.009), compared with those not meeting these criteria. Golimumab concentrations were significantly higher in patients who avoided golimumab dose escalation/discontinuation

during follow-up (p=0.012). Golimumab thresholds of 0.85, 1.90, 2.29, 1.79, 2.29 and 1.56 µg/ml as associated with clinical remission, combined remission, endoscopic healing, histologic remission, disease clearance and long-term event-free persistence with golimumab, respectively. The study concluded that golimumab trough levels during maintenance are associated with favorable treatment outcomes including endoscopic healing, histologic remission and long-term persistence on golimumab. However, the authors noted that a prospective study is required in which patients with low SGC undergo dose optimization with the aim of reaching the identified thresholds and which also investigates the prognostic impact of the intervention on outcomes. The study was conducted in Spain and the results may not be applicable to other races or ethnic groups. Limitations of the study include short term follow-up and small patient population.

Outtier et al. (2021) conducted a multicenter open-label prospective study that assessed the effect of vedolizumab (VDZ) dose escalation on serum drug concentrations and clinical outcome in patients with a loss of response during maintenance therapy. The study included patients, (n=59, 31 UC and 28 CD) aged 18 years or older who initially responded to VDZ during induction treatment and lost response during maintenance therapy while receiving 300mg of VDZ every eight weeks (Q8W). The primary outcome measured the effect of receiving VDZ every four weeks on serum concentrations and the association of higher serum concentrations with regained response. The secondary outcomes measured the proportion of UC and CD patients who recaptured biological and/or clinical response after increasing to VDZ dosage to every four weeks. Loss of response was defined as a total Mayo score > 6 for UC and a Harvey-Bradshaw Index (HBI) score > 4 with objective signs of inflammation detected by endoscopy, ultrasound, radiography, C-reactive protein (CRP) > 5 mg/L or fecal calprotectin > 250 µg/g for CD. Clinical response was defined as a decrease of partial Mayo score with ≥ 2 points for UC or a decrease of HBI score with ≥ 3 points for CD. Biological response was defined as a CRP ≤ 5 mg/L or a decrease in CRP of > 50% in patients with a CRP > 5 mg/L at baseline. Median trough levels (TLs) increased from 8.7 (5.1-12.7) µg/mL (baseline) to 19.1 (12.4-22.4) µg/mL (Week 4) and 23.1 (16.7-28.4) µg/mL (Week 8) (all p<0.0001). Partial Mayo score (symptoms: stool frequency/bleeding) decreased three points from baseline to Week 4 (p=0.001) but no further decrease from week 4 to week 8 (p=0.16). HBI (symptoms: pain, stools) significantly decreased from baseline to Week 4 (p=0.001) and further from Week 4 to Week 8 (p=0.04) There was a numerical decrease in CRP from 6.1 mg/L at baseline to 5.6 mg/L at week 4, and 3.9 mg/L at week 8, not significant (all p>0.05). Recapture of clinical and biological response was achieved in 49% and 27% at Week 4, and 54% and 37% at Week 8, respectively. The changes in VDZ serum concentrations from baseline to Week 8 did not correlate significantly with the observed changes in CRP, partial Mayo score or HBI. While there is an association between higher drug exposure after dose escalation and regain of response, baseline VDZ serum concentrations cannot predict successful outcome of treatment escalation. Neither quartile analysis of baseline TL nor a baseline TL of < 14 µg/mL, were predictive of response to dose escalation. Author acknowledged limitations included the small patient population, a lack of multivariate analysis, and a concomitant use of medications in a small proportion of patients. Additionally, a more objective evaluation with fecal calprotectin and endoscopy is lacking and evaluating response at eight weeks after dose escalation may be too soon. Lastly, the dose escalation interval was shortened and it is unknown if the same results would be found with increasing the dose from 300 mg to 600 mg and maintaining the eight-weekly interval. The study concluded that baseline TL is not predictive of response to dose escalation. However, larger prospective cohorts are needed to further investigate. No health disparities were identified by the investigators. The population studied included patients from Belgium and the results may not be applicable to other races or ethnic groups.

Roblin et al. (2021) conducted a prospective, nonrandomized observational study that compared the efficacy and safety of two different therapeutic strategies in IBD patients treated with non-optimized adalimumab (ADA) monotherapy and losing response despite therapeutic trough levels.

Patients either had ADA dose optimization or were swapped to vedolizumab (VDZ) or ustekinumab (UST). Patients (n=131) under maintenance therapy with ADA monotherapy (40 mg every 14 days) and who experienced a secondary loss of response with trough levels > 4.9 µg/mL were included in the study. Before the LOR, all patients were in clinical remission under non-optimized ADA at the maintenance dose. The decision to optimize ADA therapy or to swap for another class of biologics was left to the discretion of the treating physician. Sixty-one patients were ADA optimized (optimization group), and the remaining 70 patients were switched to another class of biologic (swap group) including VDZ (n=40, 20 CD, 20 UC) or UST (n=30, 30 CD). The primary end point was the survival rate without therapeutic discontinuation after ADA dose optimization or switching to another class of biologics. Therapeutic discontinuation was defined as treatment failure characterized for CD by a CDAI score > 220, with fecal calprotectin concentrations > 250 µg/g stools and for UC by a total Mayo score > 6, with an endoscopic subscore > 1 or intolerance to treatment requiring drug withdrawal. Drug optimization in the swap group was not considered as a failure. Two weeks after the last ADA injection, patients who were ADA optimized received a subcutaneous (sc) injection of ADA every week; patients who switched to another class of biologic either started infusions of VDZ at the dose of 300 mg with an induction regimen (at weeks 0, 2, and 6) followed by a maintenance regimen every eight weeks or started an initial infusion of UST (at the dose of 6 mg/kg) followed by a maintenance regimen of 90 mg sc every eight weeks. During maintenance therapy, patients were reviewed every eight weeks for clinical evaluation, allowing for the calculation of CDAI or partial Mayo score. In cases of persistent active disease or disease flare, an early medical visit was performed to assess disease activity by means of CDAI and fecal calprotectin for CD and total Mayo score for UC. Patients were followed for 24 months or less in case of treatment discontinuation.

The swap group experienced a significantly longer median time without therapeutic discontinuation (> 24 months) than in the optimization group (13.3 months, p<0.001). In the optimization group, treatment discontinuation was positively associated with baseline fecal calprotectin > 500 µg/g (p=0.026) and inversely associated with variation of trough levels of adalimumab (> 2 µg/mL from baseline to week eight after optimization; p=0.03). In the swap group, no factor was associated with treatment discontinuation. A history of previous IFX treatment was more frequent in the optimization group (62% vs 26%, p=0.001), whereas the proportion of smoking patients was greater in the swap group (58% vs 20%, p=0.002). The percentages of patients without treatment discontinuation differed significantly between the swap and optimization groups at six months, 12 months, 18 months and 24 months (all p<0.001), in favor of the swap group. In the swap group, 27% of patients under UST were drug optimized and 30% under VDZ. In patients who received UST, the time without therapeutic discontinuation was longer (24 months) than in the optimization group (13.3 months; p=0.12). The median duration without treatment discontinuation did not differ in patients receiving VDZ or UST (p=0.12). At 24 months, 11 out of 70 patients (14.8%) in the swap group discontinued treatment compared to 36 out of 61 (59.6%) patients in the optimization group (p<0.001). In the optimization group, treatment discontinuation was positively associated with baseline fecal calprotectin > 500 µg/g (p=0.026) and inversely associated with variation of trough levels of adalimumab (> 2 µg/mL from baseline to week eight after optimization; p=0.03). In the swap group, no factor was associated with treatment discontinuation. Author acknowledged limitations included the nonrandomized and nonblinded study design. Second, the two therapeutic groups were not fully comparable at baseline, especially in terms of disease severity. At baseline, patients in the swap group suffered from a more severe disease, with significantly higher fecal calprotectin and CRP levels and higher activity scores than in the optimization group; and although the percentages of CD patients were close between the two groups, the percentage of active smokers was higher in the swap group. Third, when we compared the two groups of patients, IFX exposure was significantly more frequent before ADA therapy in the optimization group than in the swap group. Finally, the heterogeneous population with CD and UC patients precluded subgroup analyses of CD vs UC, and the small sample size of patients with positive AAA using drug-tolerant assay did not

allow definitive conclusion. The study concluded that in IBD patients under ADA maintenance therapy who experience a secondary loss of response and in whom trough levels are > 4.9µg/mL, swapping to another class is better than optimizing ADA. No health disparities were identified by the investigators. The population studied included patients from France and the results may not be applicable to other races or ethnic groups.

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 (SUC) 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.

Berends et al. (2019) conducted a prospective observational trial (GO-KINETIC) that investigated correlations between golimumab (GLM) serum concentrations and clinical and endoscopic outcomes during induction and maintenance treatment in patients with moderate to severe UC. Patients (n=20) were age 18 years and older with a confirmed diagnosis of moderate to severe UC starting GLM induction treatment were included in the study. Both anti-TNF naïve and previously anti-TNF exposed patients could enter the study. The primary outcome measured associations between drug exposure and clinical and endoscopic outcomes at week eight and 52 after starting GLM therapy, using the simple clinical colitis activity index (SCCAI) and endoscopic Mayo score, respectively. Secondary outcomes measured the proportion of patients with detectable antibodies to GLM, evaluation of fecal GLM concentrations and biochemical response to GLM treatment (fecal calprotectin, serum C-reactive protein (CRP) and albumin). All patients started induction treatment with 200 mg GLM SC at day one and 100 mg SC at day 14. From week 6, maintenance treatment followed with 50 mg SC or 100 mg SC based on weight every four weeks. Serum samples were collected at day 0 and at day four, seven, 14, 18, 28, 42 and 56 to measure GLM serum concentrations, anti-GLM antibody levels, CRP and albumin concentrations. Fecal samples were collected for the measurement of fecal calprotectin and fecal GLM concentrations. During maintenance treatment, follow-up occurred at week 18, 21, 30, 33, 42, 45 and 52. Total follow-up was 52 weeks. At week eight, 12 out of 20 patients (60%) showed an endoscopic response. Patients with endoscopic response at week eight had numerically higher median GLM serum concentrations at week two compared to endoscopic non-responders (p=0.384). At week 52, 3/20 patients achieved endoscopic remission and continued GLM treatment. Population pharmacokinetic

analysis showed an inverse association between albumin concentrations and GLM clearance. GLM concentrations were undetectable in fecal samples. Author noted limitations included the uncontrolled/blinded study design with a small patient population and short term follow-up. Due to the limited sample size, no firm conclusions can be drawn regarding possible associations between drug exposure and clinical and endoscopic outcomes. The authors concluded that following induction therapy, 60% of the patients showed endoscopic response. During maintenance therapy, about one third of patients discontinued GLM treatment because of loss of response. There might be a benefit for dose optimization. No health disparities were identified by the investigators.

Further long-term studies with large patient populations are needed to help identify the exact concentration ranges predictive of clinical and endoscopic remission for certolizumab, golimumab, natalizumab, ustekinumab and vedolizumab. Additionally, studies are needed to confirm that dose optimization based on therapeutic drug monitoring improves clinical outcomes (Restellini and Afif, 2021; Boland, et al., 2019; Hanžel, et al., 2019; Restellini, et al, 2018; Ricciuto, et al., 2018; Detrez, et al., 2016).

Professional Societies/Organizations

American College of Gastroenterology (ACG): The 2019 ACG clinical guideline on ulcerative colitis in adults 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).

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).

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD		No National Coverage Determination found	
LCD		No Local Coverage Determinations found	

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare & Medicaid Services (CMS) code updates may occur more frequently than policy updates.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Fecal Calprotectin

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
83993	Calprotectin, fecal

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
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

ICD-10-CM Diagnosis Codes	Description
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
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, unspecified

ICD-10-CM Diagnosis Codes	Description
K59.31	Toxic megacolon
R19.7	Diarrhea, unspecified

Not covered or reimbursable:

ICD-10-CM Diagnosis Codes	Description
	All other codes

Testing for Serological and/or Genetic Markers

Considered Experimental/Investigational/Unproven when used to report testing for serological and/or genetic 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)
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)
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

Therapeutic Drug Monitoring

Considered Experimental/Investigational/Unproven when used to report therapeutic drug monitoring (TDM) for the measurement of serum drug levels and/or antibodies individually or as part of a test panel for agents listed in the coverage policy:

CPT®* Codes	Description
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
K51.014	Ulcerative (chronic) pancolitis with abscess
K51.018	Ulcerative (chronic) pancolitis with other complication
K51.019	Ulcerative (chronic) pancolitis with unspecified complications

ICD-10-CM Diagnosis Codes	Description
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
K51.919	Ulcerative colitis, unspecified with unspecified complications
K58.0	Irritable bowel syndrome with diarrhea

ICD-10-CM Diagnosis Codes	Description
K58.1	Irritable bowel syndrome with constipation
K58.2	Mixed irritable bowel syndrome
K58.8	Other irritable bowel syndrome
K58.9	Irritable bowel syndrome, unspecified
K59.31	Toxic megacolon

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Revision Details

Type of Revision	Summary of Changes	Date
Annual Review	• No policy statement changes.	03/15/2024
Focused Review	• No policy statement changes.	11/01/2024