Description

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.

Background

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 irritable bowel syndrome (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 4 patterns of dysbiosis:

- **Putrefaction**

  Putrefaction dysbiosis results from 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 to 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 principally characterized 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, Genova Diagnostics (1) 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, 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.

The use of fecal calprotectin as a stand-alone test in the evaluation of patients with inflammatory bowel disease (IBD), including to identify patients for endoscopy, is not within the scope of this policy. Fecal calprotectin testing is addressed in policy 2.04.69.

**Regulatory Status**

Genova Diagnostics is an accredited medical laboratory, certified by 6 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).

---

**Policy**

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, 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

---

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

82239: Bile acids, total

82492: Chromatography, quantitative, column; multiple analytes, single stationary and mobile phase (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 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 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

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).

Rationale

This policy was originally created in 2001 and was updated regularly with searches of the MEDLINE database. The most recent literature search was performed for the period December 2011 through January 7, 2013. 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 is better in patients with gastrointestinal tract symptoms
who are managed with fecal analysis than in those managed without fecal analysis. No studies were identified in the initial literature review or during any of the literature searches for policy 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. Moreover, no studies were identified establishing diagnostic criteria for “intestinal dysbiosis” as a disorder.

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, or constipation) overlap in part with either irritable bowel syndrome (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 to 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, and 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 (PCR) analysis.

Representative studies are described below

A 2012 study from Japan compared the fecal microbiota profiles of 161 patients with Crohn’s disease (CD) and 121 healthy controls. (2) Healthy individuals tended to have a different distribution of fecal microbiota than Crohn’s disease patients. For example, compared to controls, Crohn’s disease patients had significantly lower levels of *Faecalibacterium*, *Eubacterium* and significantly higher levels of *Streptococcus*.

A 2011 study by Sobhani and colleagues in France evaluated fecal microbiota samples taken prior to colonoscopy from 60 patients with colorectal cancer and 119 gender-matched healthy individuals. (3) 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 and colleagues in Belgium published a study comparing fecal microbiota in 68 patients with Crohn’s disease, 84 unaffected relatives and 55 matched controls. (4) When samples from patients with Crohn’s disease were compared to all unaffected controls, significant differences were found in the concentration of 5 bacterial species. Compared to controls, Crohn’s disease patients had lower levels of *Dialister invisus*, an uncharacterized species of *Clostridium* cluster XIVa, *Faecalibacterium praunitzii* 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. (5-7) 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 and colleagues in Germany evaluated 139 patients (54 inflammatory bowel disease [IBS], 43 Crohn’s disease, 42 ulcerative colitis) undergoing diagnostic ileocolonoscopy, which provided fecal samples. (5) Samples were analyzed with enzyme-linked immunosorbent assay (ELISA). Patients with IBS had significantly higher levels of lactoferrin, calprotectin, and polymorphonuclear-elastase compared to ulcerative colitis or Crohn’s disease patients (all p<0.001). In ulcerative colitis and Crohn’s disease patients, there were higher levels of all 3 markers in those with inflammation compared to 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. (8) 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 meta-analyses have been published on the efficacy of probiotic treatment for IBS. (9-12) Most recently, in 2012, Jonkers and colleagues conducted a systematic review of studies evaluating probiotics in the management of IBS. (12) Overall, the authors identified few well designed 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 to placebo or standard care. Moreover, 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.
Medicare National Coverage

No national coverage determination.

References:


<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td></td>
<td>See Policy Guidelines</td>
</tr>
<tr>
<td>ICD-9 Procedure</td>
<td></td>
<td>Investigational for all diagnosis codes</td>
</tr>
<tr>
<td>ICD-9 Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCPCS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD-10-CM (effective 10/1/14)</td>
<td></td>
<td>Investigational for all diagnosis codes</td>
</tr>
</tbody>
</table>
FirstCarolinaCare Insurance Company, Inc. is a wholly-owned subsidiary of FirstHealth of the Carolinas, Inc.

<table>
<thead>
<tr>
<th>ICD-10-PCS (effective 10/1/14)</th>
<th>Not applicable. ICD-10-PCS codes are only used for inpatient services. There are no ICD procedure codes for laboratory tests.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Service</td>
<td>Pathology/Laboratory</td>
</tr>
<tr>
<td>Place of Service</td>
<td></td>
</tr>
</tbody>
</table>

Index
Comprehensive Digestive Stool Analysis
Fecal Analysis, Intestinal Dysbiosis
Great Smokies Diagnostic Laboratory
Genova Diagnostics
Intestinal Dysbiosis
Stool Analysis, Intestinal Dysbiosis