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.

The evidence for fecal analysis in patients who have suspected intestinal dysbiosis, irritable bowel syndrome, malabsorption, or small intestinal overgrowth of bacteria 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. 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

Fecal analysis may be suggested for people with gastrointestinal symptoms such as indigestion, constipation, diarrhea, gas, bloating or abdominal pain; symptoms that may overlap with a variety of gastrointestinal disorders such as intestinal dysbiosis, irritable bowel, malabsorption or small intestinal overgrowth of bacteria.

Policy Coding Information

There are no specific procedure codes for fecal analysis and testing for the evaluation of intestinal dysbiosis, irritable bowel syndrome, malabsorption or small intestinal overgrowth of bacteria.

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 (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 (used to test for short-chain fatty acids)
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, not otherwise specified (used to measure fecal pH)
83993: Calprotectin, fecal
84311: Spectrophotometry, analyte, not elsewhere specified (used twice, once each to test for stool Bglucuronidase 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 (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], immunochemiluminometric assay [IMCA]), qualitative or semiquantitative, multiple-step method; cryptosporidium
87329: Infectious agent antigen detection by immunoassay technique (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], immunochemiluminometric assay [IMCA]), qualitative or semiquantitative, multiple-step method; giardia
87336: Infectious agent antigen detection by immunoassay technique (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], immunochemiluminometric assay [IMCA]), 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); and
89240: Unlisted miscellaneous pathology test miscellaneous
89160: Meat fibers, feces

When a service is considered investigational

All diagnoses are considered investigational for fecal analysis and testing for the evaluation of intestinal dysbiosis, irritable bowel syndrome, malabsorption or small intestinal overgrowth of bacteria.

Fecal analysis of the following components is considered investigational as a diagnostic test.

Policy Guidelines

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, B. cereus, Campylobacter, Citrobacter, Klebsiella, Proteus, Pseudomonas, Salmonella, Shigella, S. aureus, and Vibrio
• Identification and quantitation of fecal yeast (including Candida albicans, Candida tropicalis, Rhodotorula, and Geotrichum)
• N-butyrate
• β-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

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 such as irritable bowel syndrome, inflammatory or autoimmune disorders, food allergy, atopic eczema, unexplained fatigue, arthritis, and ankylosing spondylitis, malnutrition, or neuropsychiatric symptoms including autism, and breast and colon cancer.

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 Diagnostics1 offers a “Comprehensive Digestive Stool Analysis 2.0” that evaluates a stool sample for the following components:

Digestion
• Triglycerides
• Chymotrypsin
• Iso-butyrate, iso-valerate, and n-valerate
• Meat and vegetable fibers

Absorption
• Long-chain fatty acids
• Cholesterol
• Total fecal fat
• Total short-chain fatty acids
Microbiology
- Levels of Lactobacilli, bifidobacteria, and *E. coli* and other “potential pathogens,” including *Aeromonas, Bacillus cereus, Campylobacter, Citrobacter, Klebsiella, Proteus, Pseudomonas, Salmonella, Shigella, Staphylococcus aureus*, and *Vibrio*
- Identification and quantitation of fecal yeast (including *Candida albicans, Candida tropicalis, Rhodotorula, and Geotrichum*

Metabolic Markers
- *N*-butyrate (considered key energy source for colonic epithelial cells)
- 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

Immunology
- Fecal secretory IgA (as a measure of luminal immunologic function)
- Calprotectin

The comprehensive stool analysis package has an optional parasitology component.

A related topic, fecal microbiota transplantation (FMT), the infusion of intestinal microorganisms to restore normal intestinal flora has been rigorously studied for the treatment of patients with recurrent *Clostridium difficile* infection (CDI). Use of the procedure to treat any other condition remains controversial and no specific stool testing, other than the identification of CDI, is currently recommended.

**Rationale/Scientific Background**

This evidence review was originally created in 2001 and has been updated regularly with searches of the MEDLINE database. Most recently, the literature was reviewed through November 09, 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.

The literature has included discussion regarding the relationship between intestinal microflora and various disorders. 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 in comparison 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. Although the diagnosis of bacterial overgrowth may be made clinically and the condition treated empirically with antibiotics, the laboratory criterion standard for diagnosis consists of culture of a jejunal fluid sample. Recently, hydrogen breath tests, commonly used to evaluate lactose intolerance, have been adapted for use in diagnosing both small intestinal bacterial overgrowth and IBS.

Measurements of fecal fat (ie, qualitative, quantitative, fat differential) are established diagnostic techniques for malabsorption. In contrast, a literature search did not identify any published studies regarding the diagnostic performance of fecal analysis of digestion, absorption, microbiology, metabolic markers, or immunology as a workup of malabsorption syndrome, small intestine bacterial overgrowth, or intestinal dysbiosis. Chronic intestinal candidiasis has been linked with various gastrointestinal tract complaints, as well as systemic complaints, such as chronic fatigue syndrome. However, similar to intestinal dysbiosis, chronic intestinal candidiasis is an ill-defined condition without established diagnostic parameters.

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 (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 in literature updates 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 leads to improved health outcomes. All of the studies were conducted outside of the United States and all 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*, *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 gender-matched...
healthy individuals. 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. 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. 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 enzyme-linked immunosorbent assay. Patients with IBS had significantly higher levels of lactoferrin, calprotectin, and polymorphonuclear-elastase compared with ulcerative colitis or Crohn disease patients (all p<0.001). In ulcerative colitis and Crohn disease patients, there were higher levels of all 3 markers in those with inflammation compared with 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 been published on 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, the authors identified few well-designed randomized controlled trials and only a limited number of trials suitable for meta-analysis. The 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 a total of 37 randomized controlled trials evaluating probiotics for managing lower gastrointestinal symptoms. The authors 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 studies reported a statistically significant benefit of probiotics compared with placebo. The investigators 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.

**Ongoing and Unpublished Clinical Trials**

A search of ClinicalTrials.gov in November 2015 did not identify any ongoing or unpublished trials that would likely influence this review.

The evidence for fecal analysis in patients who have suspected intestinal dysbiosis, irritable bowel syndrome, malabsorption, or small intestinal overgrowth of bacteria 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. 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

**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 Act (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.

**Reference Resources**

Blue Cross and Blue Shield Association Medical Policy reference Manual; Fecal Analysis in the Diagnosis of Intestinal Dysbiosis 2.04.26; December 2016.


Document Precedence

Blue Cross and Blue Shield of Vermont (BCBSVT) Medical Policies are developed to provide clinical guidance and are based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. The applicable group/individual contract and member certificate language, or employer’s benefit plan if an ASO group, determines benefits that are in effect at the time of service. Since medical practices and knowledge are constantly evolving, BCBSVT reserves the right to review and revise its medical policies periodically. To the extent that there may be any conflict between medical policy and contract/employer benefit plan language, the member’s contract/employer benefit plan language takes precedence.

Audit Information

BCBSVT reserves the right to conduct audits on any provider and/or facility to ensure compliance with the guidelines stated in the medical policy. If an audit identifies instances of non-compliance with this medical policy, BCBSVT reserves the right to recoup all non-compliant payments.

Administrative and Contractual Guidance

Benefit Determination Guidance

NEHP/ABNE members may have different benefits for services listed in this policy. To confirm benefits, please contact the customer service department at the member’s health plan.

Federal Employee Program (FEP) members may have different benefits that apply. For further information please contact FEP customer service or refer to the FEP Service Benefit Plan Brochure.

Coverage varies according to the member’s group or individual contract. Not all groups are required to follow the Vermont legislative mandates. Member Contract language takes precedence over medical policy when there is a conflict.

If the member receives benefits through an Administrative Services (ASO) only group, benefits may vary or not apply. To verify benefit information, please refer to the

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member’s employer benefit plan documents or contact the customer service department. Language in the employer benefit plan documents takes precedence over medical policy when there is a conflict.

Policy Implementation/Update information

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<tr>
<th>Date</th>
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<td>01/2016</td>
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<tr>
<td>02/2017</td>
<td>Policy updated with literature review through November 09, 2016; reference 2. Policy statement unchanged.</td>
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Eligible providers
Qualified healthcare professionals practicing within the scope of their license(s).

Approved by BCBSVT Medical Directors       Date Approved
Gabrielle Bercy-Roberson, MD, MPH
Senior Medical Director
Chair, Health Policy Committee

Joshua Plavin, MD, MPH
Chief Medical Officer