Fecal Analysis in the Diagnosis of Intestinal Dysbiosis

Policy Number: 2.04.26  Last Review: 7/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for fecal analysis in the diagnosis of intestinal dysbiosis. This is considered investigational.

When Policy Topic is covered
Not Applicable

When Policy Topic is not covered
Fecal analysis of the following components is considered investigational as a diagnostic test for the evaluation of intestinal dysbiosis, irritable bowel syndrome, malabsorption, or small intestinal overgrowth of bacteria:

- Triglycerides
- Chymotrypsin
- Iso-butyrate, iso-valerate, and n-valerate
- Meat and vegetable fibers
- Long chain fatty acids
- Cholesterol
- Total short chain fatty acids
- Levels of Lactobacilli, bifidobacteria, and E. coli and other “potential pathogens,” including Aeromonas, Bacillus cereus, Campylobacter, Citrobacter, Klebsiella, Proteus, Pseudomonas, Salmonella, Shigells, S. aureus, Vibrio
- Identification and quantitation of fecal yeast (including C. albicans, C. tropicalis, Rhodoptorul, and Geotrichum)
- N-butyrate
- Beta-glucoronidase
- pH
- Short chain fatty acid distribution (adequate amount and proportions of the different short chain fatty acids reflect the basic status of intestinal metabolism)
- Fecal secretory IgA
Intestinal dysbiosis may be defined as a state of disordered microbial ecology that is believed to cause disease. Laboratory analysis of fecal samples is proposed as a method of identifying individuals with intestinal dysbiosis and other gastrointestinal disorders.

For individuals who have suspected intestinal dysbiosis, irritable bowel syndrome (IBS), malabsorption, or small intestinal bacterial overgrowth who receive fecal analysis testing, the evidence includes several cohort and case-control studies comparing fecal microbiota in patients with a known disease and healthy controls. Relevant outcomes are test accuracy and validity, symptoms, and functional outcomes. The available retrospective cohort studies on fecal analysis have suggested that some components of fecal microbiome and inflammatory markers may differ across patients with IBS subtypes. No studies were identified on the diagnostic accuracy of fecal analysis versus another diagnostic approach or compared health outcomes in patients managed with and without fecal analysis tests. No studies were identified that directly informed on the use of fecal analysis in the evaluation of intestinal dysbiosis, malabsorption, or small intestinal bacterial overgrowth. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Background**

The gastrointestinal tract is colonized by a large number and variety of microorganisms including bacteria, fungi, and archaea. The concept of intestinal dysbiosis rests on the assumption that abnormal patterns of intestinal flora, such as overgrowth of some commonly found microorganisms, have an impact on human health. Symptoms and conditions attributed to intestinal dysbiosis include chronic disorders (eg, irritable bowel syndrome [IBS], inflammatory or autoimmune disorders, food allergy, atopic eczema, unexplained fatigue, arthritis, ankylosing spondylitis), malnutrition, or neuropsychiatric symptoms (eg, autism), and breast and colon cancer.

The gastrointestinal tract symptoms attributed to intestinal dysbiosis (ie, bloating, flatulence, diarrhea, constipation) overlap in part with either IBS or small intestinal bacterial overgrowth syndrome. The diagnosis of IBS is typically made clinically, based on a set of criteria referred to as the Rome criteria. The small intestine normally contains a limited number of bacteria, at least as compared with the large intestine. Small intestine bacterial overgrowth may occur due to altered motility (including blind loops), decreased acidity, exposure to antibiotics, or...
surgical resection of the small bowel. Symptoms include malabsorption, diarrhea, fatigue, and lethargy. The laboratory criterion standard for diagnosis consists of culture of a jejunal fluid sample, but this requires invasive testing. Hydrogen breath tests, commonly used to evaluate lactose intolerance, have been adapted for use in diagnosing both small intestinal bacterial overgrowth.

**Fecal Markers of Dysbiosis**

Laboratory analysis of both stool and urine has been investigated as markers of dysbiosis. Reference laboratories specializing in the evaluation of dysbiosis may offer comprehensive testing of various aspects of digestion, absorption, microbiology, and metabolic markers. For example, Genova Diagnostics offers the Comprehensive Digestive Stool Analysis 2.0 test, which evaluates a stool sample for components listed in Table 1.

### Table 1: Components of the Comprehensive Digestive Stool Analysis 2.0 Test

<table>
<thead>
<tr>
<th>Markers</th>
<th>Analytes</th>
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<tbody>
<tr>
<td><strong>Digestion</strong></td>
<td></td>
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<tr>
<td></td>
<td>• Triglycerides</td>
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<td></td>
<td>• Chymotrypsin</td>
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<td></td>
<td>• Iso-butyrate, iso-valerate, and n-valerate</td>
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<td></td>
<td>• Meat and vegetable fibers</td>
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<td><strong>Absorption</strong></td>
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<td></td>
<td>• Long-chain fatty acids</td>
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<td></td>
<td>• Cholesterol</td>
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<td>• Total fecal fat</td>
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<td></td>
<td>• Total short-chain fatty acids</td>
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<tr>
<td><strong>Microbiology</strong></td>
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<td></td>
<td>• Levels of Lactobacilli, bifidobacteria, and <em>Escherichia coli</em> and other</td>
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<td></td>
<td>&quot;potential pathogens,&quot; including <em>Aeromonas, Bacillus cereus, Campylobacter, Citrobacter, Klebsiella, Proteus, Pseudomonas, Salmonella, Shigella, Staphylococcus aureus, and Vibrio</em></td>
</tr>
<tr>
<td></td>
<td>• Identification and quantitation of fecal yeast (including <em>Candida albicans, Candida tropicalis, Rhodotorula, and Geotrichum</em>)</td>
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<tr>
<td><strong>Metabolic</strong></td>
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<tr>
<td></td>
<td>• $N$-butyrate (considered key energy source for colonic epithelial cells)</td>
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<td></td>
<td>• $\beta$-glucuronidase</td>
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<td></td>
<td>• pH</td>
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<td></td>
<td>• Short-chain fatty acid distribution (adequate amount and proportions of the different short-chain fatty acids reflect the basic status of intestinal metabolism)</td>
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<tr>
<td><strong>Immunology</strong></td>
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<tr>
<td></td>
<td>• Fecal secretory immunoglobulin A (as a measure of luminal immunologic function)</td>
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<td></td>
<td>• Calprotectin</td>
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</tbody>
</table>

The comprehensive stool analysis package has an optional parasitology component.

Fecal calprotectin as a stand-alone test is addressed in a separate policy.
A related topic, fecal microbiota transplantation (FMT), the infusion of intestinal microorganisms to restore normal intestinal flora, is addressed in a separate policy. FMT has been rigorously studied for the treatment of patients with recurrent \textit{Clostridium difficile} infection (CDI). No specific stool testing, other than the identification of CDI, is currently recommended.

**Regulatory Status**
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). The Genova Diagnostics test is available under the auspices of CLIA. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

**Rationale**
This evidence review was created in November 2001 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through October 25, 2017.

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. The following is a summary of the literature to date.

**Fecal Testing for Intestinal Dysbiosis**

**Clinical Context and Test Purpose**
The purpose of fecal analysis in patients who have various gastrointestinal conditions is to differentiate intestinal microflora that may be related to those conditions.

The question addressed in this evidence review is: Does fecal testing help identify individuals who have suspected intestinal dysbiosis, irritable bowel syndrome (IBS), malabsorption, or small intestinal bacterial overgrowth better than standard diagnostic approaches to these gastrointestinal conditions?

The following PICOTS were used to select literature to inform this review.
**Patients**
The relevant populations of interest are those with suspected intestinal dysbiosis, IBS, malabsorption, or small intestinal bacterial overgrowth.

**Interventions**
The intervention of interest is use of fecal testing to determine whether this method diagnosis individuals with gastrointestinal conditions more accurately than standard approaches.

**Comparators**
The comparator of interest includes the standard approach to diagnosing specific intestinal conditions.

**Outcomes**
The general outcomes of interest are the correct diagnosis of gastrointestinal conditions potentially associated with alterations in intestinal microflora.

**Timing**
These tests might be used during evaluation and treatment of acute and chronic intestinal disorders.

**Setting**
The setting is ambulatory primary care or gastroenterology consultation.

**Technical Reliability**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Clinically Valid**
Establishing that fecal analysis to identify intestinal dysbiosis is beneficial would involve evidence that the net health outcome in patients with gastrointestinal tract symptoms is better with fecal analysis tests than without. No studies were identified in the initial literature review or during the literature searches for evidence review updates that compared health outcomes in individuals managed with and without fecal analysis to identify intestinal dysbiosis. There were also no studies on the accuracy of fecal analysis vs another method for diagnosing IBS, small intestine bacterial overgrowth, or other conditions. Additionally, no studies were identified establishing diagnostic criteria for intestinal dysbiosis as a disorder.

Emmanuel et al (2016) retrospectively analyzed fecal biomarker results, dichotomized to normal or abnormal, from 3553 patients who underwent stool testing and met Rome III symptom criteria for IBS. Records were identified from samples sent to Geneva Diagnostics from 2013-2014 for which patient questionnaires were completed (patient questionnaires are sent with every test kit; demographic surveys were completed for 7503 of 24,258 of the fecal
specimens obtained during study period, and Rome III questionnaire results were completed for 5990 of those) and the case definition of IBS was based on patient reporting of symptoms on the Rome III questionnaire. Of the 3553 patient samples included, 13.6%, 27.5%, and 58.1%, respectively, reported having constipation-predominant (IBS-C), diarrhea-predominant (IBS-D), and mixed subtypes (IBS-M) of IBS. Most patients (93.5%) had at least 1 abnormal result. There were differences by IBS subgroup, with IBS-D patients demonstrating higher rates of abnormal fecal calprotectin, eosinophil protein X, and bacterial potential pathogens (13.4%, 12.2%, and 75% of subjects, respectively) than IBS-C patients (7.1%, 4.4%, and 71.0%, respectively) and IBS-M patients (10.9%, p<0.004 vs IBS-D; 8.0%, p<0.003 vs IBS-D; 71.6%, p=0.010 vs IBS-D).

A 2014 retrospective analysis of data from the Genova Diagnostics database on 2256 patients who underwent stool testing was published by Goepp et al. Patients had symptoms suggestive of IBS (eg, 48% had abdominal pain, 14% had diarrhea). Eighty-three percent of patients had at least one abnormal test result. The most common abnormal result, occurring in 73% of cases, was low growth in the beneficial bacteria lactobacillus and/or bifidobacterium. Next most common was testing positive for eosinophil protein X and fecal calprotectin, occurring in 14% and 12% of samples, respectively. A limitation of the study was that it did not include a confirmation of the diagnosis of IBS (ie, using Rome criteria) and thus the accuracy of the Genova tests compared with clinical diagnosis could not be determined.

Several studies identified compared microbiota in patients who had known disease with healthy controls in an attempt to identify a microbiotic profile associated with a particular disease. None of these studies evaluated whether fecal analysis in patients with IBS or other conditions led to improved health outcomes. All were conducted outside of the United States and used quantitative real-time polymerase chain reaction analysis.

Representative studies are described next.

A 2012 study from Japan compared the fecal microbiota profiles of 161 patients with Crohn disease and 121 healthy controls. Healthy individuals tended to have a different distribution of fecal microbiota than Crohn disease patients. For example, compared with controls, Crohn disease patients had significantly lower levels of Faecalibacterium and Eubacterium and significantly higher levels of Streptococcus.

A 2011 study by Sobhani et al in France evaluated fecal microbiota samples taken before colonoscopy from 60 patients with colorectal cancer and 119 sex-matched healthy individuals. Total bacteria levels did not differ significantly between colorectal cancer and non–colorectal cancer groups. There were significant elevations of the Bacteroides/Prevotella group in the colorectal cancer population.

In 2011, Joossens et al in Belgium published a study comparing fecal microbiota in 68 patients with Crohn disease, 84 unaffected relatives, and 55 matched controls. When samples from patients who had Crohn disease were compared with all
unaffected controls, significant differences were found in the concentration of 5 bacterial species. Compared with controls, Crohn disease patients had lower levels of *Dialister invisus*, an uncharacterized species of *Clostridium* cluster XIVa, *Faecalibacterium prausnitzii*, and *Bifidobacterium adolescentis* as well as an increase in *Ruminococcus gnavus*.

Also, several studies have evaluated whether fecal markers can distinguish between individuals with various gastrointestinal diseases.\(^7\)\(^-\)\(^9\) The studies have included patients with known disease; none evaluated fecal analysis for the diagnosis of patients with chronic intestinal symptoms and without an established diagnosis. For example, Langhorst et al (2008) in Germany evaluated 139 patients (54 with IBS, 43 Crohn disease, 42 ulcerative colitis) undergoing diagnostic ileocolonoscopy, who provided fecal samples.\(^7\) Samples were analyzed with enzyme-linked immunosorbent assay. Patients with IBS had significantly higher levels of lactoferrin, calprotectin, and polymorphonuclear-elastase than patients who had ulcerative colitis or Crohn disease (all p<0.001). In the ulcerative colitis and Crohn disease groups, there were higher levels of all 3 markers in patients who had inflammation compared with those who did not.

Another area of research is the effectiveness of probiotics for treating patients with IBS. Presumably, if probiotics improve symptoms, then some degree of intestinal dysbiosis had been present. A number of systematic reviews have assessed the efficacy of probiotic treatment for IBS.\(^10\)\(^-\)\(^14\) For example, in 2012, Jonkers et al conducted a systematic review of studies evaluating probiotics in the management of IBS.\(^13\) Overall, reviewers identified few well-designed randomized controlled trials and only a limited number of trials suitable for meta-analysis. Pooled analyses did not find statistically significant benefits associated with probiotics compared with placebo or standard of care. A 2013 systematic review by Hungin et al identified 37 randomized controlled trials evaluating probiotics for managing lower gastrointestinal symptoms.\(^14\) Reviewers concluded that specific probiotics help relieve symptoms in some patients with IBS. They cited 9 randomized controlled trials that reported overall IBS symptoms as a primary end point; 5 of 8 trials reported a statistically significant benefit of probiotics compared with placebo. Reviewers did not pool study findings. None of the trials identified in these systematic reviews reported use fecal analysis as part of its diagnostic or treatment protocols.

**Clinically Useful**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials. No studies supporting the clinical utility of fecal testing were identified.

Indirect evidence of clinical utility rests on clinical validity. It is not possible to construct a chain of evidence because there is insufficient evidence of clinical validity to draw conclusions on clinical utility.
Summary of Evidence
For individuals who have suspected intestinal dysbiosis, irritable bowel syndrome, malabsorption, or small intestinal bacterial overgrowth who receive fecal analysis testing, the evidence includes several cohort and case-control studies comparing fecal microbiota in patients who had a known disease with healthy controls. Relevant outcomes are test accuracy and validity, symptoms, and functional outcomes. The available retrospective cohort studies on fecal analysis have suggested that some components of the fecal microbiome and inflammatory markers may differ across patients with irritable bowel syndrome subtypes. No studies were identified on the diagnostic accuracy of fecal analysis vs another diagnostic approach or compared health outcomes in patients managed with and without fecal analysis tests. No studies were identified that directly informed on the use of fecal analysis in the evaluation of intestinal dysbiosis, malabsorption, or small intestinal bacterial overgrowth. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements
No guidelines or statements were identified.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in November 2017 did not identify any ongoing or unpublished trials that would likely influence this review.

References

**Billing Coding/Physician Documentation Information**

82270  Blood, occult, by peroxidase activity (eg, guaiac), qualitative; feces, consecutive collected specimens with single determination, for colorectal neoplasm screening (ie, patient was provided three cards or single triple card for consecutive collection)

82272  Blood, occult, by peroxidase activity (eg, guaiac), qualitative, feces, 1-3 simultaneous determinations, performed for other than colorectal neoplasm screening

82274  Blood, occult, by fecal hemoglobin determination by immunoassay, qualitative, feces, 1-3 simultaneous determinations

82239  Bile acids; total

82542  Column chromatography, includes mass spectrometry, if performed (eg, HPLC, LC, LC/MS, LC/MS-MS, GC, GC/MS-MS, GC/MS, HPLC/MS), non-drug analyte(s) not elsewhere specified, qualitative or quantitative, each specimen

82656  Elastase, pancreatic (EL-1), fecal, qualitative or semi-quantitative

82710  Fat or lipids, feces; quantitative

82715  Fat differential, feces, quantitative

82725  Fatty acids, nonesterified

83520  Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified

83630  Lactoferrin, fecal; qualitative

83631  Lactoferrin, fecal; quantitative

83986  pH, body fluid, except blood

83993  Calprotectin, fecal

84311  Spectrophotometry, analyte not elsewhere specified

86403  Particle agglutination; screen, each antibody

87045  Culture, bacterial; stool, aerobic, with isolation and preliminary examination (eg, KIA, LIA), Salmonella and Shigella species

87046  Culture, bacterial; stool, aerobic, additional pathogens, isolation and presumptive identification of isolates, each plate
87075  Culture, bacterial; any source, except blood, anaerobic with isolation and presumptive identification of isolates
87102  Culture, fungi (mold or yeast) isolation, with presumptive identification of isolates; other source (except blood)
87177  Ova and parasites, direct smears, concentration and identification
87209  Smear, primary source with interpretation; complex special stain (eg, trichrome, iron hematoxylin) for ova and parasites
87328  Infectious agent antigen detection by enzyme immunoassay technique, qualitative or semiquantitative, multiple-step method; cryptosporidium
87329  Infectious agent antigen detection by enzyme immunoassay technique, qualitative or semiquantitative, multiple-step method; giardia
87336  Infectious agent antigen detection by enzyme immunoassay technique, qualitative or semiquantitative, multiple-step method; Entamoeba histolytica dispar group
89160  Meat fibers, feces

CPT Codes 82491, 82492 were deleted 1/1/2016

Additional Policy Key Words
N/A

Policy Implementation/Update Information
7/1/06  New policy, considered investigational.
7/1/07  No policy statement changes.
7/1/08  No policy statement changes.
7/1/09  No policy statement changes.
7/1/10  No policy statement changes.
7/1/11  No policy statement changes.
7/1/12  No policy statement changes.
7/1/13  No policy statement changes.
7/1/14  No policy statement changes.
7/1/15  No policy statement changes.
7/1/16  Added CPT code 82542. No policy statement changes.
7/1/17  No policy statement changes.
7/1/18  No policy statement changes.