Name of Blue Advantage Policy:
Fecal Analysis in the Diagnosis of Intestinal Dysbiosis

Policy #: 407               Latest Review Date: January 2019
Category: Laboratory/Pathology   Policy Grade: C

Background:
Blue Advantage medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:

1. Safe and effective;
2. Not experimental or investigational*;
3. Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:
   • Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient’s condition or to improve the function of a malformed body member;
   • Furnished in a setting appropriate to the patient’s medical needs and condition;
   • Ordered and furnished by qualified personnel;
   • One that meets, but does not exceed, the patient’s medical need; and
   • At least as beneficial as an existing and available medically appropriate alternative.

*Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill Original Medicare for covered services that are related to clinical trials that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).
Description of Procedure or Service:
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.

Intestinal Dysbiosis
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, in addition to gastrointestinal disorders, include chronic disorders (e.g., irritable bowel syndrome, inflammatory or autoimmune disorders, food allergy, atopic eczema, unexplained fatigue, arthritis, ankylosing spondylitis), malnutrition, or neuropsychiatric symptoms or neurodevelopmental conditions (e.g., autism), and breast and colon cancer.

The gastrointestinal tract symptoms attributed to intestinal dysbiosis (i.e., bloating, flatulence, diarrhea, constipation) overlap in part with either irritable bowel syndrome or small intestinal bacterial overgrowth syndrome. The diagnosis of irritable bowel syndrome 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 the 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 small intestinal bacterial overgrowths.

Fecal Markers of Dysbiosis
Laboratory analysis of both stool and urine has been investigated as markers of dysbiosis. Commercial laboratories may offer testing for comprehensive panels or individual components of various aspects of digestion, absorption, microbiology, and metabolic markers. Representative components of fecal dysbiosis testing are summarized in Table 1.

Table 1. Components of Fecal Dysbiosis Marker Analysis

<table>
<thead>
<tr>
<th>Markers</th>
<th>Analytes</th>
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<tbody>
<tr>
<td>Digestion</td>
<td>• Triglycerides</td>
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<tr>
<td></td>
<td>• Chymotrypsin</td>
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<tr>
<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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<tr>
<td>Absorption</td>
<td>• Long-chain fatty acids</td>
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<tr>
<td></td>
<td>• Cholesterol</td>
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<td></td>
<td>• Total fecal fat</td>
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<td></td>
<td>• Total short-chain fatty acids</td>
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<tr>
<td>Microbiology</td>
<td>• Levels of Lactobacilli, bifidobacteria, and Escherichia coli and other “potential pathogens,” including Aeromonas, Bacillus cereus, Campylobacter, Citrobacter, Klebsiella, Proteus, Pseudomonas, Salmonella, Shigella, Staphylococcus aureus, and Vibrio</td>
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</tbody>
</table>
Fecal calprotectin as a stand-alone test is addressed separately in Medical Policy #472- Fecal Calprotectin Testing.

A related topic, fecal microbiota transplantation (FMT), the infusion of intestinal microorganisms to restore normal intestinal flora is addressed in Medical Policy #584- Fecal Microbiota Transplantation. FMT has been rigorously studied for the treatment of patients with recurrent *Clostridium difficile* infection (CDI).

**Policy:**

**Effective for dates of service on or after April 20, 2010:**

**Blue Advantage** will treat **fecal analysis** of the following components as a **non-covered** benefit and as **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, Rhodotorula, and Geotrichum*)
- N-butyrate
- Beta-glucuronidase
- 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
Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:
The most recent literature review was updated through October 4, 2018.

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 and related immunologic responses that may be related to those conditions.

The question addressed in this evidence review is: Does fecal dysbiosis testing used in individuals who have gastrointestinal conditions such as suspected intestinal dysbiosis, irritable bowel syndrome (IBS), malabsorption, or small intestinal bacterial overgrowth improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant populations of interest are those with gastrointestinal conditions such as suspected intestinal dysbiosis, IBS, malabsorption, or small intestinal bacterial overgrowth.

Interventions
The intervention of interest is use of fecal dysbiosis testing. The rationale for intestinal dysbiosis testing is that alterations in intestinal flora (e.g. overgrowth of some commonly found microorganisms) and related immunologic responses have an impact on human health and disease. The further assumption is that therapeutic (antibiotics, prebiotic, probiotic, or fecal
microbiota transplantation) or lifestyle management interventions can be made to address the alterations.

**Comparators**
The following practices are currently being used to manage various gastrointestinal conditions: the standard approach to diagnosing specific intestinal conditions, which can include using laboratory tests, imaging, and endoscopy as indicated.

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

**Timing**
These tests might be used during evaluation and treatment of acute and chronic intestinal disorders. The duration of follow-up is condition specific and is expected to be weeks to months.

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

**Study Selection Criteria**
For the evaluation of clinical validity of fecal dysbiosis testing, methodologically credible studies were selected using the following principles:
- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from development cohort

**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**
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).

Establishing that fecal analysis to identify intestinal dysbiosis is beneficial would involve evidence that the fecal dysbiosis testing provides an incremental benefit to net health outcome in patients with gastrointestinal tract symptoms as compared to current clinical pathways. 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.

Retrospective Studies
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 Genova 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. The Genova Comprehensive Digestive Stool Analysis evaluates digestion/absorption markers, gut metabolic markers, and gut microbiology markers. 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 constipation-predominant IBS patients (7.1%, 4.4%, and 71.0%, respectively) and mixed subtypes of IBS 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 in 2014 by Goepp et al.

Patients had symptoms suggestive of IBS, e.g., 48% had abdominal pain and 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, i.e., using Rome criteria and thus the accuracy of the Genova tests compared with clinical diagnosis could not be determined.

Nonrandomized Observational Studies
Studies using quantitative real-time polymerase chain reaction analysis have 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 the fecal analysis in patients with IBS or other conditions led to improved health outcomes.
Andoh et al (2012) reported on 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*, *Eubacterium* and significantly higher levels of *Streptococcus*.

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

In 2011, Joossens et al published a study comparing fecal microbiota in 68 patients with Crohn disease, 84 unaffected relatives, and 55 matched controls. When samples from patients with Crohn disease were compared with all unaffected controls, significant differences were found in the concentration of five 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*.

Fecal markers in addition to microbiology profiles have been evaluated whether the testing can distinguish between individuals with various gastrointestinal diseases. Langhorst et al (2008) in Germany evaluated 139 patients (54 IBS, 43 Crohn disease, 42 ulcerative colitis) undergoing diagnostic ileocolonoscopy, which provided fecal samples. Samples were analyzed with enzyme-linked immunosorbent assay (ELISA). Patients with IBS had significantly higher levels of lactoferrin, calprotectin, and polymorphonuclear-elastase than patients who had ulcerative colitis or Crohn disease patients (all p<0.001). In the ulcerative colitis and Crohn disease groups, there were higher levels of all three markers in those with inflammation compared with those who did not.

**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 patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**
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.

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 randomized or comparative intervention studies supporting the clinical utility of fecal testing were identified.
**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 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 gastrointestinal conditions such as suspected intestinal dysbiosis, irritable bowel syndrome (IBS), malabsorption, or small intestinal bacterial overgrowth who receive testing with fecal analysis, 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 the 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.

**Practice Guidelines and Position Statements**
None identified.

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

**Key Words:**
Comprehensive Digestive Stool Analysis 2.0, Fecal Analysis, Intestinal Dysbiosis, Genova Diagnostics, Stool Analysis, comprehensive stool analysis

**Approved by Governing Bodies:**
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. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of comprehensive testing for fecal dysbiosis.
**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

**Current Coding:**

CPT Codes:

The following CPT codes may be used to identify individual components of fecal analysis of intestinal dysbiosis:

- **82239** Bile acids, total
- **82542** Column chromatography, includes mass spectrometry, if performed (e.g., 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 *(Effective 01/01/16)*
- **82656** Elastase, pancreatic (EL1), fecal, qualitative or semi-quantitative
- **82710** Fat or lipids, feces; quantitative (used to test for fecal triglycerides)
- **82715** Fat differential, feces, quantitative (used to test for fecal cholesterol)
- **82725** Fatty acids, nonesterified (used to test for long chain fatty acids)
- **83520** Immunoassay, for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified (used for eosinophil protein X)
- **83630** Lactoferrin, fecal; qualitative
- **83986** pH, body fluid, except blood (used to measure fecal pH)
- **83993** Calprotectin, fecal
- **84311** Spectrophotometry, analyte, not elsewhere specified (used twice, once each to test for stool B-glucuronidase and chymotrypsin)
- **87102** Culture, fungi, isolation, with presumptive identification of isolates: other source (used for fecal culture for fungi)
- **87328** Infectious agent antigen detection by immunoassay technique, qualitative or semiquantitative, multiple-step method; cryptosporidium
- **87329** Infectious agent antigen detection by immunoassay technique, qualitative or semiquantitative, multiple-step method; giardia
- **87336** Infectious agent antigen detection by immunoassay technique, qualitative or semiquantitative, multiple-step method; Entamoeba histolytica dispar group
- **89160** Meat fibers, feces

Fecal analysis may also include other standard components such as stool culture (87045-87046; 87075), stool parasitology (87177; 87209), and fecal occult blood (82272-82274).
Previous Coding:

CPT codes:

82491  Chromatography, quantitative, column (e.g., gas liquid or HPLC); single analyte not elsewhere specified, single stationary and mobile phase (Deleted 01/01/2016)

82492  Chromatography, quantitative, column; multiple analytes, single stationary and mobile phase (used to test for short-chain fatty acids) (Deleted 01/01/2016)

References:


Policy History:
Adopted for Blue Advantage, February 2010
Available for comment February 4-April 19, 2010
Medical Policy Panel, February 2010
Medical Policy Group, June 2010
Medical Policy Group, February 2013
Medical Policy Group, February 2014
Medical Policy Group, February 2015
Medical Policy Group, January 2016
Medical Policy Group, December 2016
Medical Policy Group, January 2018
Medical Policy Group, January 2019

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.