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

Policy #: 407
Category: Laboratory/Pathology

Latest Review Date: February 2014
Policy Grade: C

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
Description of Procedure or Service:
Intestinal dysbiosis may be defined as a state of disordered microbial ecology that is believed to cause disease, including conditions such as irritable bowel syndrome (IBS) and malabsorption. Laboratory analysis of fecal samples is proposed as a method of identifying individuals with intestinal dysbiosis.

The concept of dysbiosis rests on the assumption that patterns of intestinal flora, specifically overgrowth of some microorganisms found commonly in intestinal flora, have an impact on human health. Symptoms and conditions attributed to dysbiosis include chronic intestinal disorders including IBS, 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. Leo Galland, MD, a researcher who has focused his studies on dysbiosis, has proposed four patterns of dysbiosis.

Putrefaction
Putrefaction dysbiosis is caused by a diet high in fat and animal flesh and low in insoluble fiber, (i.e., typical of a Western-style diet). It is thought that, compared with normal patterns of intestinal flora, this diet produces an increased concentration of Bacteroides sp. and a decreased concentration of bifidobacteria in stools. The increased concentration of Bacteroides sp. is thought to be associated with increased urease, ultimately leading to a rising fecal pH. Bacteroides sp. is also thought to be associated with increased beta-glucuronidase, which functions to deconjugate bile acids, which are thought to be toxic to the colonic epithelium, causing diarrhea. Increased levels of beta-glucuronidase may also have an impact on estrogen metabolism.

Fermentation
A fermentation pattern of dysbiosis has been attributed to bacterial overgrowth. In mild cases, fermentation may be characterized principally by carbohydrate intolerance, manifested by abdominal distention, flatulence, diarrhea, constipation, and feelings of malaise.

Deficiency
Antibiotic therapy or decrease in dietary fiber may result in relative deficiencies of normal fecal flora, including bifidobacteria, lactobacillus, and Escherichia coli.

Sensitization
A sensitization pattern of dysbiosis has been characterized as an abnormal immune response to the endotoxins and antigens associated with normal intestinal flora.

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, the Great Smokies Diagnostic Laboratory offers a “Comprehensive Digestive Stool Analysis” 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, Vibrio.
- Identification and quantitation of fecal yeast (including Candida albicans, C. 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)

Results are reported both individually or combined into a “dysbiosis risk index,” which is based on gut microbiology, pH, and short chain fatty acids.

Policy:
Fecal analysis of the following components does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and 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 \textit{C. albicans}, \textit{C. tropicalis}, \textit{Rhodotorula}, and \textit{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

\textit{Blue Cross and Blue Shield of Alabama} 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. \textit{Blue Cross and Blue Shield of Alabama} administers benefits based on the member’s contract and corporate 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.

\textbf{Key Points}

The literature at the time of policy development included much discussion regarding the relationship between intestinal microflora and various disorders. The gastrointestinal tract symptoms attributed to intestinal dysbiosis (i.e., 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 gold 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 (i.e., 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.

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 prior to 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 noncolorectal 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 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* 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 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 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 three markers in those with inflammation compared with those without inflammation.

A 2009 review article by researchers at McMaster University in Canada states that current understanding of how intestinal microbiota interact with the host and affect the expression of gastrointestinal tract and other systemic diseases is still in its infancy. They recommend further research into correlations between microbiota profiles and symptoms in chronic conditions such as IBS.

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 (RCTs) 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 RCTs evaluating probiotics for managing lower gastrointestinal symptoms. The authors concluded from that specific probiotics help relieve symptoms in some patients with IBS. They cited nine RCTs that reported overall IBS symptoms as a primary end point: five of eight 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.

**Summary**
Laboratory analysis of fecal samples is proposed as a method of identifying individuals with intestinal dysbiosis (defined as a state of disordered microbial ecology). There is insufficient evidence that fecal analysis to identify intestinal dysbiosis improves the net health outcome in patients with gastrointestinal tract symptoms. Moreover, there is insufficient evidence that fecal analysis aids in the diagnosis or management of patients with irritable bowel syndrome, malabsorption, or small intestine bacterial overgrowth.

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

**Key Words:**
Comprehensive Digestive Stool Analysis, Fecal Analysis, Intestinal Dysbiosis, Great Smokies Diagnostic Laboratory, Stool Analysis, comprehensive stool analysis

**Approved by Governing Bodies:**
Genova Diagnostics is an accredited medical laboratory, certified by six separate health agencies, including the Centers for Medicare & Medicaid Services which oversees clinical labs in the United States under the federal Clinical Laboratory Improvement Amendment (CLIA).

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP: FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.
**Current Coding:**

**CPT Codes:**

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

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>82239</td>
<td>Bile acids, total</td>
</tr>
<tr>
<td>82491</td>
<td>Chromatography, quantitative, column (eg, gas liquid or HPLC); single analyte not elsewhere specified, single stationary and mobile phase</td>
</tr>
<tr>
<td>82492</td>
<td>Chromatography, quantitative, column; multiple analytes, single stationary and mobile phase (used to test for short-chain fatty acids)</td>
</tr>
<tr>
<td>82656</td>
<td>Elastase, pancreatic (EL1), fecal, qualitative or semi-quantitative</td>
</tr>
<tr>
<td>82710</td>
<td>Fat or lipids, feces; quantitative (used to test for fecal triglycerides)</td>
</tr>
<tr>
<td>82715</td>
<td>Fat differential, feces, quantitative (used to test for fecal cholesterol)</td>
</tr>
<tr>
<td>82725</td>
<td>Fatty acids, nonesterified (used to test for long chain fatty acids)</td>
</tr>
<tr>
<td>83520</td>
<td>Immunoassay, for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified (used for eosinophil protein X)</td>
</tr>
<tr>
<td>83630</td>
<td>Lactoferrin, fecal; qualitative</td>
</tr>
<tr>
<td>83986</td>
<td>pH, body fluid, except blood (used to measure fecal pH)</td>
</tr>
<tr>
<td>83993</td>
<td>Calprotectin, fecal</td>
</tr>
<tr>
<td>84311</td>
<td>Spectrophotometry, analyte, not elsewhere specified (used twice, once each to test for stool B-glucuronidase and chymotrypsin)</td>
</tr>
<tr>
<td>87102</td>
<td>Culture, fungi, isolation, with presumptive identification of isolates: other source (used for fecal culture for fungi)</td>
</tr>
<tr>
<td>87328</td>
<td>Infectious agent antigen detection by enzyme immunoassay technique, qualitative or semiquantitative, multiple-step method; cryptosporidium</td>
</tr>
<tr>
<td>87329</td>
<td>Infectious agent antigen detection by enzyme immunoassay technique, qualitative or semiquantitative, multiple-step method; giardia</td>
</tr>
<tr>
<td>87336</td>
<td>Infectious agent antigen detection by enzyme immunoassay technique, qualitative or semiquantitative, multiple-step method; Entamoeba histolytica dispar group</td>
</tr>
<tr>
<td>89160</td>
<td>Meat fibers, feces</td>
</tr>
</tbody>
</table>

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).
References:


Policy History:
Medical Policy Group, February 2010 (2)
Medical Policy Administration Committee, February 2010
Available for comment February 23-April 8, 2010
Medical Policy Panel, February 2010
Medical Policy Group, June 2010 (2): Key Points and References updated
Medical Policy Panel, February 2013
Medical Policy Group, February 2013 (2): 2013 Updates to Key Points and References; no change in policy statement
Medical Policy Panel, February 2014
Medical Policy Group, February 2014 (1): Update to Key Points and References; no change in policy statement

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.