02.04.33 Fecal Calprotectin and Lactoferrin Testing in the Diagnosis and Management of Inflammatory Bowel Disease

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Related Policies:

02.04.84 Serologic Testing for Biomarkers of Irritable Bowel Syndrome (IBS)

Summary

Description

Calprotectin is a calcium- and zinc-binding protein that is a potential marker of intestinal inflammation. Fecal calprotectin testing is proposed as a noninvasive means to diagnose inflammatory bowel disease (IBD). Other potential uses are to evaluate treatment response for individuals with IBD and as a marker of relapse.

Fecal lactoferrin is an iron-binding protein found inside neutrophils. The amount of lactoferrin released by neutrophils have been shown to correlate with the severity of inflammation in the gastrointestinal (GI) tract. Fecal lactoferrin testing is proposed as a noninvasive means to diagnose inflammatory bowel

disease (IBD). Other potential uses are to evaluate treatment response for individuals with IBD and as a marker of relapse.

Summary of Evidence

For individuals who have a suspicion of IBD when endoscopy with biopsy is being considered, who receive fecal calprotectin testing to guide decision to undergo endoscopy, the evidence includes prospective and retrospective diagnostic accuracy studies and systematic reviews. Relevant outcomes are test validity, symptoms, change in disease status, quality of life (QOL), hospitalizations, and medication use. Twenty-eight studies in a systematic review evaluated the diagnostic accuracy of fecal calprotectin in patients suspected of having IBD for whom noninflammatory bowel disease, such as irritable bowel syndrome (IBS), remains a consideration. Studies varied in the fecal calprotectin protein level cutoff used to indicate the presence of disease, but most used a cutoff of 50 µg/g, which is the recommended lower bound. Studies have indicated that, at this threshold, the test has a sensitivity of 93% to 99% for IBD and a negative predictive value of 73% to 100% for intestinal inflammation. Out of 100 cases of suspected IBD, approximately 49 invasive tests would be avoided with 1 case missed. In another meta-analysis involving 19 studies where the majority of studies again used the cutoff of 50 µg/g, investigators determined that out of 100 hypothetical patients, 18 non-disease patients would have a colonoscopy performed and 1 patient with IBD would not be referred for a colonoscopy. Additionally, it was determined that incorporating a fecal calprotectin test into the regular diagnostic work-up would reduce the need for colonoscopy by 66.7%. Therefore, fecal calprotectin can be used to inform a decision of whether to proceed with endoscopy. Moreover, a recent review found that fecal calprotectin is the most sensitive noninvasive test in distinguishing IBD from non-IBD with a sensitivity of 99%. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have active IBD who receive fecal calprotectin testing to monitor disease activity, the evidence includes systematic reviews and 2 randomized controlled trials (RCTs). Relevant outcomes are test validity, symptoms, change in disease status, QOL, hospitalizations, and medication use. A systematic review determined that a fecal calprotectin level of 50 µg/g was the optimum threshold for triaging patients for endoscopy when they have symptoms of active disease, and another found high sensitivity in assessing IBD activity. More RCTs are needed to determine whether guiding treatment based on fecal calprotectin levels can improve disease management. A 2017 RCT included fecal calprotectin as 1 of several indicators of inflammation to test the effect of tight control of IBD on health outcomes. The independent contribution of fecal calprotectin could not be determined from this study design. In another RCT, self-monitoring with a home-based fecal calprotectin test among patients with established IBD demonstrated an increase in the proportion of patients seeking medical treatment; compliance to home-based testing in this study was low (29%). The use of a home-based fecal calprotectin test that is not available in the US limits the applicability of this study. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. However, even though there is a paucity of data in the peer-reviewed scientific literature, relevant society guidelines (see Practice Guidelines and Position Statements below) support the use of fecal calprotectin in identified individuals who have active IBD. Therefore, those who have active IBD will be considered medically necessary for individuals when the policy criteria below have been met.

For individuals who have IBD in remission who receive fecal calprotectin testing to predict relapse, the evidence includes systematic reviews and RCT. Relevant outcomes are test validity, symptoms, change in disease status, QOL, hospitalizations, and medication use. A systematic review of studies that monitored fecal calprotectin in patients with IBD in remission demonstrated that fecal calprotectin levels began to rise 2 to 3 months before clinical relapse; an ideal fecal calprotectin cutoff for monitoring purposes was not identified. A meta-analysis of 24 prospective studies that monitored fecal calprotectin in patients in remission described an optimal cut-off value for fecal calprotectin of 152 µg/g and a pooled sensitivity and

specificity of fecal calprotectin of 72% and 74%, respectively. Another review found that fecal calprotectin had a sensitivity of 78% and specificity of 73% in predicting recurrence, although magnetic resonance enterography and ultrasound performed better. One RCT found no significant difference in the rate of relapse in patients whose medication was modified based on fecal calprotectin or standard clinical indicators, however, this RCT had design and conduct limitations that affected the interpretation of its results. Additional high-quality RCTs are needed to determine whether adding fecal calprotectin to standard clinical practice improves the management of IBD patients in remission. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. However, even though there is a paucity of data in the peer-reviewed scientific literature, relevant society guidelines (see Practice Guidelines and Position Statements below) support the use of fecal calprotectin in identified individuals who have IBD in remission. Therefore, those who have IBD in remission will be considered medically necessary for individuals when the policy criteria below have been met.

For individuals who have a suspicion of IBD, who have active IBD, or IBD in remission who receive fecal lactoferrin testing to diagnose, monitor disease activity, or predict relapse the evidence includes systematic reviews and meta-analyses. For disease activity there was 1 systematic review and meta-analysis and for disease diagnosis there was 1 meta-analysis. There were no systematic reviews or RCTs for those who have IBD and are in remission. Relevant outcomes are test validity, symptoms, change in disease status, QOL, hospitalizations, and medication use. For those being diagnosed the" sensitivity and specificity values for assessing ulcerative colitis (UC) activity were 0.81 [95% confidence interval (CI), 0.64-0.92] and 0.82 (95% CI, 0.61-0.93), respectively. And the pooled sensitivity and specificity values for assessing Crohn's disease (CD) activity were 0.82 [KP5] [HC6] (95% CI, 0.73-0.88) and 0.71 (95% CI, 0.63-0.78), respectively." "The pooled FL sensitivity and pooled specificity were 0.82 (95% confidence interval [CI]: 0.72, 0.89) and 0.95 (95% CI: 0.88, 0.98), respectively. The positive and negative likelihood ratios were 16.63 and 0.18, respectively. The area under the summary receiver-operating characteristic curve (SROC) was 0.95 (95% CI: 0.93, 0.97), and the diagnostic odds ratio was 90.04 (95% CI: 37.01, 219.02). The pooled FL sensitivity and specificity for Crohn's disease (CD) diagnosis (sensitivity =75%, specificity =100%) was not as good as it was for ulcerative colitis (UC) diagnosis (sensitivity =82%, specificity =100%)." Studies varied in the fecal lactoferrin cutoffs used to indicate the presence of disease." A limitation to the fecal lactoferrin test itself is it does not measure systemic inflammation, rather it measures local inflammation in the GI ("neutrophilic intestinal inflammation") but is not specific to IBD. Because of this, the FL level elevations could be indicative of other conditions, such as colorectal polys or cancer. Thus, it may be a better tool at detecting disease activity vs differentiating IBD from other diseases. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. However, even though there is a paucity of data in the peer-reviewed scientific literature, relevant society guidelines (see Practice Guidelines and Position Statements below) support the use of fecal lactoferrin in identified individuals. Therefore, those who have a suspicion of IBD, who have active IBD, or IBD in remission will be considered medically necessary for individuals when the policy criteria below have been met.

2018 Input

Clinical input was sought to help determine whether the use of fecal calprotectin testing for individuals with suspected IBD when endoscopy with biopsy is being considered would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 3 respondents, including 1 specialty society-level response and 2 physician-level responses identified through specialty societies including physicians affiliated with academic medical centers.

For individuals who have suspected IBD (when endoscopy with biopsy is being considered) who receive fecal calprotectin testing, clinical input supports this use provides a clinically meaningful improvement in

net health outcome and indicates this use is consistent with generally accepted medical practice. Specifically, fecal calprotectin testing can inform the decision by using a positive fecal calprotectin result to refer for endoscopy with biopsy, or to use negative fecal calprotectin results to exclude IBD and avoid endoscopy with biopsy, with acceptably low tradeoffs in missed diagnoses of IBD in those who have false-negative fecal calprotectin results. Input further highlighted that the use of fecal calprotectin is particularly important in pediatric populations, where children may not be able to fully participate as medical historians and may have non-specific and/or atypical symptoms.

Further details on clinical input are included in the Supplemental Information and Appendix.

OBJECTIVE

The objective of this evidence review is to determine whether fecal calprotectin and lactoferrin testing improves the net health outcome in individuals with or suspected of having inflammatory bowel disease.

PRIOR APPROVAL

Not applicable.

POLICY

Medically Necessary

Fecal calprotectin or lactoferrin testing may be considered **medically necessary** to establish the diagnosis, management of active disease, or disease relapse of inflammatory bowel disease (IBD) [(i.e., Crohn's disease or ulcerative colitis (UC)].

Investigational

Fecal calprotectin or lactoferrin testing is considered **investigational** when the criteria above is not met including but not limited to when not used in diagnosis or decision making for of inflammatory bowel disease (IBD) (i.e. Crohn's disease or ulcerative colitis (UC)) because the evidence is insufficient to determine the technology results in an improvement in the net health outcomes.

POLICY GUIDELINES

Note:
Iowa House File 2668 (Iowa Code section 514C.36) requires that certain health plans issued or renewed on or after January 1, 2025 "provide coverage for biomarker testing for the purposes of diagnosing, treating, appropriately managing, or monitoring a disease or condition in a covered person when the biomarker testing has demonstrated clinical utility." Iowa House File 2668 defines clinical utility as "sufficient medical and scientific evidence indicating that the use of a biomarker test will provide meaningful information that affects treatment decisions and guides improvement of net health outcomes, including an improved quality of life or longer survival." Wellmark has reviewed this Medical Policy in light of Iowa House File 2668.

A fecal calprotectin level of less than 50 µg/g is suggestive of a low likelihood of inflammatory bowel disease.

A fecal lactoferrin with a threshold value in the range of 4.0–7.25 mg/g is recommended to optimize sensitivity.

Coding
See the Codes table for details.

BACKGROUND

Inflammatory Bowel Disease
Inflammatory bowel disease (IBD) is a chronic condition that encompasses 2 main forms: Crohn's disease and ulcerative colitis. These conditions overlap in clinical and pathologic characteristics but have distinct features. Crohn's disease can involve the entire gastrointestinal (GI) tract and is characterized by transmural inflammation. Ulcerative colitis involves inflammation limited to the mucosal layer of the colon, almost always involving the rectum.

IBD is suggested by the presence of 1 or more of a variety of signs and symptoms that can be GI (e.g., abdominal pain, bloody diarrhea, perianal fistulae), systemic (e.g., weight loss, fatigue, growth failure in children), or extraintestinal (e.g., characteristic rashes, uveitis, arthritis) in nature. Patients may present with or develop a range of severity of symptoms in the disease course, including life-threatening illness.

Diagnosis
Diagnosing IBD is associated with well-defined management changes. A typical diagnostic approach to IBD includes stool testing for enteric pathogens, blood tests (complete blood count, inflammatory markers) to differentiate etiologies and evaluate disease severity, as well as small bowel imaging and endoscopy (upper GI, colonoscopy) with biopsies.

Fecal Calprotectin
In some cases, the clinical manifestations of IBD can be non-specific and suggestive of other disorders, including infectious colitis, colon cancer, and functional bowel disorders, including irritable bowel syndrome (IBS).

Thus, there is a need for simple, accurate, noninvasive tests to detect intestinal inflammation. Potential noninvasive markers of inflammation fall into several categories, including serologic and fecal. Serologic markers such as C-reactive protein and anti-neutrophil cytoplasmic antibodies tend to have low sensitivity and specificity for intestinal inflammation because they are affected by inflammation outside the GI tract. Fecal markers, in contrast, have the potential to be more specific to the diagnosis of GI tract disorders, because their levels are not elevated in extra-digestive processes. Fecal leukocyte testing has been used to evaluate whether there is intestinal mucosal inflammation. The level of fecal leukocytes can be determined by the microscopic examination of fecal specimens; however, leukocytes are unstable and must be evaluated promptly by skilled personnel. There is interest in identifying stable proteins in stool specimens, which may be representative of the presence of leukocytes, rather than evaluating leukocyte levels directly.

Calprotectin is a protein that could be used as a marker of inflammation. It is a calcium- and zinc-binding protein that accounts for approximately 30 to 60% of the neutrophil’s cytoplasmic proteins. It is released from neutrophils during activation or apoptosis/necrosis and has a role in regulating inflammatory processes. In addition to potentially higher sensitivity and specificity than serologic markers, another advantage of calprotectin as a marker is that it has been shown to be stable in feces at room temperature for up to one week, leaving enough time for patients to collect samples at home and send them to a laboratory for testing. A sample of a few grams of stool is sufficient enough for testing. A 50 mg/g fecal calprotectin concentration in a stool sample is usually recommended as the cutoff for the normal concentration for adults and children older than 4 years. Moderate increases in fecal calprotectin levels, up to 100 mg/g, have been described for individuals older than 65 years. The concentration of fecal

calprotectin is physiologically higher for neonates, infants, and young children, and thus fecal calprotectin concentrations in this population should be interpreted with caution.

Among potential disadvantages of fecal calprotectin as a marker of inflammation are that fecal calprotectin levels increase after the use of some medications (i.e., nonsteroidal anti-inflammatory drugs; proton pump inhibitors), and that levels may change with other factors such as age, low fiber intake, and lack of exercise; other clinical situations associated with mucosal inflammation may also cause elevated fecal calprotectin levels such as GI bleeding. Moreover, there is uncertainty about the optimal cutoff to distinguish between IBD and noninflammatory disease.

Fecal calprotectin testing has been used to differentiate between organic (e.g., inflammation) and functional (no visible problem in the GI tract like IBS) disease. Some consider fecal calprotectin to be a marker of neutrophilic intestinal inflammation rather than a marker of organic disease and believe it has utility to distinguish between IBD and non-IBD. In practice, the test might be suitable for selecting patients with IBD symptoms for endoscopy (i.e., deciding which patients do not require endoscopy). Fecal calprotectin testing has also been proposed to evaluate the response to IBD treatment and for predicting relapse. If found to be sufficiently accurate, the results of calprotectin testing could be used to change treatment, such as adjusting medication levels.

Fecal Lactoferrin

Abraham et al reported (2018) fecal lactoferrin is an iron-binding protein found inside neutrophils. The amount of lactoferrin released by neutrophils has been shown to correlate with the severity of inflammation in the gastrointestinal (GI) tract. Fecal lactoferrin can be tested using commercial enzyme-linked immunosorbent assays to provide quantitative or qualitative results. Fecal lactoferrin testing may be useful when an individual presents with nonspecific GI symptoms, such as abdominal pain and diarrhea. These non-specific symptoms could be due to a functional etiology, such as IBS, or from IBD or GI infections. Fecal lactoferrin has limitations. Lactoferrin is an assessment of local gut inflammation vs. systemic inflammation. This is not always evident in IBD. In several diseases such as in colorectal cancer and polyps lactoferrin levels were also elevated. Symptoms are not likely to be related to infection or inflammation if the fecal lactoferrin results are undetectable, low, or normal (baseline cutoff level less than 7.25 µg/g). The result of high fecal lactoferrin would prompt further evaluation for IBD or infection (i.e., stool panel testing, endoscope). Fecal lactoferrin testing can help physicians with an inflammatory bowel disease (IBD) diagnosis. The initial evaluation of IBD severity and correlation to endoscopic findings, the monitoring of IBD activity, and potentially the prediction of IBD relapse.

Treatment

Guideline-based treatments of IBD include oral and rectal salicylates, glucocorticoids, immunomodulators (e.g., methotrexate), and multiple biologic therapies (e.g., infliximab), depending on disease severity.

Regulatory Status

Below are some identified gastrointestinal tests which have been reviewed by the U.S. Food and Drug Administration (FDA) or the Clinical Laboratory Improvement Amendments (CLIA). (*Please note, this is not an all-inclusive list*)

- Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory developed tests must meet the general regulatory standards. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing.

In March 2006, the PhiCal™ ® (Genova Diagnostics), an enzyme-linked immunosorbent assay test for measuring concentrations of fecal calprotectin in fecal stool, was cleared for marketing by the U.S. Food

and Drug Administration (FDA) through the 510(k) process. This test is indicated as an aid in the diagnosis of IBD and to differentiate IBD from IBS, when used with other diagnostic testing and clinical considerations.

The PhiCal ™ ®, as modified by Quest Diagnostics, is classified as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). The modified PhiCal ™ ® is available under the auspices of CLIA. Laboratories that offer laboratory-developed tests must be licensed by CLIA for high-complexity testing.

In 2014, CalPrest® (Eurospital SpA) and, in 2016, CalPrest®NG (Eurospital SpA) were cleared for marketing by the FDA through the 510(k) process. According to the FDA summary, CalPrest® “is identical” to the PhiCal™ test in that they have the same manufacturer. Compared with CalPrest®, the “differences in CalPrest® NG include the name of the test on the labels, detection antibody, the use of a Horse-radish peroxidase/TMB conjugate/substrate system, the provided Stop solution, the concentration of calibrators and controls in the kit and the dynamic range of the assay.”

The fCAL® ELISA Calprotectin Test (Bühlmann Laboratories) received FDA clearance in 2018 for the quantitative measurement of fecal calprotectin in human stool. In 2018, LIAISON® Calprotectin test (DiaSorin Inc.) also received FDA clearance and was determined to be substantially equivalent to the predicate PhiCal™ device.

In 2019, ALPCO received 510(k) clearance from the FDA for its new fecal Calprotectin Chemiluminescence ELISA test. This test exhibits a clinical specificity of 95.1% and provides the "lowest false positive rate of any currently cleared calprotectin test without sacrificing clinical sensitivity." In 2023, ALPCO received 510(k) clearance from the FDA for its Calprotectin Immunoturbidimetric Assay, and it was determined to be substantially equivalent to the Calprotectin Chemiluminescence ELISA test and is indicated for in-vitro diagnostic use as an aid in the diagnosis of IBD.

In 2022, DiaSorin Inc. submitted an application for modification of its LIAISON® Calprotectin test for the addition of the LIAISON® Q.S.E.T. Device Plus (the accessory used for stool sample collection and extraction) to the cleared assay. While the LIAISON® Calprotectin test is identical to its predicate cleared in 2018, the Q.S.E.T. Device Plus differs from its predicate Q.S.E.T. Device.

FDA product code: NXO.

Rapid fecal calprotectin tests that can be used in the home or physician’s office are commercially available in Europe and Canada (e.g., Calprosmart, Calpro AS; Quantum Blue Calprotectin, Bühlmann Laboratories). Rapid tests have not been approved by the FDA for use in the U.S.

There are numerous lactoferrin tests which are available for use. Some of which include but are not limited to:

- Lactoferrin Chek®
- Lactoferrin Ez Vue®
- Lactoferrin Scan®

Note: Multiple laboratory tests, some general and some proprietary, have been utilized for the diagnosis and ongoing management of IBD. Many individual tests do not require FDA approval for laboratory practices.

RATIONALE

This evidence review was created in April 2011 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through January 2026.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

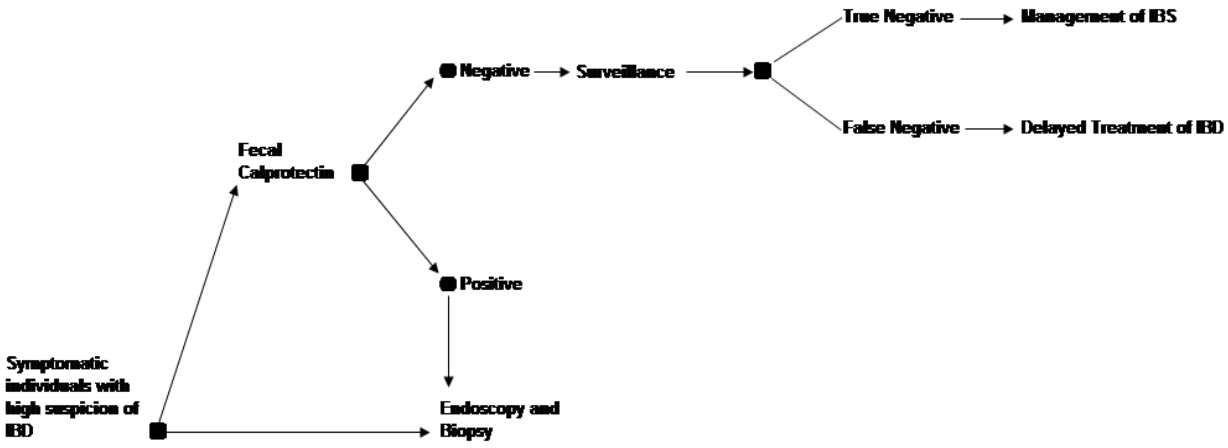
Suspected Inflammatory Bowel Disease

Clinical Context and Test Purpose

In individuals who have suspected inflammatory bowel disease (IBD), the purpose of this testing is to inform the decision whether to proceed to endoscopy with biopsy to confirm a diagnosis of IBD, either ulcerative colitis (UC) or Crohn's disease.

Both irritable bowel syndrome (IBS) and IBD can share common presenting symptoms such as diarrhea and abdominal pain. IBS is generally managed by antidiarrheal agents, diet, and lifestyle changes. IBD has a more serious prognosis. For example, Crohn's disease can result in a bowel obstruction or fistulas requiring surgical intervention. Ulcerative colitis has similar complications but is more localized.

In individuals whose symptoms have not responded to conservative management, endoscopy with biopsy would be required to confirm a diagnosis of IBD and inform treatment choice, which may include biologic disease-modifying agents. However, in a significant proportion of patients undergoing endoscopy with biopsy, IBD is not present. If this noninvasive testing can predict which individuals are unlikely to have IBD, fewer individuals would be subjected to endoscopy with biopsy.



The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals who present with signs and symptoms of suspected of IBD for whom endoscopy with biopsy is being considered. Alternative causes of abdominal pain and diarrhea would have been ruled out and there would be no other indication for endoscopy such as rectal bleeding or risk factors (e.g., age) for cancer.

Interventions
The test being considered is fecal calprotectin analysis, which detects the process of inflammation in the intestines. The labeling of the U.S. Food and Drug Administration (FDA) cleared PhiCal assay recommends the following interpretative guidelines: normal/healthy: less than 50 µg/g; indeterminate: 50 to 120 µg/g; abnormal: greater than 120 µg/g. Fecal calprotectin is also available as a laboratory-developed test and the upper threshold is being defined. Some laboratories use an upper threshold of 250 µg/g or higher to define a high probability of IBD.

Comparators
The following practice is currently being used to make decisions about diagnosing IBD: the reference standard is endoscopy with biopsy. In clinical practice, other tests such as magnetic resonance imaging, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and complete hemogram are part of the evaluation for IBD.

Outcomes
The outcome of a fecal calprotectin test is used to inform the decision of whether to proceed to endoscopy with biopsy.

The beneficial outcome of correctly being classified as low risk for IBD is avoiding an unnecessary invasive test. The harmful outcome of incorrect classification as low risk for IBD is omission or deferral of a necessary biopsy, with a consequent delay of appropriate treatment.

For purposes of evaluating the clinical validity of fecal calprotectin testing to predict the results of endoscopy, the time frame is the availability of endoscopy results.

Study Selection Criteria
For the evaluation of the clinical validity of the fecal calprotectin test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology.
- Included a suitable reference standard (endoscopy or clinical follow-up).
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
Shi et al (2022) published an umbrella review that summarized the sensitivity and specificity of fecal calprotectin (and 16 other noninvasive tests for IBD, including ESR, CRP, and fecal lactoferrin) from published systematic reviews and meta-analyses, including the Petryszyn et al (2019) and Waugh et al

(2013) studies discussed below. Diagnostic performance and test validity were classified into 3 clinical scenarios: diagnosis, activity assessment, and prediction of recurrence. A total of 106 assessments were included from 43 studies. For diagnosis, in distinguishing IBD from non-IBD, fecal calprotectin had a pooled sensitivity of 0.99 (95% confidence interval [CI], 0.92 to 1.00), the highest among all tests, and specificity of 0.65 (95% CI, 0.54 to 0.74). The performance of fecal calprotectin in patients with Crohn's disease (sensitivity, 0.95; specificity, 0.84) was generally better than in patients with ulcerative colitis (sensitivity and specificity, 0.78). In distinguishing IBD from IBS, fecal calprotectin was again the most sensitive test. With a cutoff of 50 µg/g, fecal calprotectin had a sensitivity of 0.97 (95% CI, 0.91 to 0.99) and specificity of 0.76 (95% CI, 0.66 to 0.84).

Petryszyn et al (2019) conducted a meta-analysis that evaluated the efficacy of fecal calprotectin as a diagnostic marker of IBD in patients with symptoms suspicious for the disease. The analysis included 19 studies (15 prospective and 4 retrospective; published through December 2018) with 5032 patients. Patients were over 16 years of age and had gastrointestinal symptoms, chronic diarrhea, or any other reason that may raise IBD suspicion. In the majority of included studies, the diagnostic fecal calprotectin cutoff value was 50 µg/g (n=14). An IBD diagnosis was confirmed in 620 (12.3%) patients, with prevalence ranging from 2.7% to 68.1%. The calculated pooled sensitivity was 0.882 (95% CI, 0.827 to 0.921), while the pooled specificity was 0.799 (95% CI, 0.693 to 0.875). There was a higher sensitivity of fecal calprotectin among studies with an IBD prevalence $\leq$30% as compared to among studies with a prevalence >30% (0.902 [95% CI, 0.856 to 0.935] versus 0.825 [95% CI, 0.661 to 0.920]; p=.041). Regarding risk of bias, the overall methodological quality of included studies was deemed to be "good"; however, 11 studies included some patients that were not representative of those who would receive the fecal calprotectin test in clinical practice, and selection bias may have existed in 5 studies. The authors concluded that out of 100 hypothetical cases with an IBD prevalence of 12.3%, 18 non-disease patients would have a colonoscopy performed and 1 patient with IBD would not be referred for a colonoscopy. Additionally, it was determined that incorporating a fecal calprotectin test into the regular diagnostic work-up would reduce the need for colonoscopy by 66.7%.

Waugh et al (2013) published a systematic review as part of the U.K. Health Technology Assessment program. Investigators included 28 studies using fecal calprotectin tests to evaluate inflammation of the lower intestine in newly presenting patients. Studies using fecal calprotectin tests to monitor disease progression or response to treatment were excluded. Endoscopy with histology was the preferred reference standard, although some studies included used imaging or clinical follow-up. Studies were pooled when there was a minimum of 4 using the same calprotectin cutoff. A pooled analysis of 5 studies using fecal calprotectin detected by enzyme-linked immunosorvent assay to differentiate between IBD and IBS in adults at a cutoff of 50 µg/g was performed (Table 1). One study was rated as low risk of bias and 3 studies had at least 3 domains with high or unclear risk of bias. The pooled studies had a combined sensitivity of 93% and a combined specificity of 94% to predict the presence of inflammatory disease on biopsy (1 study evaluated the absence of inflammatory disease). Table 2 summarizes clinical validity results and Tables 3 and 4 present individual study characteristics and results, with Table 4 presented in the order of increasing prevalence of IBD. Out of 100 cases with a prevalence of 20%, 76 invasive tests would be avoided with 1 case of IBD missed. At a prevalence of 68%, 35 invasive tests would be avoided with 5 cases missed.

Table 1: Characteristics of Studies at a Threshold of 50 µg/g

					11-Item QUADAS Quality Assessment
					No. of Studies Rated as High or Unclear Risk of Bias

Study	Studies Included	Study Populations Included	Study Designs Included	Study Reference Standards Included	No Domains	1-2 Domains	>2 Domains	Domains With >3 Studies at High-Risk of Bias
Waugh et al (2013)	5 studies	Adults newly presenting with IBD or IBS referred by general practitioners	Diagnostic accuracy of FC to detect inflammation of the lower intestine	Most used endoscopy with biopsy	1	1	3	Blinding of reference standard
Waugh et al (2013)	6 studies	Adults and children newly referred with IBD or non-IBD	Diagnostic accuracy of FC to detect inflammation of the lower intestine	-Most used endoscopy with biopsy -Some studies in children used clinical follow-up	0	5	1	Blinding of reference standard

FC: fecal calprotectin; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome

Table 2: Clinical Validity Study Results at a Threshold of 50 µg/g

Study	Scenario (N)	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV Range, %	NPV Range, %	Disease Prevalence Range (95% CI), %
Waugh et al (2013)	To detect IBD in adults with IBS or IBD (5 studies, n=596 patients)	93 (83 to 97)	94 (73 to 99)	24 to 100	73 to 100	10.9 to 69.0 (5.8 to 77.3)
Waugh et al (2013)	To detect IBD in children and adults with IBD or non-IBD (6 studies, n=516 patients)	99 (95 to 100)	74 (59 to 86)	62 to 96	93 to 100	21.4 to 61.1 (13.2 to 72.5)

CI: confidence interval; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; NPV: negative predictive value; PPV: positive predictive value.

Table 3: Characteristics of Diagnostic Accuracy Studies (Inflammatory Bowel Disease versus Irritable Bowel Syndrome) in Adults with a Cutoff of 50 µg/g

Study	Study Population	Setting	Reference Standard	No. of Domains[a] at High or Unclear Risk of Bias
Basumani et al (2012)	New referrals with diarrhea ≥ 4 wk to rule out IBD	District General Hospital, England	Histology	4
Ostlund et al (2008)	Consecutive patients were referred with lower abdominal symptoms to the endoscopy unit. Excluded 25 patients with polyps or CRC.	Endoscopy unit, The Netherlands	Colonoscopy and biopsy	2
Li et al (2006)	Outpatients and inpatients with IBS or IBD, healthy controls; patients followed up after polyp removal with no recurrence. Excluded 60 patients with CRC.	Hospital, Peking	Colonoscopy with biopsy in IBD group	6
Schoepfer et al (2008)	Outpatients and inpatients with IBS or IBD. Excluded patients with CRC.	Gastroenterology Department, University Hospital, Switzerland	Colonoscopy including terminal ileum and biopsies	0
El-Badry et al (2010)	GI symptoms for at least 6 mo, and endoscopy necessary to exclude organic pathology. Excluded patients with CRC, diverticulitis, and polyps.	Internal Medicine Department, Egypt	Colonoscopy into ileum with biopsies	3

CRC: colorectal cancer; GI: gastrointestinal; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome.
[a] QUADAS ratings.

Table 4: Results of Diagnostic Accuracy Studies (Inflammatory Bowel Disease versus Irritable Bowel Syndrome) in Adults with a Cutoff of 50 µg/g Stratified by Increasing Prevalence

Study	N	Prevalence (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95 % CI)	NPV (95 % CI)	PLR (95 % CI)	NLR (95 % CI)
Basumani et al (2012)	110	10.91 (5.77 to 18.28)	1.00 (0.74 to 1.00)	0.60 (0.50 to 0.70)	0.24 (0.13 to 0.37)	1.00 (0.94 to 1.00)	2.51 (1.97 to 3.21)	0
Ostlund et al (2008	114	20.18 (13.24 to 28.72)	0.96 (0.78 to 1.00)	0.87 (0.78 to 0.93)	0.65 (0.47 to 0.81)	0.99 (0.93 to 1.00)	7.25 (4.25 to 12.38)	0.05 (0.01 to 0.34)
Li et al (2006)	120	50.00 (40.74 to 59.26)	0.93 (0.84 to 0.98)	0.95 (0.86 to 0.99)	0.95 (0.86 to 0.99)	0.93 (0.84 to 0.98)	18.67 (6.18 to 56.63)	0.07 (0.03 to 0.18)
Schoepfer et al (2008)	94	68.09 (57.67 to 77.33)	0.83 (0.71 to 0.91)	1.00 (0.88 to 1.00)	1.00 (0.93 to 1.00)	0.73 (0.57 to 0.86)	NR	0.17 (0.10 to 0.29)
El-Badry et al (2010)	29	68.97 (49.17 to 84.72)	0.85 (0.62 to 0.97)	1.00 (0.66 to 1.00)	1.00 (0.81 to 1.00)	0.75 (0.43 to 0.95)	NR	0.15 (0.05 to 0.43)

CI: confidence interval; NLR: negative likelihood ratio; NPV: negative predictive value; NR: not reported; PLR: positive likelihood ratio; PPV: positive predictive value.

Six studies using fecal calprotectin with an enzyme-linked immunosorvent assay to differentiate between IBD and non-IBD in children and adults were pooled. Five of the studies included only children, most of whom had been referred to pediatric gastroenterologists. The children had undergone fecal calprotectin testing prior to endoscopy with biopsy or were followed clinically. No studies were at low-risk of bias and 5 studies had 1 to 2 domains with high or unclear risk of bias, as evaluated on the QUADAS quality assessment. The highest risk of bias was for blinding of the reference standard. The combined sensitivity was 99%, with a lower combined specificity (74%) to detect the absence of inflammatory disease on biopsy. Modeling indicated that the use of fecal calprotectin in children would result in fewer children undergoing an unnecessary invasive test (i.e., endoscopy with biopsy). Out of 100 cases, at a prevalence of 36%, 47 invasive tests would be avoided with 1 case of IBD missed. At a prevalence of 51%, 36 invasive tests would be avoided with 1 case of IBS missed. Individual study characteristics and results, presented in the order of the increasing prevalence of IBD.

Table 5: Characteristics of Diagnostic Accuracy Studies (Inflammatory Bowel Disease versus Non-Inflammatory Bowel Disease) in Children and Adults with a Cutoff of 50 µg/g

Study	Study Population	Setting	Reference Standard	No. of Domains[a] at High or Unclear Risk of Bias
Damms and Bischoff et al (2008)	Patients ages >18 y referred for colonoscopy for GI disorders or CRC screening	Gastroenterology departments at 3 hospitals and 3 outpatient clinics in Germany	Colonoscopy: for CRC screening medical check-up	2
Van de Vijver et al (2012)	Children ages 6 to 18 y referred for further investigation of high suspicion of IBD from pediatrician's global assessment, physical examination, and blood results	Pediatric outpatient clinics at 6 general hospitals and 1 tertiary care hospital in the North Netherlands Paediatric IBD Consortium	68 patients had endoscopy; others had follow-up for at least 6 mo to confirm a diagnosis of IBS	1
Henderson et al (2012)	All children who had a fecal calprotectin measurement as part of initial diagnostic workup before endoscopy	Pediatric gastroenterology department at a children's hospital in U.K.	• IBD patients: standard clinical, histologic, and radiologic findings • Non-IBD (control) patients: upper and lower endoscopy	2
Sidler et al (2008)	Children ages 2 to 18 y referred for further investigation of GI symptoms (chronic diarrhea, bloody stools, abdominal pain) suggestive of an OBD	Pediatric gastroenterology outpatient clinic at children's hospital in Australia	• Upper GI endoscopy and complete ileocolonoscopy with biopsy	1
Tomas et al (2007)	Patients referred for further investigation of GI symptoms (intense abdominal pain, chronic diarrhea, weight loss, rectal bleeding)	Pediatric gastroenterology unit of university hospital in Spain	• Clinical criteria, laboratory, image, and endoscopic test results	6

Study	Study Population	Setting	Reference Standard	No. of Domains[a] at High or Unclear Risk of Bias
Fagerberg et al (2005)	Children ages 6 to 17 y with GI symptoms and blood tests suggestive of inflammation who were scheduled for colonoscopy to rule out IBD	Pediatric gastroenterology departments at hospitals in Sweden	Complete ileocolonoscopy with biopsy	1

CRC: colorectal cancer; GI: gastrointestinal; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; OBD; organic bowel disease.
[a] QUADAS ratings.

Table 6: Results of Diagnostic Accuracy Studies (Inflammatory Bowel Disease versus Non-Inflammatory Bowel Disease) in Children and Adults with a Cutoff of 50 µg/g Stratified by Increasing Prevalence

Study	N	Prevalence (95% CI)	Sensitivity (95 % CI)	Specificity (95 % CI)	PPV (95 % CI)	NPV (95 % CI)	PLR (95 % CI)	NLR (95 % CI)
Damms et al (2008)	84	21.43 (13.22 to 31.74)	1.00 (0.81 to 1.00)	0.79 (0.67 to 0.88)	0.79 (0.60 to 0.88)	1.00 (0.93 to 1.00)	4.71 (2.96 to 7.50)	0
Van de Vijver et al (2012)	117	35.9 (27.24 to 45.29)	1.00 (0.92 to 1.00)	0.73 (0.62 to 0.83)	0.68 (0.55 to 0.79)	1.00 (0.94 to 1.00)	3.8 (2.6 to 5.5)	0
Henderson et al (2012)	190	47.89 (40.61 to 55.25)	0.98 (0.92 to 1.00)	0.44 (0.34 to 0.55)	0.62 (0.53 to 0.70)	0.96 (0.85 to 0.99)	1.8 (0.15 to 2.1)	0.05 (0.01 to 0.20)
Sidler et al (2008)	61	50.82 (37.70 to 63.86)	1.00 (0.89 to 1.00)	0.67 (0.47 to 0.83)	0.76 (0.60 to 0.88)	1.00 (0.83 to 1.00)	3.00 (1.81 to 4.98)	0
Tomas et al (2007)	28	53.57 (33.87 to 72.49)	1.00 (0.78 to 1.00)	0.92 (0.64 to 1.00)	0.94 (0.70 to 1.00)	1.00 (0.74 to 1.00)	13.00 (1.98 to 85.46)	0
Fagerberg et al (2005)	36	61.11 (43.46 to 76.86)	0.95 (0.77 to 1.00)	0.93 (0.66 to 1.00)	0.96 (0.77 to 1.00)	0.93 (0.66 to 1.00)	13.36 (2.02 to 88.54)	0.05 (0.01 to 0.33)

CI: confidence interval; NLR: negative likelihood ratio; NPV: negative predictive value; PLR: positive likelihood ratio; PPV: positive predictive value.

Clinically Useful
A test is clinically useful if the results inform management decisions that improve the net health outcome of care. The net health outcome can be improved if individuals receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for individuals managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No RCTs were identified that assessed the use of fecal calprotectin testing to diagnose suspected IBD.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Indirect evidence supports the clinical usefulness of fecal calprotectin in patients with suspected IBD for whom endoscopy is being considered. The evidence on clinical validity (sensitivity, specificity, negative predictive value [NPV]) permits inference on clinical usefulness as a result of avoidance of endoscopy with biopsy in patients who are unlikely to have an inflammatory disease.

Section Summary: Clinically Useful
A systematic review and meta-analysis of 28 studies pooled 11 studies that used a 50 µg/g threshold to evaluate intestinal inflammation. Five studies (n=596 patients) showed an NPV in the range of 73% to 100% in adults with IBS or IBD. The pooling of 6 studies in adults and children (n=1100) with IBD or non-IBD showed an NPV of 93% to 100%. Together, these results would suggest that fecal calprotectin testing at a threshold of 50 µg/g can identify patients who are unlikely to have IBD and can forgo a more invasive test (endoscopy with biopsy). In another meta-analysis involving 19 studies, investigators determined that incorporating a fecal calprotectin test into the regular diagnostic work-up would reduce the need for colonoscopy by 66.7%. A recent umbrella review found that fecal calprotectin is the most sensitive noninvasive test in distinguishing IBD from non-IBD (sensitivity, 0.99), and IBD from IBS (sensitivity, 0.97 [cutoff 50 µg/g]. Although the sensitivity and specificity of fecal calprotectin were generally balanced, sensitivity was slightly better than specificity.

Active Inflammatory Bowel Disease

Clinical Context and Test Purpose
In individuals who have active IBD, the purpose of fecal calprotectin testing is to allow clinicians to monitor disease activity and guide therapeutic decision-making.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with active IBD (ie, Crohn's disease or ulcerative colitis).

Interventions
The test being considered is fecal calprotectin analysis.

Comparators
The following practice is currently being used to make decisions about monitoring active IBD: a repeat endoscopy with biopsy (reference standard). In clinical practice, other tests such as ESR, CRP, and complete hemogram are part of the evaluation for monitoring disease activity in IBD.

Outcomes
The beneficial outcome of a true test result, if correctly classified as low disease activity, is the avoidance of endoscopy and unnecessary medications.

If correctly classified as high activity, the administration of appropriate treatment is another beneficial outcome.

Outcomes may be assessed in clinical practice and in the research setting with standardized measures, such as the Crohn Disease Activity Index (CDAI), a validated 8-item score used as a marker of Crohn's disease remission, with values less than 150 considered consistent with remission and values greater than 450 considered a marker of severe Crohn's disease.

The relevant time period for the impact of testing is weeks to months.

Study Selection Criteria
For the evaluation of the clinical validity of the fecal calprotectin test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology.
- Included a suitable reference standard (endoscopy).
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Reviews
The umbrella review by Shi et al (2022), discussed previously in the section on suspected IBD, also reported the diagnostic performance of fecal calprotectin in assessing disease activity. The review, which included the study by Mosli et al (2015) summarized below, found that fecal calprotectin with a cutoff of 50 µg/g had the highest sensitivity (0.92; 95% CI, 0.90 to 0.94) among the noninvasive tests evaluated in assessing IBD activity. However, ultrasound and magnetic resonance enterography (MRE) performed better, with comparable sensitivity and higher specificity.

A systematic review by Mosli et al (2015) evaluated the sensitivity and specificity of fecal calprotectin in adults and some children with previously diagnosed ulcerative colitis or Crohn's disease to detect endoscopically confirmed active disease (Table 7). Nineteen studies with 1069 patients with ulcerative colitis and 1033 patients with Crohn's disease met eligibility criteria. Individual studies used a variety of cutoffs for fecal calprotectin, ranging from 6 to 280 µg/g. Pooled sensitivity and specificity estimates for fecal calprotectin were 88% and 73%, respectively. (Table 8). The optimal threshold was determined to be 50 µg/g. At a threshold of 50 µg/g, the NPV for inflammation at a prevalence of 0.50 was 86%, and the positive predictive value (PPV) was 76%. This information might be used to triage patients for endoscopy when they have symptoms of active disease.

A systematic review by Parra-Izquierdo et al (2025) evaluated the diagnostic accuracy of non-invasive evaluation options, including intestinal ultrasound and fecal calprotectin, in adults with endoscopically confirmed ulcerative colitis (Table 7). Only 2 eligible studies with 72 total patients were included. Each study used a cutoff of ≥100 µg/g for fecal calprotectin. Pooled sensitivity and specificity estimates for fecal calprotectin were 85% and 60%, respectively (Table 8). The limited number of studies included and high degree of heterogeneity limits interpretation of these results.

Table 7. Characteristics of Clinical Validity Reviews Assessing Monitoring of Active Disease

					11-Item QUADAS Quality Assessment			
					No. of Studies Rated as High or Unclear Risk of Bias			
Study	Studies Included	Study Populations Included	Study Designs Included	Study Reference Standards Included	No Domains	1 to 2 Domains	>2 Domains	Indicators with >6 Studies at High or Unclear Risk of Bias
Mosli et al (2015)	19	1069 UC and 1033 CD patients (mostly adults) with symptomatic disease	Prospective cohorts or case-controls for evaluating disease activity	Endoscopy	2	9	8	• Inappropriate exclusions· Blinding of index test • Interval between tests • Exclusions in the analysis
Parra-Izquierdo et al (2025)	2	72 patients with UC	1 prospective cohort study and 1 prospective cross-sectional diagnostic accuracy study	Histological analysis via endoscopy	2	0	0	NA

CD: Crohn diseases; NA: not applicable; QUADAS: Quality Assessment of Diagnostic Accuracy Studies; UC: ulcerative colitis.

Table 8. Results of Clinical Validity Reviews Assessing Detection of Endoscopically Confirmed Active Disease

Study	Scenario	Sensitivity (95% CI), %	Specificity (95% CI), %	Range PPV, %	Range NPV, %
Mosli et al (2015)	To monitor disease activity in patients with CD or UC on maintenance therapy (N=2102)	88 (84 to 90)	73 (66 to 79)	52 to 91	67 to 95
Parra-Izquierdo et al (2025)	Diagnostic accuracy and detection of histologic remission in patients with UC via fecal calprotectin ≥100 µg/g (N=72)	85 (72 to 92)	60 (38 to 79)	78 to 95	44 to 73

CI: confidence interval; CD: Crohn disease; NPV: negative predictive value; PPV: positive predictive value; UC: ulcerative colitis

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome. The net health outcome can be improved if individuals receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for individuals managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

For monitoring disease activity in patients with active IBD, inferences cannot be made from clinical validity studies to clinical usefulness. How fecal calprotectin would be used to make decisions about endoscopy or intensification of therapy is not described in the Mosli et al (2015) review. Intervention studies will provide direct evidence of fecal calprotectin for monitoring disease activity in patients with active IBD.

Östlund et al (2021) reported on a 12-month RCT comparing self-monitoring of IBD using an at-home fecal calprotectin test (IBDoc® [not available in the US]) along with a digital application for answering symptom questionnaires plus standard of care versus standard of care alone in 153 patients with established IBD selected from the Swedish Inflammatory Bowel Disease Register (SWIBREG). Data were collected retrospectively from medical records. A primary outcome was not identified but the objective of the study was to evaluate home testing acceptance and adherence. The reported low compliance in the intervention group (~29%) and use of a test that is not available in the US limit the applicability of results from this study. Female gender was the only factor significantly associated with increased adherence to the test.

Colombel et al (2018) reported on an open-label multicenter RCT, the Efficacy and Safety Study to Evaluate Two Treatment Algorithms in Subjects with Moderate to Severe Crohn's Disease (CALM) that compared the effect of tight control of Crohn's disease with standard clinical management. The primary endpoint was mucosal healing with an absence of deep ulcers at 48 weeks after randomization (Tables 9 and 10). This trial did not test whether using fecal calprotectin, as decision criteria for treatment changes, improved the capability to achieve tight control. Although a post hoc analysis found that, in the tight management arm, fecal calprotectin levels frequently influenced the decision to escalate treatment, the contribution of fecal calprotectin to the tight control cannot be determined from this study design.

Table 9. Summary of Key Randomized Controlled Trial Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Östlund et al (2021)	Sweden	NR	NR	158 patients with established IBD from the Swedish Inflammatory Bowel Disease Register (SWIBREG)	Home-based fecal calprotectin test along with a digital application for answering symptom questionnaires plus standard of care	Standard of care alone
Colombel et al (2018)	U.S., E.U.	74	2011 to 2016	244 adults with moderate-to-severe active CD (CDEIS, >6; CDAI, 150 to 450) and naive to immunomodulators and biologics	Tight control[a] including FC ≥250 µg/g and CRP >5 mg/L	Clinical management[b]

CD: Crohn disease; CDAI: Crohn's Disease Activity Index; CDEIS: Crohn's Disease Endoscopic Index of Severity; CRP: C-reactive protein; FC: fecal calprotectin; IBD: inflammatory bowel disease; NR: not reported.
[a] Tight control was determined by FC level ≥250 µg/g, CRP level ≥5 mg/L, CDAI score ≥150, or prednisone use in the previous week.
[b] Clinical management was based on a CDAI score decrease of <100 points versus baseline or CDAI score ≥200, or prednisone use in the previous week.

Table 10. Summary of Key Randomized Controlled Trial Results

Study				
Östlund et al (2021)	**Patients who received increased medical treatment during the study, n (%)**	**Patients who received decreased medical treatment during the study, n (%)**		
IBD-Home group	28/84 (33)	13/84 (16)		
Control	11/74 (15)	10/74 (14		
p-value	.007	.727		
IBD-Home group (compliers)	14/24 (58)	5/24 (21)		

IBD-Home group (non-compliers)	14/60 (23)	8/60 (13)		
p-value	.002	.201		
Colombel et al (2018)	**Mucosal Healing at 48 Weeks**	**Adverse Events**	**Steroid-Free Remission at 48 Weeks**	**Deep Remission**
	244	244	244	244
Tight control	56/122 (46)	105 (86)	73 (59.8)	45 (36.9)
Clinical monitoring	37/122 (30)	100 (82)	48 (39.3)	28 (23.0)
RR (95% CI)	16.1 (3.9 to 28.3)			
p	.010		.001	.014

Values are n/n (%), n (%), or as otherwise indicated.
CI: confidence interval; IBD-Home: inflammatory bowel disease monitoring using an at-home fecal calprotectin test; RR: relative risk.

Tables 11 and 12 display notable limitations identified in each study.

Table 11. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Östlund et al (2021)	4. Study population was patients with established IBD (median of 8 years since diagnosis), which may have impacted uptake of home testing	4. Test used (Bühlmann HBFCT IBDoc®) is not available in the US	1. Not clearly defined	1, 4. Primary outcome not defined; medical interventions not defined	
Colombel et al (2018)		4. In addition to FCP, CRP, prednisone use, and different thresholds of CDAI were used in the tight control arm			

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CDAI: Crohn's Disease Activity Index; CRP: C-reactive protein; FCP: fecal calprotectin. IBD: inflammatory bowel disease
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 12. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Östlund et al (2021)	4. Randomized by the day in the month patients were born	1,2. Blinding not described			1. Poor adherence (29% in the intervention group)	
Colombel et al (2018)		1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician		1. 25% loss to follow-up (analysis was intention-to-treat)		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical utility of fecal calprotectin testing has not been established for monitoring active IBD, a chain of evidence cannot be constructed.

Section Summary: Active Inflammatory Bowel Disease

Studies to manage IBD have not used consistent cutoff values. A systematic review determined that 50 µg/g was the optimum threshold; at a prevalence of 0.50, fecal calprotectin had an NPV of 86% and PPV of 76%. A recent umbrella review found that fecal calprotectin with a threshold of 50 µg/g had the highest sensitivity (0.92; 95% CI, 0.90 to 0.94) among the noninvasive tests evaluated in assessing IBD activity. However, ultrasound and MRE perform better, with comparable sensitivity and higher specificity. One

RCT using fecal calprotectin testing along with other measures to monitor disease activity in patients with IBD on maintenance therapy was identified. The investigators reported that tight control using both clinical status and biologic markers (fecal calprotectin level, ≥250 µg/g; CRP level, ≥5 mg/L) resulted in greater mucosal healing in patients with Crohn's disease. The contribution of fecal calprotectin to the tight control could not be determined from this study design. In another RCT, self-monitoring with a home-based fecal calprotectin test among patients with established IBD demonstrated an increase in the proportion of patients seeking medical treatment; compliance to home-based testing in this study was low (29%). The use of a home-based fecal calprotectin test that is not available in the US limits the applicability of this study.

Inflammatory Bowel Disease in Remission

Clinical Context and Test Purpose

In individuals with IBD in remission, the purpose of fecal calprotectin testing is to predict relapse. The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with IBD (ie, Crohn's disease or ulcerative colitis) who are in remission.

Interventions

The test being considered is fecal calprotectin analysis.

Comparators

The following practice is currently being used to make decisions about monitoring IBD in remission: endoscopy with biopsy (reference standard). The following tests are currently used to make decisions about monitoring for IBD relapse in individuals in the relevant population: symptoms, inflammatory markers (ESR, CRP), and complete blood count.

Outcomes

The beneficial outcome of a true test result, if correctly classified as low disease activity, is the avoidance of unnecessary medications.

If correctly classified as high activity, the administration of appropriate treatment is another beneficial outcome.

In making a decision to increase medications, fecal calprotectin testing as an adjunct to clinical assessment is being used as a test to support a “rule in” decision, so PPV is the key measure of clinical validity.

Outcomes of interest are an improvement in symptoms and disease activity scores. Outcomes may be assessed in clinical practice and in the research setting with standardized measures, such as the CDAI, a validated 8-item score used as a marker of Crohn's disease remission, with values less than 150 considered consistent with remission and values greater than 450 considered a marker of severe Crohn's disease.

The relevant time period for the impact of testing is weeks to months.

Study Selection Criteria

For the evaluation of the clinical validity of the fecal calprotectin test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology.
- Included a suitable reference standard (endoscopy).
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Reviews

Shi et al (2023) conducted a meta-analysis to evaluate the diagnostic accuracy of fecal calprotectin for predicting relapse in IBD. A total of 24 prospective studies (N=2260) were included in the analysis. Methodological assessment of studies was based on the second QUADAS-2 checklist. The pooled sensitivity and specificity of fecal calprotectin for IBD was 0.720 (95% CI, 0.528 to 0.856) and 0.740 (95% CI, 0.618 to 0.834), respectively. An optimal fecal calprotectin cut-off value for predicting IBD relapse of 152 µg/g was identified. Characteristics and results are shown in Tables 13 and 14.

The umbrella review by Shi et al (2022), discussed in the previous sections, also reported the diagnostic performance of fecal calprotectin in predicting recurrence. The review included studies assessed by Heida et al (2017) summarized below. Fecal calprotectin was the only test used for IBD, with a sensitivity of 0.78 (95% CI, 0.72 to 0.83) and specificity of 0.73 (95% CI, 0.68 to 0.77). The sensitivity and specificity of fecal calprotectin for Crohn's disease were 0.75 (95% CI, 0.64 to 0.84) and 0.71 (95% CI, 0.64 to 0.76), respectively. For ulcerative colitis, sensitivity and specificity were 0.75 (95% CI, 0.70 to 0.79) and 0.77 (95% CI, 0.74 to 0.80), respectively. Radiological examinations (particularly MRE and ultrasound), however, were more prominent in predicting recurrence.

Heida et al (2017) conducted a systematic review to determine the accuracy of fecal calprotectin monitoring in asymptomatic patients (Table 13). Six studies met the review inclusion criteria and evaluated fecal calprotectin levels every 1 to 3 months. Methodological assessment of studies was based on the second QUADAS checklist. One-third of patients had a relapse during the study period, although the definitions of relapse varied across studies. Five of the 6 studies used an upward trend of fecal calprotectin between 2 measurements as the threshold. Asymptomatic patients with IBD who had fecal calprotectin levels above the study's cutoff had a 53% to 83% probability of developing disease relapse within the next 2 to 3 months, while patients with normal fecal calprotectin levels had a 67% to 94% probability of remaining in remission in the next 2 to 3 months (Table 14). Calprotectin levels began to rise 2 to 3 months before clinical relapse. The investigators could not identify the best fecal calprotectin cutoff for monitoring purposes.

Table 13. Characteristics of Clinical Validity Reviews Assessing Prediction of Relapse

Study	Studies Included	Study Populations Included	Study Designs Included	Study Reference Standards Included

Shi et al (2023)	24	2260 patients with IBD in remission	Prospective studies that assessed FC	5 studies used endoscopy 19 studies used clinical symptoms or therapy change
Heida et al (2017)	6	552 patients with UC in remission	Prospective studies that assessed FC every 1 to 3 mo	5 studies used endoscopy 1 study used clinical activity score

Adapted by Heida et al (2017).
FC: fecal calprotectin; IBD: irritable bowel disease; UC: ulcerative colitis.

Table 14. Results of Clinical Validity Reviews Assessing Prediction of Relapse

Study	Scenario	Sensitivity Range, %	Specificity Range, %
Shi et al (2023)	Prediction of relapse (2260 patients) of whom 31.6% relapsed during observation	52.8 to 85.6	61.8 to 83.4
Heida et al (2017)	Prediction of relapse (552 patients) of whom 33.3% relapsed during observation	53 to 83	67 to 94

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if individuals receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for individuals managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

A prospective, nonblinded, controlled trial by Lasson et al (2015) randomized patients with ulcerative colitis in remission at high risk of relapse in a 3:2 ratio to medication dosing decisions based on fecal calprotectin levels or to usual care (Table 15). The fecal calprotectin monitoring group was included in the systematic review by Heida et al (2017) described above. Both groups submitted fecal samples at baseline and on a monthly basis. In the intervention group, a fecal calprotectin cutoff of 300 µg/g was used for escalating the 5-aminosalicylic acid dose to the maximally tolerable dose. The high dose was continued for 3 months and then reduced when fecal calprotectin levels fell below 200 µg/g. The primary outcome was the number of patients to relapse by 18 months. At 1 year, there was no significant difference in relapse rates between the 2 groups (Table 16). For 10 of the 18 patients in the intervention group who had a relapse, fecal calprotectin levels did not rise above the 300 µg/g cutoff for medication dosage escalation. In the subgroup of patients who had levels of 300 µg/g or more, there was a significantly lower rate of relapse in the intervention group (28.6%) than in the control group (57.1%). Trial limitations included lack of blinding, exclusion of patients without intention-to-treat analysis, and insufficient power (Tables 17 and 18).

Table 15. Summary of Key Randomized Controlled Trial Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Lasson et al (2015)	Sweden	5	2009 to 2012	• 91 adults with UC on maintenance therapy with oral 5-ASA medication • Patients were in remission but at high risk of relapse	Escalation to a maximally tolerable dose based on FC ≥300 µg/g and lowered when FC <200 µg/g	Usual care based on symptoms

5-ASA: 5-aminosalicylic acid; FC: fecal calprotectin; UC: ulcerative colitis.

Table 16. Summary of Key Randomized Controlled Trial Results

Study	Rate of Relapse at 1 Year
Lasson et al (2015)	
Fecal calprotectin monitoring, n/N (%)	18/51 (35.3)
Usual care, n/N (%)	20/40 (50)
p	.23

Tables 17 and 18 display notable limitations identified in the study.

Table 17. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Lasson et al (2015)			3. Treatment of a flare-up based on patient complaint and not predetermined in the study protocol		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 18. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Lasson et al (2015)		1. Not blinded			2. 9 patients not providing at least 9 samples were excluded from the experimental group 3. Not intention-to-treat 3. Target sample size not achieved	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Section Summary: Inflammatory Bowel Disease in Remission

A recent umbrella review found that fecal calprotectin had a sensitivity of 0.78 and specificity of 0.73 in predicting recurrence, although radiological examinations (MRE and ultrasound) performed better. A 2023 meta-analysis of 24 prospective studies that monitored fecal calprotectin in patients in remission described an optimal cut-off value for fecal calprotectin of 152 µg/g and a pooled sensitivity and specificity of fecal calprotectin of 0.720 and 0.740, respectively. A 2017 systematic review of 6 prospective studies in patients in remission found no consistency in the thresholds used to determine treatment. One RCT evaluated the relapse rates in patients with ulcerative colitis whose medication doses were managed with fecal calprotectin test results (≥ 300 µg/g) and, in its primary analysis, found no significant difference in relapse rates. Trial limitations were in the domains of blinding, power, follow-up, and analysis. In addition, this trial did not enroll the planned number of patients and might have been underpowered. There is a need for high-quality RCTs to determine whether monitoring fecal calprotectin in individuals who are in remission can reduce relapse rates and improve the quality of life for patients with IBD.

Fecal Lactoferrin

Clinical Context and Test Purpose

Calprotectin has been used in individuals who present with signs and symptoms of suspected of IBD, who have been diagnosed with IBD (fecal lactoferrin testing could allow clinicians to monitor disease activity and guide therapeutic decision-making), and when needed to predict relapse in individuals with IBD who are in remission.

A marker to predict relapse could improve the net health outcome if preemptive treatment was found to eliminate recurrences or reduce their severity.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with the relevant population of interest is individuals who present with signs and symptoms of suspected of IBD or those with Crohn's disease or ulcerative colitis.

Interventions
The test being considered is fecal lactoferrin analysis.

Comparators
The following practice is currently being used to make decisions about monitoring IBD: endoscopy with biopsy (reference standard). The following tests are currently used to make decisions about monitoring for IBD relapse in individuals in the relevant population: symptoms, inflammatory markers (ESR, CRP), and complete blood count.

Outcomes
The beneficial outcome of a true test result, if correctly classified as low disease activity, is the avoidance of unnecessary medications.

If correctly classified as high activity, the administration of appropriate treatment is another beneficial outcome.

In making a decision to increase medications, fecal lactoferrin testing as an adjunct to clinical assessment is being used as a test to support a “rule in” decision, so PPV is the key measure of clinical validity.

Outcomes of interest are an improvement in symptoms and disease activity scores.

The relevant time period for the impact of testing is weeks to months.

Study Selection Criteria
For the evaluation of the clinical validity of the fecal calprotectin test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology.
- Included a suitable reference standard (endoscopy).
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Review
Dai et al (2020) published a systematic review and meta-analysis on fecal lactoferrin for the assessment of inflammatory bowel disease activity monitoring. They reviewed 10 studies with 133 individuals. “The pooled sensitivity and specificity values for assessing ulcerative colitis (UC) activity were 0.81 [95% confidence interval (CI), 0.64-0.92] and 0.82 (95% CI, 0.61-0.93), respectively. And the pooled sensitivity and specificity values for assessing Crohn's disease (CD) activity were 0.82 (95% CI, 0.73-0.88) and 0.71 (95% CI, 0.63-0.78), respectively. The diagnostic performance of the FL assay in the UC patients appeared to be superior

to that in the CD patients." They concluded that fecal lactoferrin is a useful tool with "high sensitivity and modest specificity for assessing IBD activity".

Wang et al (2015) published a meta-analysis on the diagnostic accuracy of fecal lactoferrin for IBD. Studies varied in the fecal lactoferrin cutoffs used to indicate the presence of disease. The authors reported," the pooled FL sensitivity and pooled specificity were 0.82 (95% confidence interval [CI]: 0.72, 0.89) and 0.95 (95% CI: 0.88, 0.98), respectively. The positive and negative likelihood ratios were 16.63 and 0.18, respectively. The area under the summary receiver-operating characteristic curve (SROC) was 0.95 (95% CI: 0.93, 0.97), and the diagnostic odds ratio was 90.04 (95% CI: 37.01, 219.02). The pooled FL sensitivity and specificity for Crohn's disease (CD) diagnosis (sensitivity =75%, specificity =100%) was not as good as it was for ulcerative colitis (UC) diagnosis (sensitivity =82%, specificity =100%)." Overall, the authors concluded there is modest sensitivity and high specificity for fecal lactoferrin to diagnose IBD vs other disorders with a better evaluation rate for UC vs CD. Fecal lactoferrin may be recommended be used with additional tests (blood inflammatory markers and/or fecal calprotectin) for those with active disease or require additional disease management.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if individuals receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for individuals managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. Indirect evidence supports the clinical usefulness of fecal lactoferrin in individuals with suspected IBD for whom endoscopy is being considered, who have been diagnosed with IBD (fecal calprotectin testing could allow clinicians to monitor disease activity and guide therapeutic decision-making), and when needed to predict relapse in individuals with IBD who are in remission. The evidence on clinical validity (sensitivity, specificity, negative predictive value [NPV]) permits inference on clinical usefulness as a result of avoidance of endoscopy with biopsy in individuals who are unlikely to have an inflammatory disease.

Section Summary: Fecal Lactoferrin

Two systematic reviews concluded with pooled results from these meta-analyses indicated that sensitivity rates ranged from 0.81 to 0.82 and the specificity rates ranged from 0.82 to 0.95. However, the clinical utility of this remains uncertain. There is a need for high-quality RCTs to determine whether monitoring fecal lactoferrin in individuals who are in remission can reduce relapse rates and improve the quality of life (QOL) for individuals with IBD.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2018 Input

Clinical input was sought to help determine whether the use of fecal calprotectin testing for individuals with suspected inflammatory bowel disease (IBD) when endoscopy with biopsy is being considered would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 3 respondents, including 1 specialty society-level response and 2 physician-level responses identified through specialty societies including physicians affiliated with academic medical centers.

For individuals who have suspected IBD (when endoscopy with biopsy is being considered) who receive fecal calprotectin testing, clinical input supports this use provides a clinically meaningful improvement in net health outcome and indicates this use is consistent with generally accepted medical practice. Specifically, fecal calprotectin testing can inform the decision by using a positive fecal calprotectin result to refer for endoscopy with biopsy, or to use negative fecal calprotectin results to exclude IBD and avoid endoscopy with biopsy, with acceptably low tradeoffs in missed diagnoses of IBD in those who have false-negative fecal calprotectin results. Input further highlighted that the use of fecal calprotectin is particularly important in pediatric populations, where children may not be able to fully participate as medical historians and may have non-specific and/or atypical symptoms.

2014 Input

In response to requests, input was received through 4 physician specialty societies and 4 academic medical centers while this policy was under review in 2014. One specialty society submitted 2 responses. Input was mixed on whether fecal calprotectin testing is considered investigational for the diagnosis of intestinal conditions and whether the results of diagnostic testing are being used to change patient management. Clinicians who disagreed with the investigational designation tended to argue that a medically necessary use of the test for diagnosis would be to differentiate inflammatory from noninflammatory conditions. There was near consensus that fecal calprotectin testing is considered investigational in the management of intestinal conditions. Most reviewers did not think that, when the test is used for the management of intestinal disorders, results change patient management. There was near consensus that the manufacturer’s recommended cutoff of 50 µg/g should be used to indicate a positive fecal calprotectin test.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Gastroenterology (ACG)

In 2018, the American College of Gastroenterology (ACG) published a guideline on the management of Crohn's disease (CD) in adults, which was most recently updated in 2025.The College gave a strong recommendation based on a moderate level of evidence that fecal calprotectin with a cutoff >50 to 100 µg/g should be used to differentiate the presence of IBD from noninflammatory disease (ie, irritable bowel syndrome [IBS]) in patients with suspected IBD. A summary statement without a recommendation stated

that "while colonoscopy remains the gold standard for assessment of postoperative CD recurrence, incorporating FC [fecal calprotectin] monitoring into routine care can reduce the need for invasive procedures and enhance early detection of postoperative recurrence."

In 2025, ACG published a guideline update on the management of ulcerative colitis (UC) in adults. The guideline recommended the use of fecal calprotectin in UC to assess response to therapy, to evaluate suspected relapse, and throughout maintenance (strong recommendation, moderate quality of evidence).

A 2021 ACG guideline on the management of IBS likewise suggests evaluating fecal calprotectin (or fecal lactoferrin) and C reactive protein (CRP) in patients without alarm features and with suspected IBS and diarrhea symptoms to rule out IBD (Strong recommendation; moderate quality of evidence for fecal calprotectin).

American Gastroenterological Association (AGA)

In 2018, the American Gastroenterological Association (AGA) published a guideline on functional gastrointestinal symptoms in patients with IBD. The AGA recommends a stepwise approach to rule-out ongoing inflammatory activity in IBD patients that includes fecal calprotectin, endoscopy with biopsy, and imaging. The AGA recommends that in those patients with indeterminate fecal calprotectin levels and mild symptoms, calprotectin monitoring at 3-to-6-month intervals may allow anticipatory management of impending flares. However, "the optimal cutoff for biomarkers remains a source of debate" and overtreatment for symptoms that are due to functional pathophysiology rather than inflammation can increase adverse effects with no symptomatic benefit.

A 2019 guideline from the AGA on laboratory evaluation of functional diarrhea and diarrhea-predominant IBS in adults gave a conditional recommendation based on low quality evidence to use either fecal calprotectin or fecal lactoferrin to screen for IBD. A threshold value of 50 µg/g for fecal calprotectin was recommended to optimize sensitivity for IBD.

A 2021 clinical practice update from the AGA on the management of IBD in older adults, states that: "Fecal calprotectin or lactoferrin may help prioritize patients with a low probability of IBD for endoscopic evaluation. Individuals presenting with hematochezia or chronic diarrhea with intermediate to high suspicion for underlying IBD, microscopic colitis, or colorectal neoplasia should undergo colonoscopy."

Two 2023 guidelines from the AGA were published on the role of biomarkers for the management of UC and CD. The recommendations regarding fecal calprotectin testing from both guidelines are summarized in Table 19.

Table 19. AGA Clinical Practice Guideline Recommendations on Role of Biomarkers for the Management of UC

Recommendation	Strength of Recommendation	Certainty of Evidence
Ulcerative colitis		
In patients with UC in symptomatic remission, the AGA suggests a monitoring strategy that combines biomarkers and symptoms, rather than symptoms alone	Conditional	Moderate
In patients with UC in symptomatic remission, the AGA suggests using fecal calprotectin < 150 µg/g, normal fecal lactoferrin, or	Conditional	Low (for fecal calprotectin)

normal CRP to rule out active inflammation and avoid routine endoscopic assessment of disease activity		
In patients with UC in symptomatic remission but elevated stool or serum markers of inflammation (fecal calprotectin > 150 µg/g, elevated fecal lactoferrin, elevated CRP), the AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment	Conditional	Very low
In patients with UC with moderate to severe symptoms suggestive of flare, the AGA suggests using fecal calprotectin > 150 µg/g , elevated fecal lactoferrin, or elevated CRP to rule inactive inflammation and inform treatment adjustment and avoid routine endoscopic assessment solely for establishing presence of active disease	Conditional	Low (for fecal calprotectin)
In patients with UC with mild symptoms, with elevated stool or serum markers of inflammation (fecal calprotectin > 150 µg/g, elevated fecal lactoferrin, or elevated CRP), the AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment.	Conditional	Very low
In patients with UC with mild symptoms, with normal stool or serum markers of inflammation (fecal calprotectin < 150 µg/g, normal fecal lactoferrin, or normal CRP), the AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment.	Conditional	Very low
In patients with UC, the AGA makes no recommendation in favor of, or against, a biomarker-based monitoring strategy over an endoscopy-based monitoring strategy to improve long-term outcomes.	No recommendation	Knowledge gap
Crohn's disease		
In patients with CD in symptomatic remission, the AGA suggests a monitoring strategy that combines biomarkers and symptoms, rather than symptoms alone	Conditional	Low
In patients with CD in symptomatic remission with recent confirmation of endoscopic remission (without any change in clinical status, on stable therapy), the AGA suggests using fecal calprotectin <150 µ/g and/or CRP <5 mg/L to rule out active inflammation, and avoid routine endoscopic assessment of disease activity	Conditional	Low to moderate
In patients with CD in symptomatic remission without recent confirmation of endoscopic remission, the AGA suggests endoscopic evaluation to rule out active inflammation, rather than relying solely on fecal calprotectin or CRP	Conditional	Low to moderate

In patients with CD in symptomatic remission, with elevated biomarkers of inflammation (fecal calprotectin >150 µ/g, CRP >5 mg/L), the AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment	Conditional	Low
In patients with symptomatically active CD, the AGA suggests a biomarker-based assessment and treatment adjustment strategy, rather than relying on symptoms alone	Conditional	Moderate
In patients with CD with mild symptoms and elevated biomarkers of inflammation (fecal calprotectin >150 µ/g, CRP >5 mg/L), the AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment	Conditional	Very low
In patients with CD with mild symptoms and normal biomarkers of inflammation (fecal calprotectin <150 µ/g, CRP <5 mg/L), the AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment	Conditional	Very low
In patients with CD with moderate to severe symptoms, the AGA suggests using fecal calprotectin >150 µ/g or CRP > 5 mg/L, to rule in active inflammation and inform treatment adjustment and avoid routine endoscopic assessment of disease activity	Conditional	Low to moderate
In patients with CD with moderate to severe symptoms with normal biomarkers of inflammation (fecal calprotectin <150 µ/g, CRP <5 mg/L), the AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment	Conditional	Low
In asymptomatic patients with CD after surgically induced remission within the past 12 months, who are at low risk of postoperative recurrence or who have 1 or more risk factors for recurrence but are on postoperative pharmacologic prophylaxis, the AGA suggests using fecal calprotectin <50 µ/g to avoid routine endoscopic assessment of disease activity	Conditional	Moderate
In asymptomatic patients with CD after surgically induced remission within the past 12 months, who are at high baseline risk of recurrence and are not receiving postoperative pharmacologic prophylaxis, the AGA suggests endoscopic evaluation rather than relying solely on biomarkers, for assessing endoscopic recurrence	Conditional	Low to moderate
In patients with CD, the AGA makes no recommendation in favor of, or against, a biomarker-based monitoring strategy over an endoscopy-based monitoring strategy to improve long-term outcomes.	No recommendation	Knowledge gap

AGA: American Gastroenterological Association; UC: ulcerative colitis

The European Crohn's and Colitis Organization (ECCO) and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR)

In 2019 the ECCO-ESGAR published a joint guideline for the Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications which stated:

- “Response to treatment in active ulcerative colitis [UC] should be determined by a combination of clinical parameters, endoscopy, and laboratory markers such as C-reactive protein [CRP] and faecal calprotectin.”
- “In patients with UC who clinically respond to medical therapy, mucosal healing [MH] should be determined endoscopically or by faecal calprotectin [FC] approximately 3 to 6 months after treatment initiation.”

International Organization for the Study of Inflammatory Bowel Disease

In 2021, the Selecting Therapeutic Targets in IBD (STRIDE) group, which was initiated by the International Organization for the Study of IBD (IOIBD), updated its recommendations for treating to target in Crohn's disease and UC. In this update, the reduction of fecal calprotectin to an acceptable range has been added as a formal intermediate treatment target. Per STRIDE-II: "Normalization of CRP (to values under the upper limit of normal) and fecal calprotectin (to 100–250 mg/g) is an intermediate treatment target in UC and CD. Consider changing treatment if this target has not been achieved." The strength of this recommendation is 8.2 out of 10 (“10” denotes complete agreement and “1” complete disagreement); 80% of votes scored between 7 to 10 using this scale. The Group also notes that the cutoff value of fecal calprotectin is dependent on the desired outcome; lower thresholds (e.g., <100 mg/g) have been proposed for deep healing (both endoscopic and transmural healing) or histological healing, and higher values (e.g., <250 mg/g) for less stringent outcomes (e.g., Mayo Endoscopic Subscore of 0 or 1 in UC).

National Institute for Health and Care Excellence (NICE)

The National Institute for Health and Care Excellence (2013; recommendation 1.1 was updated in 2017), published guidance on fecal calprotectin testing for inflammatory diseases of the bowel. The guidance made the following recommendations:

> 1.1 “Faecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS) in adults with recent-onset lower gastrointestinal symptoms for whom specialist assessment is being considered, if:
>
> 1. cancer is not suspected, having considered the risk factors (for example, age)…
>
> 1.2 Faecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of IBD or non-IBD (including IBS) in children with suspected IBD who have been referred for specialist assessment….”

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review can be located at clinicaltrials.gov.

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CODES

To report provider services, use appropriate CPT codes, HCPCS codes, Revenue codes, and/or ICD diagnosis codes.

Codes	Number	Description
CPT		
	83630	Lactoferrin, fecal; qualitative
	83631	Lactoferrin, fecal; quantitative
	83993	Calprotectin, fecal
HCPCS		
	No code(s)	
Type of Service	Laboratory	
Place of Service	Outpatient	

POLICY HISTORY

Date	Reason	Action
February 2026	Annual Review	Policy Renewed
February 2025	Annual Review	Policy Renewed
October 2024	Annual Review	Policy Revised
October 2023	Annual Review	Policy Revised
October 2022	Annual Review	Policy Renewal
October 2021	Annual Review	Policy Revised
October 2020	Annual Review	Policy Revised
June 2020	Interim Review	Policy Revised
October 2019	Annual Review	Policy Revised
October 2018	Annual Review	Policy Revised
October 2017	Annual Review	Policy Revised

Date	Reason	Action
October 2016	Annual Review	Policy Revised
November 2015	Annual Review	Policy Revised
December 2014	Annual Review	Policy Renewed
February 2014	Annual Review	Policy Renewed
March 2013	Annual Review	Policy Renewed
March 2012	Annual Review	Policy Renewed
April 2011	Literature Review	New Policy

Appendix

Appendix 1:

2018 Clinical Input

Objective

Clinical input was sought to help determine whether the use of fecal calprotectin testing for individuals with suspected IBD when endoscopy with biopsy is being considered would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 3 respondents, including 1 specialty society-level response and 2 physician-level responses identified through specialty societies including physicians affiliated with academic medical centers.

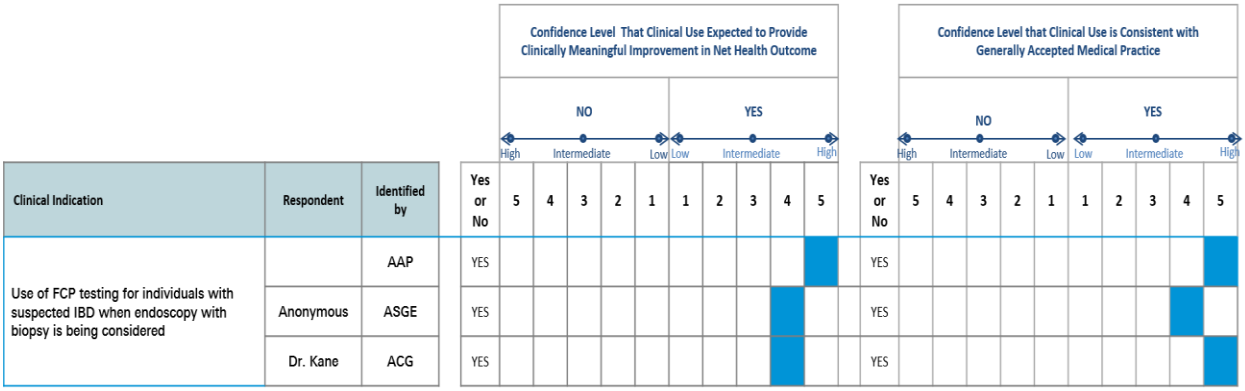
Respondents

Clinical input was provided by the following specialty societies and physician members identified by a specialty society or clinical health system:

- American Academy of Pediatrics (AAP).
- Anonymous, MD, Gastroenterology/Inflammatory Bowel Disease, identified by the American Society for Gastrointestinal Endoscopy (ASGE).
- Sunanda V. Kane, MD, MSPH, FACG, Gastroenterology, identified by the American College of Gastroenterology (ACG).

Clinical input provided by the specialty society at an aggregate level is attributed to the specialty society. Clinical input provided by a physician member designated by a specialty society or health system is attributed to the individual physician and is not a statement from the specialty society or health system. Specialty society and physician respondents participating in the Evidence Street® clinical input process provide review, input, and feedback on topics being evaluated by Evidence Street. However, participation in the clinical input process by a specialty society and/or physician member designated by a specialty society or health system does not imply an endorsement or explicit agreement with the Evidence Opinion published by BCBSA or any Blue Plan.

Ratings



Appendix Table 1. Respondent Profile

Specialty Society						
No.	*Name of Organization*			*Clinical Specialty*		
1	American Academy of Pediatrics			Pediatrics, Pediatric Gastroenterology, Hepatology and Nutrition		
Physician						
No.	*Name*	*Degree*	*Institutional Affiliation*	*Clinical Specialty*	*Board Certification and Fellowship Training*	
Identified by American Society for Gastrointestinal Endoscopy						
2	Anonymous	MD		Gastroenterology/Inflammatory Bowel Disease	Gastroenterology	
Identified by American College of Gastroenterology						
3	Sunanda V. Kane	MD, MSPH	Mayo Clinic	Gastroenterology	Gastroenterology; Internal Medicine	

Appendix Table 2. Respondent Conflict of Interest Disclosure

No.	**1. Research support related to the topic where clinical input is being sought**	**2. Positions, paid or unpaid, related to the topic where clinical input is being sought**	**3. Reportable, more than $1000, health care-related assets or sources of income for myself, my spouse, or my dependent children related to the topic**	**4. Reportable, more than $350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the**

					where clinical input is being sought		**topic where clinical input is being sought**	
	Yes/No	*Explanation*	*Yes/No*	*Explanation*	*Yes/No*	*Explanation*	*Yes/No*	*Explanation*
1	No		No		No		No	
2	No		No		No		No	
3	No		No		No		No	

Individual physician respondents answered at an individual level. Specialty Society respondents provided aggregate information that may be relevant to the group of clinicians who provided input to the Society-level response

Responses

1. We are seeking your opinion on whether using FCP testing for the above indication provides a clinically meaningful improvement in net health outcome. Please respond based on the evidence and your clinical experience. Please address these points in your response:
    - Relevant clinical scenarios (eg, a chain of evidence) where the technology is expected to provide a clinically meaningful improvement in net health outcome;
    - Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for this indication;
    - Considerations for use in the pediatric population; and\
    - Supporting evidence from the authoritative scientific literature (please include PMID).

No.	Response
1	Our opinion is that the use of FCP testing for individuals with suspected IBD provides a clinically meaningful improvement in healthcare by adding important and actionable information to the clinical decision-making involved in referring for endoscopy with biopsy (if FCP is elevated) or in deciding that endoscopy with biopsy is not warranted (if FCP is within normal limits). In brief, ALL EVIDENCE SUGGESTS that FCP adds the most diagnostic value to symptoms compared with blood markers. Adding fecal calprotectin to the diagnostic workup of pediatric patients with symptoms suggestive of IBD considerably decreases the number of patients in the group in whom challenges in clinical decision making are most prevalent. There is no relevant inclusion/exclusion criteria, as IBD can affect children and adults of all ages, all ethnicities and with all co-morbidities, and should be considered in the appropriate clinical scenarios. The use of FCP is particularly important in pediatric populations, where children may not be able to fully participate as medical historians and may have non-specific and/or atypical symptoms. There is much supporting evidence from the authoritative literature. We call your attention particularly to the following: • Holtman GA, Lisman-van Leeuwen Y, Day AS, et al. Use of Laboratory Markers in Addition to Symptoms for Diagnosis of Inflammatory Bowel Disease in Children: A

No.	Response
	Meta-analysis of Individual Patient Data. *JAMA Pediatr*. Oct 2017;171(10): 984-991. PMID 28806445 "Of 16 eligible studies, authors of 8 studies (n = 1120 patients) provided their data sets. All blood markers and fecal calprotectin individually significantly improved the discrimination between pediatric patients with and those without IBD, when added to evaluation of symptoms. The best marker-fecal calprotectin-improved the area under the curve of symptoms by 0.26 (95% CI, 0.21-0.31). The second best marker-erythrocyte sedimentation rate-improved the area under the curve of symptoms by 0.16 (95% CI, 0.11-0.21). When fecal calprotectin was added to the model, the proportion of patients without IBD correctly classified as low risk of IBD increased from 33% to 91%. The proportion of patients with IBD incorrectly classified as low risk of IBD decreased from 16% to 9%. The proportion of the total number of patients assigned to the intermediate-risk category decreased from 55% to 6%."
2	a. FCP testing for individuals with suspected IBD would provide a clinically meaningful improvement in net health outcome if a positive test would be used to identify patients who are most likely to need endoscopy for suspected inflammatory bowel disease and if a negative test would be used to safely exclude inflammatory bowel disease and avoid endoscopic evaluation. FCP has been shown to have high sensitivity and specificity for differentiating between IBD and functional gastrointestinal disorders. The ACG (PMID: 29610508) endorses the use of FCP as "a helpful test that should be considered to help differentiate the presence of IBD from irritable bowel syndrome (strong recommendation, moderate level of evidence". NICE endorses the use of FCP as a decision diagnostic for inflammatory bowel disease and irritable bowel syndrome and use of this test is consistent with generally accepted medical practice. A recent expert opinion (Reenars C, Bossuyt P, Hindrycks P et al: Expert opinion for use of faecal calprotectin in diagnosis and monitoring of inflammatory bowel disease in daily clinical practice. *United European Gastroenterology Journal.* 2018 accessible at: https://doi.org/10.1177/2050640618784046) that utilized an electronic Delphi process and reports concordance rate within the expert panel provides further support for the use of FCP in clinical practice, stating: • "FC >250 mg/g identifies patients who are most likely to have intestinal inflammation and justifies further endoscopic examination. (91%) • FC between 100 and 250 mg/g could require a second measurement within three months. (97%) • FC <100 mg/g has a very high negative predictive value for IBD, justifying its use as a screening test to reduce the number of endoscopies and thereby the costs of health care management. This strategy delays the diagnosis in only a small proportion of patients. (97%)" b. The BSG guidelines state, "It should not be used in patients with acute diarrhoea, bloody diarrhoea, or in older patients where the need to rule out polyps or cancer mandates colonoscopy anyway." These are reasonable exclusion criteria. c. I defer to pediatric GI specialist d. See references below: o Banerjee A, Srinivas M, Eyre R, et al. Faecal calprotectin for differentiating between irritable bowel syndrome and inflammatory bowel disease: a useful screen in daily gastroenterology practice. *Frontline Gastroenterol.* Jan

No.	Response
	2015;6(1):20-26. PMID 28839790Menees SB, Powell C, Kurlander J, et al. A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. *Am J Gastroenterol*.Mar 2015;110(3):444-54. PMID 25732419 o Kennedy NA, Clark A, Walkden A, et al. Clinical utility and diagnostic accuracy of faecal calprotectin for IBD at first presentation to gastroenterology services in adults aged 16-50 years. *J Crohns Colitis.* Jan 2015;9(1):4109. PMID 25135754 o van Rheenen PF, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis. *BMJ.* July 2010;15;341. PMID 20634346 o Yang Z, Clark N, Park KT. Effectiveness and cost-effectiveness of measuring fecal calprotectin in diagnosis of inflammatory bowel disease in adults and children. *Clin Gastroenterol Hepatol.* Feb 2014;12(2):253-62. PMID 23883663 o Waugh N, Cummins E, Royle P, et al. Faecal calprotectin testing for differentiating amongst inflammatory and non-inflammatory bowel diseases: systematic review and economic evaluation. Health Technol Assess. Nov 2013;17(55):xv-xix. 1-211. PMID 24286461 o Lin JF, Chen JM, Zuo JH, et al. Meta-analysis: fecal calprotectin for assessment of inflammatory bowel disease activity. *Inflamm Bowel Dis.* Aug 2014;20(8):1407-15. PMID 24983982 o Dhaliwal A, Zeino Z, Tomkins C, et al. Utility of faecal calprotectin in inflammatory bowel disease (IBD): what cut-offs should we apply? *Frontline Gastroenterol.* Jan 2015;6(1):14-19. PMID 25580205 o Chang MH, Chou JW, Chen SM, et al. Faecal calprotectin as a novel biomarker for differentiating between inflammatory bowel disease and irritable bowel syndrome. *Mol Med Rep.* Jul 2014;10(1):522-6. PMID 24788223 o Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Guideline: Management of Crohn's Disease in Adults. *Am J Gastroenterol.* Apr 2018;113(4):481-517. PMID 29610508 o https://www.nice.org.uk/guidance/dg11/chapter/1-Recommendations o https://www.bsg.org.uk/resource/bsg-guidance-on-the-use-of-faecal-calprotectin-testing-in-ibd.html o https://doi.org/10.1177/2050640618784046
3	Fecal calprotectin (FCP) is a highly reliable and very sensitive test for inflammation in patients with colonic inflammation and has also demonstrated a high negative predictive value for patients with Crohn's disease who have had surgery. In both situations, appropriate use of this test is associated with decreased utilization of colonoscopy. Most recently, the test has demonstrated utility in a "treat to target" strategy in Crohn's disease that will transform our management, and definitely improve outcomes. In the CALM study, using a combination of CRP and FCP as targets for therapeutic adjustments resulted in a statistically greater successful mucosal healing and steroid-free remission. There are now two recent studies that specifically address the utility of fecal calprotectin to predict mucosal healing. A retrospective study in 68 patients with ulcerative colitis who had fecal calprotectin levels collected within 6 weeks of colonoscopy were reviewed. Fecal

No.	Response
	calprotectin significantly correlated with mucosal healing and histological activity with a sensitivity of 86% and a specificity of 87%. In a prospective study of 80 Canadian IBD patients undergoing scheduled colonoscopy had fecal calprotectin levels obtained 48 hours prior to their procedure. Fecal calprotectin alone had a positive predictive value for mucosal healing of 77% and in combination with clinical symptoms increased it to 84%. Fecal calprotectin is cost-effective care. From a resource utilization standpoint, FCP is far less expensive than endoscopic evaluations (as well as cross-sectional radiologic imaging) and far more preferable from a patient tolerability point of view. Any rationale that calprotectin is sensitive for any inflammation, and therefore not helpful, is precisely why it is helpful for discerning active disease in patients with known IBD versus patients in a non-inflammatory state with similar symptoms (IBS, bile salt diarrhea, functional diarrhea). The goal is to be able to prevent a patient from an invasive test like endoscopy, which also significantly saves costs. A recent study demonstrated that the complication rate for colonoscopy is higher in IBD patients also suggests that anything we can do to reduce the need for a colonoscopy will improve care. Since we now treat to the goal of mucosal healing, for which there is sufficient evidence of improved outcomes, having a noninvasive test to assess for any disease activity promotes quality of care and reduces programmatic costs. • Colombel JF, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. *Lancet*. Dec 2018;390(10114):2779-2789. PMID 29096949 • Boschetti G, Laidet M, Moussata D, et al. Levels of fecal calprotectin are associated with the severity of postoperative endoscopic recurrence in asymptomatic patients with Crohn's disease. *Am J Gastroenterol*. Jun 2015;110(6):865-872. PMID 25781366 • Patel A, Panchal H, Dubinsky M. Fecal Calprotectin Levels Predict Histologic Healing in Ulcerative Colitis. *Inflamm Bowel Dis*. Sep 2017;23(9):1600-1604. PMID 28590341 • Ma C, Lumb R, Walker EV, et al. Noninvasive Fecal Immunochemical Testing and Fecal Calprotectin Predict Mucosal Healing in Inflammatory Bowel Disease: A Prospective Cohort Study. *Inflamm Bowel Dis*. Sep 2017;23(9):1643-1649. PMID 28644184 • Ferreira J, Akbari M, Gashin L, et al. Prevalence and lifetime risk of endoscopy-related complications among patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. Oct 2013;11(10):1288-93. PMID: 23669305 • Laharie D, Mesli S, El Hajbi F, et al. Prediction of Crohn's disease relapse with faecal calprotectin in infliximab responders: a prospective study. *Aliment Pharmacol Ther*. Aug 2011;34(4):462-469. PMID: 21671970 • Turner D, Leach ST, Mack D, et al. Faecal calprotectin, lactoferrin, M2-pyruvate kinase and S100A12 in severe ulcerative colitis: a prospective multicentre comparison of predicting outcomes and monitoring response. *Gut*. Sep 2010;59(9):1207-1212. PMID: 20801771

2. An important health outcome is avoiding negative endoscopy with biopsy, and for there to be a meaningful clinical benefit FCP must yield true negative results with an acceptably low trade-off in a missed diagnosis of IBD in those who have false-negative FCP results. Considering the clinical scenario described in your response to question 1, address these points:

a. What would be the negative predictive value of FCP testing required to achieve a clinically meaningful reduction in the frequency of negative endoscopy and biopsy?
b. Under what circumstances might negative FCP results still require endoscopy with biopsy?
c. Supporting evidence from the authoritative scientific literature (please include PMID).

No.	*Response*
1	Overall, there is strong evidence to believe that FCP has true negative results with acceptably low tradeoffs in missed diagnoses of IBD in those who have false-negative FCP results. In particular, evidence suggests that FCP can predict the onset of inflammatory bowel disease with high accuracy and precision. In one study, FCP screening in adults saved $417/patient but delayed diagnosis for 2.2/32 patients with IBD among 100 screened patients. In children, FCP screening saved $300/patient but delayed diagnosis for 4.8/61 patients with IBD among 100 screened patients. If endoscopic biopsy analysis is considered standard for diagnosis, modeling suggests that direct endoscopic evaluation would cost an additional $18,955 in adults and $6250 in children to avoid 1 false-negative result from FC screening. • Yang Z, Clark N, Park KT. Effectiveness and Cost-effectiveness of Measuring Fecal Calprotectin in Diagnosis of Inflammatory Bowel Disease. *Clinical Gastroenterology and Hepatology.* Feb 2014;12(2):253 - 262.e2. PMID 23883663 To ask about the negative predictive value of FCP testing required to achieve a clinically meaningful reduction in the frequency of negative endoscopy and biopsy is a false premise, as it misses the fact that FCP results reflect pre-test likelihood of having the disease. Sensitivity analyses suggest that the cost-effectiveness of FC screening varies with the sensitivity of the test and the pre-test probability of IBD in adults and children. Pre-test probabilities for IBD of ≤75% in adults and ≤65% in children make FC screening cost-effective, but it can be cost-ineffective if the probabilities were ≥85% and ≥78% in adults and children, respectively. Compared with the FC cutoff level of 100 µg/g, the cutoff level of 50 µg/g cost an additional $55 and $43 for adults and children, respectively, but it yielded 2.4 and 6.1 additional accurate diagnoses of IBD per 100 screened adults and children, respectively. What this means is that screening adults and children to measure fecal levels of calprotectin is effective and cost-effective in identifying those with IBD on a per-case basis when the pre-test probability is ≤75% for adults and ≤65% for children. Negative FCP results might still require endoscopy with biopsy or imaging in non-inflammatory predominant Crohn's such as stricturing small bowel disease with no colonic involvement. Children with this disease present with growth failure, but no diarrhea or other colonic inflammatory symptoms or findings. If it is a chronic disease, there may not even be active inflammation; serum markers may all be negative and FCP may be negative as well. Generally speaking, these children may have other signs of chronic disease, including anemia, but even blood counts may be unreliable in positively predicting that endoscopy with biopsy will find granulomatous disease.
2	a. A meta-analysis (PMID: 20634346) that included six studies in adults and seven in children and teenagers, which included studies where data were collected prospectively in a consecutive series of patients with suspected inflammatory bowel disease where patients first underwent FCP testing and then endoscopy, found that in adults the pooled sensitivity of FCP testing was 0.93 (95% confidence interval 0.85 to 0.97) and the pooled specificity was 0.96 (0.79 to 0.99). Per this analysis, in a hypothetical population of 100 adults with suspected inflammatory bowel disease (and an overall mean prevalence of 32%) 3 patients without the disease would go on to have endoscopy and 2 patients with the disease would be missed, reducing the number of adults requiring endoscopy by 67%. These are acceptable values. A limitation of this analysis is that cut-off level is not clear, since results are described as normal or not normal. A systematic review and economic

No.	Response
	evaluation (PMID 24286461) used an FCP cut-off level of 50 µg/g and reported a pooled sensitivity of 93% and specificity of 94% for distinguishing between IBD and IBS. A retrospective cohort study (PMID 25135754) found that using a threshold of ≥ 50 µg/g for IBD vs. functional disease yielded a sensitivity of 0.97, specificity of 0.74, positive predictive value of 0.37 and negative predictive value of 0.99. These are favorable test characteristics. In any clinical scenario, the NPV of FCP will depend on the cut-off values that are used to define a negative, positive and intermediate test. result. In addition, as recommended by the BSG, local laboratory quality assurance processes and care pathways should be established. b. As a specialist, I use the FCP to help guide my decision making on performing endoscopy, so I am not sure of a clinical scenario in which I ordered a negative FCP result and still followed it by endoscopy with biopsy. However, there have been instances where a primary care provider has sent FCP as part of an initial workup for diarrhea. The FCP is negative, but upon evaluation at GI clinic, we learn that patient has a family h/o CD, elevated CRP, and labs concerning for possible malabsorption (low vitamin D, low albumin) where we are concerned about ileal CD or celiac disease and endoscopy with biopsy is still pursued. As has been reported in the literature, some studies suggest that FCP appears to better reflect disease activity in UC rather than CD and that FCP results are less reliable in patients with pure ileal CD, although data/ studies are mixed. Another area of uncertainty is an intermediate test result, which may lead to either repeat testing with FCP to establish a trend or an endoscopy with biopsy for follow-up. c. See references below • van Rheenen PF, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis. *BMJ.* July 2010;15;341. PMID 20634346 • Kennedy NA, Clark A, Walkden A, et al. Clinical utility and diagnostic accuracy of faecal calprotectin for IBD at first presentation to gastroenterology services in adults aged 16-50 years. *J Crohns Colitis.* Jan 2015;9(1):4109. PMID 25135754 • Smith LA, Gaya DR. Utility of faecal calprotectin analysis in adult inflammatory bowel disease. *World J Gastroenterol.* Dec 2012;18(46):6782-9. PMID 23239916 • Costa F, Mumolo MG, Ceccarelli L, et al. Calprotectin in a stronger predictive marker of relapse in ulcerative colitis than in Crohn's disease. *Gut.* Mar 2005;54(3):364-8. PMID 15710984 • Schoepfer AM, Beglinger C, Straumann A, et al. Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. *Am J Gastroenterol.* Jan 2010;105(1);162-9. PMID 19755969 • https://www.bsg.org.uk/resource/bsg-guidance-on-the-use-of-faecal-calprotectin-testing-in-ibd.html
3	The negative predictive value of any test is based on the background prevalence of the disease in question. Since FCP would be used to detect inflammation, the prevalence is high for various other GI conditions. Therefore a negative predicted value greater than 75% (which is currently the care) translates to a clinically meaningful reduction in unnecessary endoscopy. The patients who have other indications for endoscopy i.e. iron deficiency, overt bleeding, or unexplained weight loss may result in a negative FCP where endoscopy is still required.

No.	Response
	• ASGE Standards of Practice Committee, Fisher DA, Shergill AK, Early DS, et al. Role of endoscopy in the staging and management of colorectal cancer. *Gastrointest Endosc*. Jul 2013;78(1):8-12. PMID 23664162 • Hassan C, Di Giulio E, Marmo R, et al. Appropriateness of the indication for colonoscopy: systematic review and meta-analysis. *J Gastrointestin Liver Dis*. Sep 2011;20(3):279-86. PMID: 21961096 • Davila RE, Rajan E, Adler DG, et al. Standards of Practice Committee. ASGE Guideline: the role of endoscopy in the patient with lower-GI bleeding. *Gastrointest Endosc*. Nov 2005;62(5):656-60. PMID 16246674

3. Based on the evidence and your clinical experience for the clinical indication below:
    a. Respond Yes or No whether the intervention would be expected to provide a clinically meaningful improvement in net health outcome; AND
    b. Rate your level of confidence in your Yes or No response using the 1 to 5 scale outlined below.

No.	Indications	Yes/No	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
1	Use of FCP testing for individuals with suspected IBD when endoscopy with biopsy is being considered	Yes					X
2	Use of FCP testing for individuals with suspected IBD when endoscopy with biopsy is being considered	Yes				X	
3	Use of FCP testing for individuals with suspected IBD when endoscopy with biopsy is being considered	Yes				X	

4. Based on the evidence and your clinical experience for the clinical indication below:
    a. Respond Yes or No whether this intervention is consistent with generally accepted medical practice; AND
    b. Rate your level of confidence in your Yes or No response using the 1 to 5 scale outlined below.

No.	Indications	Yes/No	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
1	Use of FCP testing for individuals with suspected IBD when endoscopy with	Yes					X

No.	Indications	Yes/No	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
	biopsy is being considered						
2	Use of FCP testing for individuals with suspected IBD when endoscopy with biopsy is being considered	Yes				X	
3	Use of FCP testing for individuals with suspected IBD when endoscopy with biopsy is being considered	Yes					X

5. Additional narrative rationale or comments and/or any relevant scientific citations (including the PMID) supporting your clinical input on this topic.

No.	Additional Comments
1	The AAP wishes to be clear in its opinion that no test is perfect and it is unlikely that any one test will ever perfectly discriminate between children who have IBD and those who do not. Nevertheless, the AAP believes that the evidence is overwhelmingly strong that FCP used in appropriate clinical scenarios, and in combination with a medical history and other test results, can be used to identify patients with IBD with high levels of sensitivity, especially when compared with other more traditional markers of inflammation. The AAP also believes the evidence is strong that FCP is a reliable marker of mucosal improvement, especially if it is used in combination with other measures including serum markers (i.e. C-reactive protein) and clinical symptoms scores. In turn, the AAP believes the evidence that FCP is a useful test for disease monitoring of children with IBD, especially those with colonic sites of involvement. Treating to achieve mucosal healing will improve long-term health outcomes for children and thereby could decrease morbidity related costs. Implementation of a non-invasive marker such as calprotectin to assess for presence/absence of mucosal healing is particularly valuable in children, in whom we try to perform less invasive endoscopic procedures. FCP is non-invasive and non-painful. It is easily obtained and does not require special equipment. Compared with colonoscopy, FCP is preferable as a test, which if negative may allow a physician to

No.	Additional Comments
	reassure a family that IBD is considerably less likely as a primary diagnosis. In those children with IBD, a decreasing FCP may allow reassurance that the disease is under better control. • Manceau H, Chicha-Cattoir V, Puy H, et al. Fecal calprotectin in inflammatory bowel diseases: update and perspectives. *Clin Chem Lab Med*. 2017;55(4):474-483. PMID 27658156 • D'Angelo F, Felley C, Frossard JL. Calprotectin in Daily Practice: Where Do We Stand in 2017? *Digestion*. 2017;95(4):293-301. PMID 28511188 • Lehmann FS, Burri E, Beglinger C. The role and utility of faecal markers in inflammatory bowel disease. *Therap Adv Gastroenterol*. 2015;8(1):23-36. PMID 25553077 • Jahnsen J, Roseth AG, Aadland E. [Measurement of calprotectin in faeces] Tidsskr Nor Laegeforen. 2009;129(8):743-745. PMID 19373299 • Dale I, Brandtzaeg P, Fagerhol MK, et al. Distribution of a new myelomonocytic antigen (L1) in human peripheral blood leukocytes. Immunofluorescence and immunoperoxidase staining features in comparison with lysozyme and lactoferrin. *Am J Clin Pathol*. Jul 1985;84(1):24-34. PMID 2409791 • Naess-Andresen CF, Egelandsdal B, Fagerhol MK. Calcium binding and concomitant changes in the structure and heat stability of calprotectin (L1 protein) *Clin Mol Pathol*. Oct 1995;48(5):M278-284. PMID 16696022 • Rodrigo L. [Fecal calprotectin] *Rev Esp Enferm Dig*. Dec 2007;99(12):683-688. PMID 18290690 • Bonnin Tomas A, Vila Vidal M, Rosell Camps A. [Fecal calprotectin as a biomarker to distinguish between organic and functional gastrointestinal disease] *Rev Esp Enferm Dig*. Dec 2007;99(12):689-693. PMID 18290691 • Gisbert JP, McNicholl AG. Questions and answers on the role of faecal calprotectin as a biological marker in inflammatory bowel disease. *Dig Liver Dis*. Jan 2009;41(1):56-66. PMID 18602356 • Sherwood RA. Faecal markers of gastrointestinal inflammation. *J Clin Pathol*. Nov 2012;65(11):981-985. PMID 22813730 • Roseth AG, Fagerhol MK, Aadland E, Schjonsby H. Assessment of the neutrophil dominating protein calprotectin in feces. A methodologic study. *Scand J Gastroenterol*. Sep 1992;27(9):793-798. PMID 1411288 • Kristensen V, Lauritzen T, Jelsness-Jorgensen LP, et al. Patient-performed extraction of faecal calprotectin. Clin *Chem Lab Med*. 2016;54(8):1357-1363. PMID 26812797 • Li F, Ma J, Geng S, et al. Fecal calprotectin concentrations in healthy children aged 1-18 months. *PLoS One*. Mar 2015;10(3):e0119574. PMID 25742018 • Zhu Q, Li F, Wang J, et al. Fecal calprotectin in healthy children aged 1-4 years. *PLoS One*. Mar 2016;11(3):e0150725. PMID 26950440 • Oord T, Hornung N. Fecal calprotectin in healthy children. *Scand J Clin Lab Invest*. Apr 2014;74(3):254-258. PMID 24568692 • Hestvik E, Tumwine JK, Tylleskar T, et al. Faecal calprotectin concentrations in apparently healthy children aged 0-12 years in urban Kampala, Uganda: a community-based survey. *BMC Pediatr*. Feb 2011;11:9. PMID 21284894 • Fagerberg UL, Loof L, Merzoug RD, et al. Fecal calprotectin levels in healthy children studied with an improved assay. *J Pediatr Gastroenterol Nutr*. Oct 2003;37(4):468-472. PMID 14508218 • Krzesiek E. Fecal calprotectin as an activity marker of inflammatory bowel disease in children. *Adv Clin Exp Med*. Sep-Oct 2015;24(5):815-822. PMID 26768632

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2	See PMID above
3	Please see above discussion

6. Is there any evidence missing from the attached draft review of evidence that demonstrates clinically meaningful improvement in net health outcome?

No.	Yes/No	Citations of Missing Evidence
1	No	
2	Yes	See PMID above
3	No	

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

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