Fecal Analysis in the Diagnosis of Intestinal Dysbiosis

Policy Number: 2.04.26  Last Review: 7/2017
Origination: 7/2006  Next 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, Shigella, S. aureus, Vibrio
- Identification and quantitation of fecal yeast (including C. albicans, C. tropicalis, Rhodotorul, 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.

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>
</tr>
<tr>
<td>• Triglycerides</td>
<td></td>
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<tr>
<td>• Chymotrypsin</td>
<td></td>
</tr>
<tr>
<td>• Iso-butyrate, iso-valerate, and n-valerate</td>
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<tr>
<td>• Meat and vegetable fibers</td>
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<tr>
<td><strong>Absorption</strong></td>
<td></td>
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<tr>
<td>• Long-chain fatty acids</td>
<td></td>
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<tr>
<td>• Cholesterol</td>
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<tr>
<td>• Total fecal fat</td>
<td></td>
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<tr>
<td>• Total short-chain fatty acids</td>
<td></td>
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<tr>
<td><strong>Microbiology</strong></td>
<td></td>
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<tr>
<td>• Levels of Lactobacilli, bifidobacteria, and <em>Escherichia coli</em> and other &quot;potential pathogens,&quot; including <em>Aeromonas</em>, <em>Bacillus cereus</em>, <em>Campylobacter</em>, <em>Citrobacter</em>, <em>Klebsiella</em>, <em>Proteus</em>, <em>Pseudomonas</em>, <em>Salmonella</em>, <em>Shigella</em>, <em>Staphylococcus aureus</em>, and <em>Vibrio</em></td>
<td></td>
</tr>
<tr>
<td>• Identification and quantitation of fecal yeast (including <em>Candida albicans</em>, <em>Candida tropicalis</em>, <em>Rhodotorula</em>, and <em>Geotrichum</em>)</td>
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</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
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<tr>
<td>• N-butyrate (considered key energy source for colonic epithelial cells)</td>
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</tr>
<tr>
<td>• β-glucuronidase</td>
<td></td>
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<tr>
<td>• pH</td>
<td></td>
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<tr>
<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>
<td></td>
</tr>
<tr>
<td>• Fecal secretory immunoglobulin A (as a measure of luminal immunologic function)</td>
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<tr>
<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 *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 originally created in November 2001 and has been updated regularly with searches of the MEDLINE database. Most recently, the literature was reviewed through November 9, 2016. Following is a summary of the literature to date.

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 any of 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 versus another method for diagnosing irritable bowel syndrome (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 p 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.³ Patients had symptoms suggestive of IBS (eg, 48% had abdominal pain, 14% had diarrhea). Eighty-three percent of patients had at least 1 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 with known disease and 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.⁴ 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.⁵ Total bacteria levels did not differ significantly between the 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.⁶ When samples from patients with 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* and an increase in *Ruminococcus gnavus*.

In addition, 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 in Germany evaluated 139 patients (54
with IBS, 43 Crohn disease, 42 ulcerative colitis) undergoing diagnostic
ileocolonoscopy, which provided fecal samples. Samples were analyzed with
element-linked immunosorbent assay. Patients with IBS had significantly higher
levels of lactoferrin, calprotectin, and polymorphonuclear-elastase compared with
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 with inflammation compared to those without inflammation.

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. For example, in 2012, Jonkers et al
conducted a systematic review of studies evaluating probiotics in the management
of IBS. Overall, reviewers identified few well-designed randomized controlled
trials (RCTs) 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 care. A 2013 systematic review by Hungin et
al identified 37 RCTs evaluating probiotics for managing lower gastrointestinal
symptoms. Reviewers concluded that specific probiotics help relieve symptoms in
some patients with IBS. They cited 9 RCTs 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 the systematic reviews were reported to use fecal analysis
as part of its diagnostic or treatment protocols.

**Summary of Evidence**
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
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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 (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in November 2016 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
<table>
<thead>
<tr>
<th>Date</th>
<th>Policy Information</th>
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<td>7/1/06</td>
<td>New policy, considered investigational.</td>
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<tr>
<td>7/1/07</td>
<td>No policy statement changes.</td>
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<td>7/1/08</td>
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<td>7/1/15</td>
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<tr>
<td>7/1/16</td>
<td>Added CPT code 82542. No policy statement changes.</td>
</tr>
<tr>
<td>7/1/17</td>
<td>No policy statement changes.</td>
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</table>

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