Fecal Calprotectin Test

File Name: fecal_calprotectin_test
Origination: 8/2009
Last CAP Review: 11/2017
Next CAP Review: 11/2018
Last Review: 3/2018

Description of Procedure or Service

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

Background

Inflammatory bowel disease (IBD) is a chronic inflammatory condition that encompasses two main forms: Crohn disease and ulcerative colitis, which overlap in clinical and pathologic characteristics but have distinct features. Crohn 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 one or more of a variety of signs and symptoms that can be gastrointestinal (eg, abdominal pain, bloody diarrhea, perianal fistulae), systemic (eg, weight loss, fatigue, growth failure in children), and extraintestinal (eg, characteristic rashes, uveitis, arthritis) in nature. Patients may present with or develop a range of severity levels, including life-threatening illness. Treatments include oral and rectal salicylates, glucocorticoids, immunomodulators (eg, methotrexate), and multiple biologic therapies (eg, infliximab), depending on the disease severity, which are recommended by the American Gastroenterological Association and other organizations.

Making a diagnosis of 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 evaluate disease severity, as well as small bowel imaging, and endoscopy (upper GI and colonoscopy) with biopsies.

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

Therefore, 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 (ANCA) tend to have low sensitivity and specificity for intestinal inflammation because they are affected by inflammation outside of the gastrointestinal tract. Fecal markers, in contrast, have the potential for being more specific to the diagnosis of GI tract disorders, since their levels are not elevated in extradigestive 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
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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.

Fecal calprotectin is one protein that could possibly be used as a marker of inflammation. It is a calcium- and zinc-binding protein that accounts for about 60% of the neutrophils’ 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, a potential advantage of fecal calprotectin as a marker is that it has been shown to be stable in feces at room temperature for up to a week, leaving enough time for patients to collect samples at home and send them to a laboratory for testing. In contrast, lactoferrin, another potential fecal marker of intestinal inflammation, is stable at room temperature for about 2 days.

Potential disadvantages of fecal calprotectin as a marker of inflammation include that fecal calprotectin levels increase after use of non-steroidal anti-inflammatory drugs, that levels may change with age, and that bleeding (e.g., nasal or menstrual) may cause an elevated fecal calprotectin level. Moreover, there is uncertainty about the optimal cutoff to distinguish between inflammatory bowel disease and non-inflammatory disease.

Fecal calprotectin testing has been used to distinguish between organic and functional intestinal disease. Some consider fecal calprotectin to be a marker of neutrophilic intestinal inflammation rather than a marker of organic disease and believe the appropriate use is to distinguish between inflammatory bowel disease and non-inflammatory bowel disease. In practice, the test might be suitable for selecting patients with IBD symptoms for endoscopy, for example, 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, results of calprotectin testing could potentially be used to change treatment, such as adjusting medication levels.

Regulatory Status
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 to aid in the diagnosis of inflammatory bowel disease and to differentiate IBD from irritable bowel syndrome (IBS), when used in conjunction 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 the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing.

In 2014, CalPrest® (Europolis SpA, Trieste, Italy) and in 2016, CalPrest®NG (Europolis SpA) were cleared for marketing by FDA through the 510(k) process. According to the FDA summary, CalPrest® “is identical” to the PhiCal® test “in that they are manufactured by Europolis S.p.A. Trieste, Italy. Compared with CalPrest®, the differences in CalPrest®NG include the name of the test on the labels, detection antibody, and 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.”

Rapid fecal calprotectin tests that can be used in the home or physician’s office are commercially available in Europe and Canada (eg, Calprosmart, Calpro AS, Norway; Quantum Blue Calprotectin®, Buhlmann Laboratories, Switzerland). Rapid tests have not been approved by the Food and Drug Administration for use in the United States.

Related Policy
Fecal Analysis in the Diagnosis of Intestinal Dysbiosis
Fecal Calprotectin Test

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

Fecal calprotectin testing is considered investigational. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Fecal Calprotectin Testing is covered

Not applicable.

When Fecal Calprotectin Testing is not covered

Testing for fecal calprotectin is considered investigational in the diagnosis and management of intestinal conditions, including the diagnosis and management of inflammatory bowel disease.

Policy Guidelines

The evidence for individuals with suspected inflammatory bowel disease (IBD) who receive fecal calprotectin testing, includes prospective and retrospective diagnostic accuracy studies and systematic reviews. Relevant outcomes are test accuracy, test validity, symptoms, change in disease status, quality of life, hospitalizations, and medication use. There is a large body of evidence evaluating the diagnostic accuracy of fecal calprotectin in patients considered to have IBD, and for whom irritable bowel syndrome is a consideration. In general, the studies indicate that the commercially available test has very high sensitivity for IBD. Studies varied in the cutoff of fecal calprotectin used to indicate the presence of disease, but most use a cutoff of 50 µg/g. However, there is relatively little data on the use of calprotectin in the general population and potential for spectrum effect; given the possibility of more widespread use in practice, additional clinical validity data in the target population would be indicated. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for individuals who have diagnosed inflammatory bowel disease who receive fecal calprotectin testing for treatment assessment, or disease activity assessment, or relapse prediction, includes prospective and retrospective diagnostic studies, meta-analyses, and one randomized controlled trial (RCT). Relevant outcomes are test accuracy, test validity, symptoms, change in disease status, quality of life, hospitalizations, and medication use. The diagnostic accuracy for fecal calprotectin for these indications is uncertain, as are the patient management changes associated with specific calprotectin levels. The evidence is insufficient to determine the effects of the technology on health outcomes.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.
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Applicable service codes: 83993

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Specialty Matched Consultant reviews, 2/2009

Senior Medical Director review 7/2009


Senior Medical Director review—12/2014

Senior Medical Director review – 4/2015


Medical Director review 11/2015


Medical Director review 11/2016


Medical Director review 4/2017

Specialty Matched Consultant Advisory Panel 11/2017
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Medical Director review 11/2017


Medical Director review 3/2018

<table>
<thead>
<tr>
<th>Policy Implementation/Update Information</th>
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<tbody>
<tr>
<td>8/31/09       New policy. Reviewed with Senior Medical Director 7/9/2009. “Testing for fecal calprotectin is considered investigational for all indications. BCBSNC does not cover investigational services.” Notice given 8/31/09. Policy effective date 12/7/09. (btw)</td>
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<tr>
<td>4/13/10       Description section revised. (adn)</td>
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<tr>
<td>6/22/10       Policy Number(s) removed. (amw)</td>
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<tr>
<td>11/23/10      Medical Director review. No change to policy statement. Policy status changed to “Active policy, no longer scheduled for routine literature review.” (adn)</td>
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<tr>
<td>11/8/11       Description section revised. Policy statement unchanged. When Fecal Calprotectin is Not Covered section revised to read: “Testing for fecal calprotectin is considered investigational in the diagnosis and management of intestinal conditions, including the diagnosis and management of inflammatory bowel disease.” Specialty Matched Consultant Advisory Panel review 10/26/11. Policy accepted as written. (adn)</td>
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<tr>
<td>4/30/13       Corporate Medical Policy converted to Evidence Based Guideline. “Testing for fecal calprotectin is not recommended in the diagnosis and management of intestinal conditions, including the diagnosis and management of inflammatory bowel disease.” (sk)</td>
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<tr>
<td>6/11/13       Changed Related Policy to Related Guideline. (sk)</td>
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<tr>
<td>11/26/13      Specialty Matched Consultant Advisory Panel review 10/16/13. No change to Guideline statement. (sk)</td>
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<tr>
<td>7/1/14        Reference added. No change to Guideline statement. (sk)</td>
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<tr>
<td>7/1/15        Medical Director review 4/2015. Evidence Based Guideline converted to Corporate Medical Policy. Notification given 7/1/15 for effective date 9/1/15. (td)</td>
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<tr>
<td>9/1/15        Effective date extended to 10/1/15. (td)</td>
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<tr>
<td>7/28/17       Descriptions section, Regulatory status and Policy Guidelines extensively updated. No change to policy intent. References updated. Medical Director review 4/2017. (jd)</td>
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4/13/18 Regulatory status updated; no change to policy intent. References updated. Medical Director review 3/2018. (jd)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.