Medical Coverage Policy

Effective Date.....03/15/2026
Next Review Date.....03/15/2027
Coverage Policy Number..... 0121

Fecal Calprotectin Testing

Table of Contents

Related Coverage Resources

Laboratory Testing Services
Laboratory Management Guidelines
Pharmacogenetic Testing

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted 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 fecal calprotectin testing used in the evaluation and management of inflammatory bowel disease (IBD) and other indications.

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.

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

ICD-10-CM Diagnosis Codes	Description
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
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

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

Not Covered or Reimbursable:

ICD-10-CM Diagnosis Codes	Description
	All other codes

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 gastrointestinal (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 GI 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 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, 2025). 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, fecal calprotectin (FC) 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, 2025).

Fecal Calprotectin

Fecal calprotectin (FC) is a neutrophil-derived protein that functions as a noninvasive biomarker of intestinal mucosal inflammation. FC testing supports the evaluation of individuals with chronic diarrhea by helping distinguish inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, from non-inflammatory conditions such as irritable bowel syndrome (IBS). In the initial assessment of symptomatic individuals, FC is a useful screening tool for identifying those who are more likely to require endoscopic evaluation for suspected IBD. A threshold of 50 mg/g is commonly used in adults and in children older than 4 years, although there remains a lack of consensus concerning the optimal thresholds. FC testing outperforms serum inflammatory markers and helps to avoid unnecessary endoscopy. In individuals with confirmed IBD, FC levels correlate closely with endoscopic and histologic inflammation and are valuable for monitoring disease activity, treatment response, and mucosal healing. High concentrations generally indicate active inflammation, while persistently elevated values may predict clinical relapses several

months before symptoms develop. FC testing is incorporated into treat-to-target management strategies and assists clinicians in determining when therapy should be adjusted, when endoscopy is indicated, and when to evaluate for postoperative disease recurrence in Crohn's disease. Although FC is a sensitive marker of intestinal inflammation, it is not disease-specific. Elevated results may also occur with gastrointestinal infections, colonic polyps, diverticulosis, colorectal neoplasia, gastrointestinal bleeding, or other inflammatory conditions. FC values should therefore be interpreted within the broader clinical context (Kapel, et al., 2023).

U.S. Food and Drug Administration (FDA)
Fecal calprotectin immunological test systems are FDA-regulated Class II medical devices overseen through the 510(k) pathway. These systems are indicated to quantitatively measure fecal calprotectin in human stools and serve as an aid in the diagnosis of inflammatory bowel disease (IBD). When used alongside clinical assessment and other laboratory findings, they also assist in differentiating IBD from irritable bowel syndrome (IBS) (FDA, 2026).

Device or Product	Identifier	Manufacturer
BÜHLMANN fCAL® turbo and CALEX® Cap	K232057	Buhlmann Laboratories AG
ALPCO Calprotectin Immunoturbidimetric Assay	K220763	ALPCO
LIAISON Calprotectin, LIAISON Q.S.E.T. Device Plus	K213858	DiaSorin, Inc.
Calprest® EasyCal	K191589	Eurospital S.P.A.

*FDA product codes: NXO

Note: Coverage decisions are not based solely on FDA approval. Device or product names are provided for example purposes only. Their inclusion does not indicate endorsement or preference for any specific brand or model. This list is not intended to reflect all available products or technologies.

Literature Review
Evidence from peer-reviewed literature demonstrates that fecal calprotectin (FC) is a clinically meaningful, noninvasive biomarker that supports differentiation of irritable bowel syndrome (IBS) from inflammatory bowel disease (IBD) and informs ongoing IBD management. FC has been evaluated across randomized controlled trials, prospective and retrospective cohort studies, cross-sectional analyses, and biomarker validation studies, with comparisons to endoscopic and histologic indices, serum markers, composite noninvasive models, clinical activity scores, imaging modalities, and alternative fecal biomarkers. FC correlates strongly with clinical activity and mucosal healing in ulcerative colitis (Steinsbø et al., 2025; Chen et al., 2021; State et al., 2021; Sandborn et al., 2016) and demonstrates high diagnostic accuracy for detecting treatment response in active Crohn's disease (Brodersen et al., 2025; Waljee et al., 2019), with levels appropriately decreasing following effective therapy and predicting the need for therapeutic adjustment or surgery in individuals receiving infliximab (Engström et al., 2019). FC also supports proactive monitoring strategies, including early detection of subclinical inflammation and relapse prediction in asymptomatic IBD patients (Heida et al., 2017), and effectively predicts relapse following mucosal healing in ulcerative colitis (Yamamoto et al., 2018), with systematic review and meta-analytic evidence validating FC as a reliable surrogate marker for relapse prediction (Li et al., 2019). Additional studies confirm FC's utility in guiding treatment decisions across pediatric and adult populations (Ricciuto et al., 2021; Colombel et al., 2017; El Matary et al., 2017; Abej et al., 2016) and in the postoperative setting, where elevated FC correlates with recurrence and provides high sensitivity for detecting inflammatory activity (Samnani et al., 2025; Verdejo et al., 2018; Hukkinen et al., 2016). Moreover, FC values in IBS remain comparable to healthy

controls, consistent with the absence of neutrophil-driven inflammation and supporting its utility in distinguishing IBS from IBD (Venge et al., 2025). Collectively, these findings support FC as a medically necessary tool for differentiating IBS from IBD and optimizing IBD management through inflammation detection, relapse prediction, and monitoring of treatment response.

Professional Societies/Organizations
The **American College of Gastroenterology (ACG)** 2025 clinical guideline on management of Chron's Disease in adults strongly supports the use of fecal calprotectin (FC) testing as a first-line, noninvasive biomarker to differentiate inflammatory bowel disease (IBD) from non-inflammatory conditions in symptomatic individuals. This recommendation is supported by moderate-quality evidence derived from systematic reviews, meta-analyses, and high-quality observational diagnostic studies. FC also complements stool pathogen testing in patients with suspected active Crohn's disease. Because FC is sensitive but not disease-specific, results must be interpreted within the overall clinical and diagnostic context (Lichtenstein, et al., 2025).

The 2025 **American College of Gastroenterology (ACG)** guideline update addressing ulcerative colitis in adults strongly recommends fecal calprotectin testing to assess response to therapy, evaluate suspected relapse, and monitor disease activity during maintenance. A strong recommendation indicates that the benefits clearly outweigh potential harms and that most clinicians should use this approach in routine practice. This recommendation is supported by moderate quality evidence from systematic reviews, meta-analyses, and high-quality diagnostic and monitoring studies. Fecal calprotectin is a sensitive and noninvasive marker of neutrophil mediated intestinal inflammation that correlates closely with clinical remission, endoscopic activity, and histologic healing. Meta analytic data demonstrate high diagnostic accuracy for detecting endoscopic inflammation, and elevated levels predict increased risk of relapse and the potential need for rescue therapy in acute severe colitis. Because fecal calprotectin may be affected by infections, use of nonsteroidal anti-inflammatory drugs (NSAIDs) or proton pump inhibitors, obesity, and intra patient variability, and may be normal or borderline in mild disease, results should be interpreted within the full clinical and diagnostic context (Rubin, et al., 2025).

In the 2021 **American College of Gastroenterology (ACG)** clinical guideline for the management of irritable bowel syndrome, using fecal calprotectin or fecal lactoferrin along with C-reactive protein to exclude inflammatory bowel disease (IBD) in adults without alarm features who present with suspected IBS and diarrhea is recommended. This is supported by moderate-quality evidence from cohort studies, systematic reviews, and meta-analyses demonstrating that fecal calprotectin offers superior negative predictive value compared with serologic markers such as ESR and CRP and reliably differentiates IBS from IBD across multiple cutoff thresholds. As a sensitive, noninvasive indicator of intestinal inflammation, fecal calprotectin improves diagnostic accuracy in IBS-D and helps avoid unnecessary invasive testing when interpreted within the clinical context (Lacy et al., 2021).

The **American Gastroenterological Association (AGA)** 2023 clinical practice guideline on the role of biomarkers for the management of Crohn's disease (CD) conditionally endorses fecal calprotectin (FC) as a noninvasive biomarker to assess and monitor intestinal inflammation in CD. Recommendations are based on moderate- to low-quality evidence from systematic reviews, diagnostic accuracy meta-analyses, prospective cohorts, and limited randomized data. Across studies, FC correlates more reliably with endoscopic inflammation than symptoms alone and may reduce unnecessary endoscopy when interpreted in clinical context (Ananthakrishnan, et al., 2023).

The 2023 **American Gastroenterological Association (AGA)** clinical practice guideline on the role of biomarkers for the management of ulcerative colitis (UC) supports fecal calprotectin (FC) as a valuable noninvasive biomarker for assessing inflammatory activity and guiding disease

monitoring. This conditional recommendation is based on moderate- to low-quality evidence from systematic reviews, pooled diagnostic accuracy studies, and prospective relapse-prediction cohorts. The guideline concludes that FC correlates more closely with endoscopic inflammation than symptoms alone and can meaningfully inform clinical decision-making. In asymptomatic patients, low FC levels can help rule out significant inflammation and limit the need for routine endoscopy, while elevated values in remission identify individuals at increased risk of near-term relapse. In active disease, FC helps differentiate inflammatory flares from functional symptoms and can reinforce treatment adjustment decisions in those with more pronounced symptoms. The guideline notes that FC is less reliable in limited-extent disease, such as isolated proctitis, and cannot replace endoscopy when symptoms and biomarkers disagree or when major therapy decisions are being considered (Singh, et al., 2023).

The **American Gastroenterological Association (AGA)** 2019 clinical practice guideline on the laboratory evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome (IBS-D) in adults recommends fecal calprotectin as a noninvasive screening tool to help distinguish functional diarrhea and IBS-D from inflammatory bowel disease. This conditional recommendation is supported by low-quality evidence derived from pooled diagnostic accuracy studies that evaluated FC against established reference standards for intestinal inflammation. Across these studies, FC consistently demonstrated higher sensitivity and specificity for detecting IBD than serologic inflammatory markers, though study heterogeneity, risk of bias, and imprecision limited the certainty of the overall evidence. The guideline emphasizes that FC testing can reduce unnecessary invasive evaluation by reliably identifying patients unlikely to harbor underlying IBD when used in the appropriate clinical context, namely, immunocompetent adults presenting with chronic watery diarrhea without alarm features. While FC does not diagnose IBS itself, its use helps exclude inflammatory conditions and supports a more efficient, evidence-based diagnostic pathway (Smalley, et al., 2019).

In its 2021 clinical practice update on the management of inflammatory bowel disease in older adults, the **American Gastroenterological Association (AGA)** notes a selective role for fecal calprotectin as part of the diagnostic evaluation. Because elderly patients often present with symptoms that overlap with multiple non-IBD conditions—such as ischemic colitis, diverticular-associated colitis, colorectal cancer, medication-induced colitis, or microscopic colitis—the guideline emphasizes the importance of accurate triage prior to colonoscopy. Fecal calprotectin is identified as a helpful noninvasive tool to prioritize patients with a lower probability of IBD for endoscopic evaluation when the diagnosis is uncertain or when invasive testing may carry elevated procedural risks due to comorbidity, frailty, or polypharmacy. Evidence supporting its use in this context is extrapolated from general adult studies, as elderly individuals remain underrepresented in clinical trials; thus, recommendations are based on expert consensus rather than new age-specific performance data. Overall, fecal calprotectin may aid diagnostic decision-making in older adults with low suspicion for IBD, but it is not presented as a standalone strategy and does not alter the broader diagnostic or therapeutic approach (Ananthakrishnan, et al., 2021).

Other Indications

Fecal calprotectin (FC) testing has been investigated for a broad range of potential indications, including but not limited to the evaluation and/or management of: autism spectrum disorder (Mathew et al., 2024); celiac disease (Segura et al., 2025); cerebral palsy (Mickiewicz-Góra et al., 2024); cryptoglandular disease (Becker et al., 2025); cystic fibrosis (Roca et al., 2024; Lazzarotto et al., 2023); food allergies and related conditions (Seidita et al., 2024; Nagata et al., 2024); liver disease (Dinçer et al., 2024); necrotizing enterocolitis (Erol et al., 2025; Hong et al., 2023); and Parkinson's disease (Rajkovaca Latic et al., 2024; Ahmad Fadzuli et al., 2024; Al-Kuraishy et al., 2023; Schwiertz et al., 2018). The peer-reviewed scientific literature evaluating FC in these conditions consists primarily of observational studies, feasibility studies, and

systematic reviews of non-experimental data. Across indications, the evidence is limited by small sample sizes, heterogeneous methodologies, lack of appropriate comparators, and short follow-up durations. Currently, no fecal calprotectin assays are FDA-approved for any of these indications, and the available evidence remains insufficient to draw conclusions regarding the use of FC testing for these conditions.

Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing, transportation, and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

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, 2025).

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).

References

1. Abej E, El-Matary W, Singh H, Bernstein CN. The Utility of Fecal Calprotectin in the Real-World Clinical Care of Patients with Inflammatory Bowel Disease. Can J Gastroenterol Hepatol. 2016;2016:2483261. Epub 2016 Sep 28.

2. Agrawal M, Spencer EA, Colombel JF, Ungaro RC. Approach to the Management of Recently Diagnosed Inflammatory Bowel Disease Patients: A User's Guide for Adult and Pediatric Gastroenterologists. Gastroenterology. 2021 Jul;161(1):47-65.

3. Ahmad Fadzuli NI, Lim SM, Neoh CF, Majeed ABA, Tan MP, Khor HM, Tan AH, Ramasamy K. Faecal intestinal permeability and intestinal inflammatory markers in older adults with age-related disorders: A systematic review and meta-analysis. Ageing Res Rev. 2024 Nov;101:102506. doi: 10.1016/j.arr.2024.102506. Epub 2024 Sep 19. PMID: 39306247.

4. Al-Kuraishy HM, Al-Gareeb AI, Zaidalkiani AT, Alexiou A, Papadakis M, Bahaa MM, Al-Faraga A, Batiha GE. Calprotectin in Parkinsonian disease: Anticipation and dedication. Ageing Res Rev. 2024 Jan;93:102143. doi: 10.1016/j.arr.2023.102143. Epub 2023 Nov 25. PMID: 38008403

5. Ananthakrishnan AN, Adler J, Chachu KA, Nguyen NH, Siddique SM, Weiss JM, Sultan S, Velayos FS, Cohen BL, Singh S; AGA Clinical Guidelines Committee. AGA Clinical Practice Guideline on the Role of Biomarkers for the Management of Crohn's Disease. Gastroenterology. 2023 Dec;165(6):1367-1399. doi: 10.1053/j.gastro.2023.09.029. PMID: 37981354. Accessed Jan 6, 2026. Available at URL address: https://gastro.org/clinical-guidance/

6. Ananthakrishnan AN, Nguyen GC, Bernstein CN. AGA Clinical Practice Update on management of inflammatory bowel disease in elderly patients: expert review. Gastroenterology. 2021 Jan;160(1):445-451. doi:10.1053/j.gastro.2020.08.060.

7. Bar-Gil Shitrit A, Koslowsky B, Livovsky DM, Shitrit D, Paz K, Adar T, et al. A prospective study of fecal calprotectin and lactoferrin as predictors of small bowel Crohn's disease in patients undergoing capsule endoscopy. Scand J Gastroenterol. 2017 Mar;52(3):328-333.

8. Becker MAJ, Stevens TW, de Voogd FAE, Wildenberg ME, D'Haens GRAM, Gecse KB, Buskens CJ. Clinical relevance of calprotectin in patients with perianal fistulas in Crohn's disease and cryptoglandular fistulas. United European Gastroenterol J. 2025 Apr;13(3):295-304. doi: 10.1002/ueg2.12622. Epub 2024 Dec 16. PMID: 39680482; PMCID: PMC11999044.

9. Bonis PAL, Lamont JT. Approach to the adult with chronic diarrhea in resource-abundant settings. In: UpToDate, Friedman LS, Grover S. (Eds), UpToDate, Waltham, MA. Literature review current through: Dec 2025. Topic last updated: Oct 24, 2025. Accessed Jan 9, 2026.

10. Brodersen JB, Rafaelsen SR, Juel MA, Knudsen T, Kjeldsen J, Jensen MD. Assessment of Treatment Response in Known Crohn's Disease-A Prospective Blinded Study Comparing the Diagnostic Accuracy of Intestinal Ultrasound, Magnetic Resonance Enterocolonography, Panenteric Capsule Endoscopy, and Fecal Calprotectin. Inflamm Bowel Dis. 2025 Jul 7;31(7):1891-1901. doi: 10.1093/ibd/izae254. PMID: 39495122.

11. Chen F, Hu Y, Fan YH, Lv B. Clinical Value of Fecal Calprotectin in Predicting Mucosal Healing in Patients With Ulcerative Colitis. Front Med (Lausanne). 2021 Aug 3;8:679264.

12. Edwards SJ, Barton S, Bacelar M, Karner C, Cain P, Wakefield V, et al. Prognostic tools for identification of high risk in people with Crohn's disease: systematic review and cost-effectiveness study. Health Technol Assess. 2021 Mar;25(23):1-138.

13. El-Matary W, Abej E, Deora V, Singh H, Bernstein CN. Impact of Fecal Calprotectin Measurement on Decision-making in Children with Inflammatory Bowel Disease. Front Pediatr. 2017 Jan 25;5:7.

14. Engström J, Lönnkvist M, Befrits R, Ljung T, Diaz-Tartera H, Holst M, et al. Comparison of fecal calprotectin and serum C-reactive protein in early prediction of outcome to infliximab induction therapy. Scand J Gastroenterol. 2019 Sep;54(9):1081-1088.

15. Erol S, Tayman C, Korkut S, Çakir U, Kurt A, Koyuncu I. A comparative study of serum and fecal calprotectin levels in necrotizing enterocolitis. J Pediatr (Rio J). 2025 Sep-Oct;101(5):101428. doi: 10.1016/j.jped.2025.101428. Epub 2025 Aug 21. PMID: 40784368; PMCID: PMC12495589.

16. Heida A, Park KT, van Rheenen PF. Clinical Utility of Fecal Calprotectin Monitoring in Asymptomatic Patients with Inflammatory Bowel Disease: A Systematic Review and Practical Guide. Inflamm Bowel Dis. 2017 Jun;23(6):894-902.

17. Hong L, Huang Y, Jiang S, Han J, Li S, Zhang L, Zhou Q, Cao X, Yu W, Yang Y, Cao Y. Postnatal Dynamics and Clinical Associations of Fecal Calprotectin in Very Preterm Infants: Implications for Necrotizing Enterocolitis and Feeding Intolerance. Clin Transl Gastroenterol. 2023 Aug 1;14(8):e00604. doi: 10.14309/ctg.0000000000000604. PMID: 37272666; PMCID: PMC10461937.

18. Hukkinen M, Pakarinen MP, Merras-Salmio L, Koivusalo A, Rintala R, Kolho KL. Fecal calprotectin in the prediction of postoperative recurrence of Crohn's disease in children and adolescents. J Pediatr Surg. 2016 Sep;51(9):1467-72.

19. Kapel N, Ouni H, Benahmed NA, Barbot-Trystram L. Fecal Calprotectin for the Diagnosis and Management of Inflammatory Bowel Diseases. Clin Transl Gastroenterol. 2023 Sep 1;14(9):e00617. doi: 10.14309/ctg.0000000000000617. PMID: 37440723; PMCID: PMC10522095.

20. Kaplan GG, Ng SC. Epidemiology, Pathogenesis, and Diagnosis of Inflammatory Bowel Diseases. In: Feldman M, Friedman LS, Brandt LJ. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th ed. Philadelphia, PA: Elsevier, Inc; 2021. Ch 115. pgs 1868-97.e7.

21. Lacy BE, Pimentel M, Brenner DM, Chey WD, Keefer LA, Long MD, Moshiree B. ACG Clinical Guideline: Management of Irritable Bowel Syndrome. Am J Gastroenterol. 2021 Jan 1;116(1):17-44. doi: 10.14309/ajg.0000000000001036. PMID: 33315591. Accessed Jan 6, 2026. Available at URL address: https://gi.org/guidelines/

22. Lazzarotto ES, Vasco JFM, Führ F, Riedi CA, Filho NAR. Systematic review on fecal calprotectin in cystic fibrosis. J Pediatr (Rio J). 2023 Jan-Feb;99(1):4-10. doi: 10.1016/j.jped.2022.01.006. Epub 2022 May 3. PMID: 35523321; PMCID: PMC9875247.

23. Li J, Zhao X, Li X, Lu M, Zhang H. Systematic Review with Meta-Analysis: Fecal Calprotectin as a Surrogate Marker for Predicting Relapse in Adults with Ulcerative Colitis. Mediators Inflamm. 2019 May 28;2019:2136501.

24. Lichtenstein GR, Loftus EV, Afzali A, Long MD, Barnes EL, Isaacs KL, Ha CY. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. 2025 Jun

3;120(6):1225-1264. doi: 10.14309/ajg.0000000000003465. PMID: 40701562. Accessed Jan 6, 2026. Available at URL address: https://gi.org/guidelines/

25. Mathew NE, McCaffrey D, Walker AK, Mallitt KA, Masi A, Morris MJ, Ooi CY. The search for gastrointestinal inflammation in autism: a systematic review and meta-analysis of non-invasive gastrointestinal markers. Mol Autism. 2024 Jan 17;15(1):4. doi: 10.1186/s13229-023-00575-0. PMID: 38233886; PMCID: PMC10795298.

26. Mickiewicz-Góra D, Sznurkowska K, Skonieczna-Żydecka K, Drozd A, Borkowska A, Zagierski M, Troch J, Szlagatys-Sidorkiewicz A. Markers of Intestinal Permeability and Inflammation in Enterally Fed Children with Cerebral Palsy. Nutrients. 2024 Jul 27;16(15):2447. doi: 10.3390/nu16152447. PMID: 39125328; PMCID: PMC11314602.

27. Nagata M, Inage E, Yamada H, Kudo T, Toriumi S, Sakaguchi K, Tanaka Y, Jimbo K, Ohtsuka Y, Shimizu T. Efficacy of sequential fecal-marker examination for evaluating gastrointestinal inflammation in solid food protein-induced enterocolitis syndrome. Allergol Int. 2024 Oct;73(4):556-562. doi: 10.1016/j.alit.2024.05.001. Epub 2024 May 15. PMID: 38749792.

28. Peppercorn MA, Cheifetz AS. Definitions, epidemiology, and risk factors for inflammatory bowel disease. In: UpToDate, Kane SV, Robson KM. (Eds), UpToDate, Waltham, MA. Literature review current through: Dec 2025. Topic last updated: Jan 5, 2026. Accessed Jan 9, 2026.

29. Rajkovaca Latic I, Popovic Z, Mijatovic K, Sahinovic I, Pekic V, Vucic D, Cosic V, Miskic B, Tomic S. Association of intestinal inflammation and permeability markers with clinical manifestations of Parkinson's disease. Parkinsonism Relat Disord. 2024 Jun;123:106948. doi: 10.1016/j.parkreldis.2024.106948. Epub 2024 Mar 27. PMID: 38554664.

30. Ricciuto A, Aardoom M, Orlanski-Meyer E, Navon D, Carman N, Aloi M. Predicting Outcomes in Pediatric Crohn's Disease for Management Optimization: Systematic Review and Consensus Statements From the Pediatric Inflammatory Bowel Disease-Ahead Program. Gastroenterology. 2021 Jan;160(1):403-436.e26.

31. Roca M, Masip E, Colombo C, Boon M, Hulst JM, Garriga M, de Koning BAE, Bulfamante A, de Boeck K, Ribes-Koninckx C, Calvo-Lerma J. Long-term evaluation of faecal calprotectin levels in a European cohort of children with cystic fibrosis. Arch Dis Child. 2024 Jun 19;109(7):552-556. doi: 10.1136/archdischild-2023-326221. PMID: 38123920.

32. Rubin DT, Ananthakrishnan AN, Siegel CA, Barnes EL, Long MD. ACG Clinical Guideline Update: Ulcerative Colitis in Adults. Am J Gastroenterol. 2025 Jun 3;120(6):1187-1224. doi: 10.14309/ajg.0000000000003463. PMID: 40701556. Accessed Jan 6, 2026. Available at URL address: https://gi.org/guidelines/

33. Samnani S, Ray CM, Gill P, Stein L, Buhler KA, Leong RW, Smith RL, De Cruz P, Kaplan GG, Seow CH, Lu C, Guizzetti L, Hoentjen F, Marshall JK, Singh S, Panaccione R, Novak KL, Ma C. Diagnostic Accuracy of Noninvasive Biomarkers and Imaging for Evaluating Postoperative Recurrence in Crohn's Disease. Clin Gastroenterol Hepatol. 2025 Dec;23(13):2433-2447.e9. doi: 10.1016/j.cgh.2025.03.030. Epub 2025 Jun 2. PMID: 40467019; PMCID: PMC12354279.

34. Sandborn WJ, Panés J, Zhang H, Yu D, Niezychowski W, Su C. Correlation Between Concentrations of Fecal Calprotectin and Outcomes of Patients With Ulcerative Colitis in a Phase 2 Trial. Gastroenterology. 2016 Jan;150(1):96-102.

35. Schwiertz A, Spiegel J, Dillmann U, Grundmann D, Bürmann J, Faßbender K, Schäfer KH, Unger MM. Fecal markers of intestinal inflammation and intestinal permeability are elevated in Parkinson's disease. Parkinsonism Relat Disord. 2018 May;50:104-107. doi: 10.1016/j.parkreldis.2018.02.022. Epub 2018 Feb 12. PMID: 29454662.

36. Segura V, Ruiz-Carnicer Á, Pizarro Á, González-Naranjo C, Díaz J, Coronel-Rodríguez C, Argüelles-Arias F, Garzón-Benavides M, Sousa C, Comino I. Limitations of Faecal Calprotectin in Detecting Histological Changes and Persistent Villous Atrophy in Patients With Coeliac Disease on a Gluten-Free Diet. Aliment Pharmacol Ther. 2025 Jun;61(11):1815-1819. doi: 10.1111/apt.70114. Epub 2025 Apr 2. PMID: 40170592; PMCID: PMC12074556.

37. Seidita A, Giuliano A, Soresi M, Chiavetta M, Nardi E, Mogavero G, Giannone G, Carroccio A, Mansueto P. Fecal calprotectin levels in patients with non-celiac wheat sensitivity: a proof of concept. Intern Emerg Med. 2024 Aug;19(5):1255-1266. doi: 10.1007/s11739-024-03595-7. Epub 2024 Apr 12. PMID: 38609737; PMCID: PMC11364563.

38. Singh S, Ananthakrishnan AN, Nguyen NH, Cohen BL, Velayos FS, Weiss JM, Sultan S, Siddique SM, Adler J, Chachu KA; AGA Clinical Guidelines Committee. AGA Clinical Practice Guideline on the role of biomarkers for the management of ulcerative colitis. Gastroenterology. 2023 Mar;164(3):344-372. doi:10.1053/j.gastro.2022.12.007. Accessed Jan 6, 2026. Available at URL address: https://gastro.org/clinical-guidance/

39. Smalley W, Falck-Ytter C, Carrasco-Labra A, Wani S, Lytvyn L, Falck-Ytter Y. AGA Clinical Practice Guidelines on the laboratory evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome in adults (IBS-D). Gastroenterology. 2019 Sep;157(3):851-854. doi:10.1053/j.gastro.2019.07.004. Accessed Jan 6, 2026. Available at URL address: https://gastro.org/clinical-guidance/

40. State M, Negreanu L, Voiosu T, Voiosu A, Balanescu P, Mateescu RB. Surrogate markers of mucosal healing in inflammatory bowel disease: A systematic review. World J Gastroenterol. 2021 Apr 28;27(16):1828-1840.

41. Steinsbø Ø, Aasprong OG, Aabakken L, Karlsen LN, Grimstad T. Fecal Calprotectin Correlates With Disease Extent but Remains a Reliable Marker of Mucosal Healing in Ulcerative Colitis. Am J Gastroenterol. 2025 Nov 1;120(11):2623-2631. doi: 10.14309/ajg.0000000000003339. Epub 2025 Jan 30. PMID: 39882797; PMCID: PMC12570616.

42. U.S. Food and Drug Administration (FDA). 510(k) premarket notification database. Product code(s): NXO. Page Last Updated: Jan 5, 2026. Accessed Jan 6, 2026. Available at URL address: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm

43. Venge P, Tejera VC, Petersson C, Xu S, Larsson A, Simrén M, Öhman L, Törnblom H. Elevated Fecal Biomarkers of Colo-Rectal Epithelial Cell Activity in Irritable Bowel Syndrome. Neurogastroenterol Motil. 2025 Apr;37(4):e14984. doi: 10.1111/nmo.14984. Epub 2024 Dec 17. PMID: 39688084; PMCID: PMC11996011.

44. Verdejo C, Hervías D, Roncero Ó, et al. Fecal calprotectin is not superior to serum C-reactive protein or the Harvey-Bradshaw index in predicting postoperative endoscopic recurrence in Crohn's disease. Eur J Gastroenterol Hepatol. 2018;30(12):1521–1527.

45. Waljee AK, Wallace BI, Cohen-Mekelburg S, Liu Y, Liu B, Sauder K, et al. Development and Validation of Machine Learning Models in Prediction of Remission in Patients With Moderate to Severe Crohn Disease. JAMA Netw Open. 2019 May 3;2(5):e193721.

46. Winter MW, Weinstock. Inflammatory Bowel Disease. In: Rose NR, Mackay IR. The Autoimmune Diseases. 6th ed. London, United Kingdom: Elsevier, Inc; 2020. Ch 46. pgs 871-894.

47. Yamamoto T, Shimoyama T, Umegae S, Matsumoto K. Endoscopic score vs. fecal biomarkers for predicting relapse in patients with ulcerative colitis after clinical remission and mucosal healing. Clin Transl Gastroenterol. 2018 Feb 20;9(3):136.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Review	• Title change • No clinical policy statement changes	3/15/2026
Annual Review	• Removed policy statements related to testing for serological and genetic markers for the diagnosis or management of IBD, and therapeutic drug monitoring for IBD	4/15/2025
Focused Review	• No policy statement changes	11/01/2024
Annual Review	• No policy statement changes	3/15/2024