Clinical Policy Title: Fecal biomarkers in inflammatory bowel disease

Clinical Policy Number: CCP.1279

Effective Date: April 1, 2017
Initial Review Date: October 19, 2016
Most Recent Review Date: November 6, 2018
Next Review Date: November 2019

Policy contains:
- Ulcerative colitis.
- Crohn’s disease.
- Fecal calprotectin.
- Fecal lactoferrin.

Related policies:
- CCP.1194 Measurement of serum antibodies to infliximab and adalimumab
- CCP.1055 Capsule endoscopy

ABOUT THIS POLICY: AmeriHealth Caritas has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas’ clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas’ clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas’ clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas will update its clinical policies as necessary. AmeriHealth Caritas’ clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas considers the use of fecal biomarker testing for the management of inflammatory bowel disease to be investigational and, therefore, not medically necessary.

Limitations:

None.

Alternative covered services:

- Endoscopy.
- Histology.
- Radiologic testing (e.g., computed tomography or magnetic resonance enterography).
Physician consultation.

Background

Inflammatory bowel disease is a group of intestinal disorders characterized by chronic relapsing inflammation of the digestive tract (Loddo, 2015). An estimated 1.0 to 1.3 million Americans suffer from inflammatory bowel disease; the prevalence of inflammatory bowel disease in persons of Caucasian and Ashkenazi Jewish origin is higher than that of other racial and ethnic subgroups (Centers for Disease Control and Prevention, 2016). Approximately 20 to 25 percent of patients with inflammatory bowel disease are diagnosed before 16 years of age, although onset of inflammatory bowel disease before age 5 is rare (Loddo, 2015).

While the exact cause of inflammatory bowel disease is unknown, genetic, environmental, and immune influences, and changes in microbiota have been implicated (Loddo, 2015; Harlan, 2016). It can be painful and even life-threatening, marked by episodes of relapse and remission, and adversely affects quality of life. Inflammatory bowel disease is associated with a high socioeconomic burden and increased risk of colon cancer, and has no cure (Centers for Disease Control and Prevention, 2016).

The two most common subtypes are ulcerative colitis and Crohn’s disease. Ulcerative colitis is characterized by diffuse mucosal inflammation involving primarily the colon and rectum, bloody diarrhea often with prominent symptoms of rectal urgency, and tenesmus (American College of Gastroenterology, 2010).

Crohn’s disease typically involves the ileum and/or colon but can involve any part of the digestive tract from the mouth to the anus; presenting symptoms vary from abdominal pain and typically non-bloody diarrhea to more severe forms involving penetration through the bowel wall and formation of fistula, strictures, and abscesses (Harlan, 2016). The most common complication of Crohn’s disease is intestinal blockage due to swelling and scar tissue (Centers for Disease Control and Prevention, 2016). In pediatric patients, Crohn’s disease is more commonly associated with growth failure and higher rates of surgery and hospitalizations than UC or other non-inflammatory bowel disease disorders (Abraham, 2012). However, the risks of cancer and death are low in this population (Abraham, 2012).

Diagnosis is based on clinical assessment supplemented with radiologic, endoscopic, and histologic criteria to: exclude other etiologies; define the extent and severity of inflammation; and assess the presence of strictures and fistulae (Baumgart, 2009). Inflammatory bowel disease can be confused with irritable bowel syndrome, which is a chronic non-inflammatory bowel disorder that does not result in changes in bowel tissue or increase risk of colorectal cancer. Further invasive diagnostic procedures may be required to obtain a diagnosis and formulate a treatment plan, as treatment for inflammatory bowel disease subtypes and non-inflammatory bowel disease conditions differ.

Biomarkers in inflammatory bowel disease:
New biomarkers have several potential clinical applications: providing object measurement of disease activity and severity; predicting disease course and treatment; monitoring treatment effectiveness; and optimizing drug dosing (Bonneau, 2015; Harlan, 2016). They may avoid unnecessary invasive procedures such as colonoscopies that often show no abnormality. Current biomarkers under consideration include:

- Non-specific inflammatory markers (e.g., C-reactive protein, albumin, and erythrocyte sedimentation rate).
- Fecal markers (e.g., fecal calprotectin and fecal lactoferrin).
- Antibodies (e.g., anti-Saccharomyces cerevisiae antibodies, perinuclear anti-neutrophil cytoplasmic antibodies, anti-outer membrane porin C antibodies, anti-chitobioside carbohydrate antibodies, anti-laminaribioside carbohydrate antibodies, anti-mannobioside carbohydrate antibodies, antichitin antibodies, and anti-laminarin antibodies).
- Novel genetic determinants.

**Searches**

AmeriHealth Caritas searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services.

We conducted searches on September 20, 2018. Search terms were: “Inflammatory Bowel Diseases” (MeSH), and free text terms “inflammatory bowel disease,” “Crohn’s disease,” “ulcerative colitis,” “biomarker,” and “diagnosis.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

We found eight systematic reviews and meta-analyses (Holtman, 2016; Kostakis, 2013; Menees, 2015; Murdoch, 2015; Wang, 2015; Waugh, 2013; Zhou, 2014), four guidelines and one economic analysis for this policy. Three guidelines addressed the management of persons with inflammatory bowel disease (Dignass, 2012; Lichtenstein, 2009; Van Assche, 2010). One guideline also included a cost-effectiveness
Fecal calprotectin and fecal lactoferrin were the most studied fecal biomarkers. The available evidence is of large quantity but low quality and insufficient to support the use of either biomarker for routine clinical use.

The purported clinical value of fecal biomarkers is in the primary care setting to differentiate inflammatory bowel disease from non-inflammatory causes such as irritable bowel syndrome. The results may help guide referral to specialty care for further evaluation, potentially avoiding unnecessary endoscopic procedures and delays in diagnosing inflammatory bowel disease. To be clinically useful, fecal markers would need a high negative predictive value to confidently rule out inflammatory bowel disease.

Studies of diagnostic performance enrolled a highly select group of patients referred to specialty clinics with suspected or known inflammatory bowel disease, resulting in spectrum bias that could inflate estimates of diagnostic accuracy and may not be applicable to the patient mix seen in primary care. High quality studies in the primary care setting are lacking, as is evidence that fecal biomarkers improve patient outcomes in either the primary care or specialty setting.

The optimal cutoff value used to define inflammatory or non-inflammatory disease or to predict relapse versus continued remission has not been determined. Failure to adopt a uniform cutoff value can alter relative test accuracy, and studies reported a wide range of results. Certain conditions and drugs can interfere with test interpretation. For example, fecal calprotectin levels may be elevated in non-inflammatory bowel disease conditions such as infectious enterocolitis, colorectal cancer, or with use of nonsteroidal anti-inflammatory drugs. Additional high-quality studies (e.g., patients stratified by disease type, severity, and distribution) are required to confirm the predictive value of fecal lactoferrin.

There is a lack of consensus among professional guidelines regarding the clinical value of fecal biomarkers in inflammatory bowel disease (Dignass, 2012; Lichtenstein, 2009; Van Assche 2010). Only National Institute for Health and Care Excellence recommends fecal calprotectin testing as an option to assist primary care physicians with the differential diagnosis of inflammatory bowel disease or irritable bowel syndrome in adults with recent onset lower gastrointestinal symptoms prior to referral to a specialist if cancer is not suspected, or in children with suspected inflammatory bowel disease who have been referred for specialist assessment. In both cases appropriate quality assurance processes and locally agreed care pathways must be in place for the testing. Their recommendations were based on a systematic review and economic modeling specific to the United Kingdom population (National Institute for Health and Care Excellence, 2013).

**Policy updates:**

In 2017, we identified one new predictive modeling study (Holtman, 2017), and one clinical care algorithm by the American Gastroenterological Association (2017). Results of predictive modeling suggest adding fecal calprotectin to the diagnostic workup may improve the risk classification of
pediatric patients with symptoms suggestive of inflammatory bowel disease (Holtman, 2017). However, there continues to be no direct evidence that fecal calprotectin testing changes patient management or improves clinical outcomes.

The American Gastroenterological Association (2017) includes fecal calprotectin as one of several clinical laboratory tests to assess inflammatory status in persons with Crohn’s disease but not with ulcerative colitis; whether treatment decisions should be based on inflammatory biomarkers or colonoscopy may depend on an historic correlation between the biomarker and colonoscopy in the patient. We found no new guidelines in pediatric populations that addressed the clinical use of fecal biomarkers. The new information does not change previous conclusions, and no policy changes are warranted.

In 2018, we added one guideline (Magro, 2018) and updated the National Institute for Health and Care Excellence guideline. No relevant peer-reviewed references were identified. Policy ID changed from 08.01.08 to CCP.1279.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td><strong>Holtman (2017)</strong>&lt;br&gt;Use of laboratory markers in addition to symptoms for diagnosis of inflammatory bowel disease in children:</td>
<td><strong>Key points:</strong></td>
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<tr>
<td></td>
<td>• Meta-analysis of individual patient data from eight studies (1,120 total patients with chronic gastrointestinal symptoms). Results confirmed by endoscopy and histopathology or clinical follow-up. Prediction model based on symptoms and individual laboratory markers was developed to determine diagnostic value.</td>
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<tr>
<td></td>
<td>• When fecal calprotectin was added, the proportion of patients:</td>
</tr>
<tr>
<td></td>
<td>‒ Without inflammatory bowel disease correctly classified as low risk of inflammatory bowel disease increased from 33% to 91%.</td>
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<tr>
<td></td>
<td>‒ With inflammatory bowel disease incorrectly classified as low risk of inflammatory bowel disease decreased from 16% to 9%.</td>
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<tr>
<td></td>
<td>‒ Assigned to the intermediate-risk category decreased from 55% to 6%.</td>
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<td><strong>Murdoch (2015)</strong> for the Selecting Therapeutic Targets in Inflammatory Bowel Disease program, sponsored by the International Organization for the Study of Inflammatory Bowel Disease. Biomarkers as treatment targets in inflammatory bowel disease</td>
<td><strong>Key points:</strong></td>
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<td>• Systematic review and consensus expert opinion of 50 studies. Best studied: C-reactive protein and fecal calprotectin.</td>
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<td>• In Crohn’s Disease and ulcerative colitis, C-reactive protein, fecal calprotectin and fecal lactoferrin have inadequate diagnostic characteristics to be safe surrogates for endoscopic, radiographic, or clinical end points.</td>
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<td>• C-reactive protein and fecal calprotectin are adjunctive measures that help alert the clinician to pursue further investigation; evaluations of fecal lactoferrin are very limited.</td>
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<td><strong>Wang (2015)</strong></td>
<td><strong>Key points:</strong></td>
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<td>Citation</td>
<td>Content, Methods, Recommendations</td>
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| Diagnostic accuracy of fecal lactoferrin for inflammatory bowel disease: a meta-analysis | - Meta-analysis of 14 studies (1,816 total patients).  
- Overall quality: moderate. Heterogeneous designs, varied cut-offs.  
- Inflammatory bowel disease vs. non-inflammatory bowel disease: Se 0.82, Sp 0.95.  
- Crohn’s Disease diagnosis: Se 0.75, Sp 1.00.  
- Ulcerative colitis diagnosis: Se 0.82, Sp 1.00.  
- Fecal lactoferrin as screening marker has high Sp and a modest Sp for differentiating inflammatory bowel disease and functional disorders, more so with UC than CD.  
- Fecal lactoferrin cannot replace invasive tests, but might avoid unnecessary invasive procedures. |
| Zhou (2014) Fecal lactoferrin in discriminating inflammatory bowel disease from irritable bowel syndrome | **Key points:**  
- Meta-analysis of seven studies (1,012 total patients): 609 patients with inflammatory bowel disease, 381 with IBS and 22 healthy controls.  
- Quality assessment: low to moderate. Heterogeneous patient and test characteristics.  
- Inflammatory bowel disease versus IBS:  
  - Se 0.78 (95% confidence interval [CI] 0.75 to 0.82); Sp 0.94 (95% CI 0.91 to 0.96).  
  - Positive likelihood ratio (LR) 12.31 (95% CI 5.93 to 29.15); negative LR 0.23 (95% CI 0.18 to 0.29).  
  - Area under the summary receiver-operating characteristic curve 0.94 (95% CI 0.90 to 0.98).  
  - Diagnostic odds ratio 52.65 (95% CI 25.69 to 107.91).  
- Data reliability depends on methodological quality of studies: optimal cut-off could not be determined. |
| National Institute for Health and Care Excellence (2013; updated 2017) Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel | **Key points:**  
- Systematic review and cost-effectiveness analysis from the UK perspective.  
- Recommends fecal calprotectin testing as an option to support clinicians with the differential diagnosis of inflammatory bowel disease or irritable bowel syndrome in adults with recent onset lower gastrointestinal symptoms for whom specialist assessment is being considered, if:  
  - Cancer is not suspected, having considered the risk factors.  
  - Appropriate quality assurance processes and locally agreed care pathways are in place for the testing.  
- Recommends fecal calprotectin as an option to support clinicians with the differential diagnosis of inflammatory bowel disease or non-inflammatory bowel disease (including irritable bowel syndrome) in children with suspected inflammatory bowel disease who have been referred for specialist assessment, if appropriate quality assurance processes and locally agreed care pathways are in place for the testing. |
| Dignass (2012) for European Crohn’s and Colitis Organisation (ECCO) Guideline: Diagnosis and management of ulcerative colitis | **Key points:**  
- Routine use of the most widely studied serologic markers, perinuclear anti-neutrophil cytoplasmic antibodies and anti-Saccharomyces cerevisiae antibodies, is not justified.  
- Fecal calprotectin has limited clinical use, but its high negative predictive value may have value in patients with a low likelihood of other pathology.  
- Endoscopy and radiological procedures are recommended. |
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<tr>
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| Van Assche (2010) for ECCO Guideline: Crohn’s disease | **Key points:**  
- Fecal calprotectin and fecal lactoferrin are emerging as surrogate markers of mucosal healing, but the predictive value of uniform thresholds at an individual level has not been clearly demonstrated. Fecal calprotectin may be used to identify gut inflammation.  
- Serologic testing may be used as an adjunct to diagnosis, but the best available tests (anti-Saccharomyces cerevisiae antibodies and antineutrophil cytoplasmic antibody) are unlikely to be useful in routine diagnosis. These and other serologic markers cannot differentiate Crohn’s disease from ulcerative colitis.  
- No genetic tests are recommended for routine use. |
| Lichtenstein (2009) for the American College of Gastroenterology Guideline: Management of Crohn’s disease in adults | **Key points:**  
- Genetic testing is currently not recommended.  
- Serologic studies are not sufficiently sensitive or specific to recommend as screening tools.  
- Presence of fecal leukocytes (i.e., abnormal fecal calprotectin or fecal lactoferrin) can confirm intestinal inflammation or inflammation in general. |

**References**

**Professional society guidelines/other:**


National Institute for Health and Care Excellence. Faecal calprotectin diagnostic tests for inflammatory


**Peer-reviewed references:**


Menees SB, Powell C, Kurlander J, Goel A, Chey WD. 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.* 2015; 110(3): 444 – 454. DOI: 10.1038/ajg.2015.6.


**Centers for Medicaid & Medicare Services National Coverage Determinations:**

No National Coverage Determinations identified as of the writing of this policy.

**Local Coverage Determinations:**

No Local Coverage Determinations identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comments</th>
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<tr>
<td>83630</td>
<td>Lactoferrin, fecal; qualitative</td>
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<tr>
<td>83993</td>
<td>Calprotectin, fecal</td>
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<tr>
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<tbody>
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<td>K50.00</td>
<td>Crohn’s disease of small intestine</td>
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<tr>
<td>K50.10</td>
<td>Crohn’s disease of large intestine</td>
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<tr>
<td>K50.80</td>
<td>Crohn’s disease of both small and large intestine</td>
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<tr>
<td>K50.90</td>
<td>Crohn’s disease, unspecified</td>
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<tr>
<td>K51.90</td>
<td>Ulcerative colitis, unspecified</td>
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<thead>
<tr>
<th>HCPCS Level II Code</th>
<th>Description</th>
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