Fecal Analysis in the Diagnosis of Intestinal Dysbiosis

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 and other gastrointestinal disorders.

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 (e.g., irritable bowel syndrome [IBS], inflammatory or autoimmune disorders, food allergy, atopic eczema, unexplained fatigue, arthritis, ankylosing spondylitis), malnutrition, or neuropsychiatric symptoms (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 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 Diagnostics1 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>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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<td></td>
<td>• Cholesterol</td>
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<td></td>
<td>• Total fecal fat</td>
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<tr>
<td></td>
<td>• Total short-chain fatty acids</td>
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<tr>
<td>Microbiology</td>
<td>• Levels of Lactobacilli, bifidobacteria, and <em>Escherichia coli</em> and other “potential pathogens,” 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>
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<td></td>
<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>
<td>Metabolic</td>
<td>• N-butyrate (considered key energy source for colonic epithelial cells)</td>
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<td></td>
<td>• β-glucuronidase</td>
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<td></td>
<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>Immunology</td>
<td>• Fecal secretory immunoglobulin A (as a measure of luminal immunologic function)</td>
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<td>• Calprotectin</td>
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</table>

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 is addressed in policy 2.04.69.

A related topic, fecal microbiota transplantation (FMT), the infusion of intestinal microorganisms to restore normal intestinal flora is addressed in Policy No. 2.01.92. FMT 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.

**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.

**Related Policies**
2.01.01 Diagnosis and Management of Idiopathic Environmental Intolerance (ie, Multiple Chemical Sensitivities)
  2.01.92 Fecal Microbiota Transplantation
  2.4.69 Fecal Calprotectin Testing

Policy

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

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-butrate, iso-valerate, and n-valerate
- Meat and vegetable fibers
- Long-chain fatty acids
- Cholesterol
- Total short-chain fatty acids
- Levels of Lactobacilli, bifidobacteria, and *Escherichia 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*)
- 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

Rationale

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.
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 in 2014 by Goepp et al. Patients had symptoms suggestive of IBS, eg, 48% had abdominal pain and 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 (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. 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 Steptococcus.

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 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’s disease, 84 unaffected relatives and 55 matched controls. When samples from patients with Crohn’s disease were compared to all unaffected controls, significant differences were found in the...
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 inflammatory bowel disease [IBS], 43 Crohn’s disease, 42 ulcerative colitis) undergoing diagnostic ileocolonoscopy, which provided fecal samples. (7) 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.

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. (10-14) Most recently, in 2012, Jonkers and colleagues conducted a systematic review of studies evaluating probiotics in the management of IBS. (13) 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. A 2013 systematic review by Hungin and colleagues identified a total of 37 RCTs evaluating probiotics for managing lower gastrointestinal symptoms. (14) The authors concluded from their analysis that specific probiotics help relieve symptoms in some patients with IBS. They cited 9 RCTs that reported overall IBS symptoms as a primary endpoint; 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.

Practice Guidelines and Position Statements

None identified

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 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.
Medicare National Coverage

No national coverage determination

References

### Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Reason</th>
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<tbody>
<tr>
<td>September 2011</td>
<td>New Policy</td>
<td>Policy updated with literature search, references updated, no change in policy statement</td>
</tr>
<tr>
<td>June 2013</td>
<td>Update Policy</td>
<td>Policy updated with literature review, reference 13 added. No change in policy statement.</td>
</tr>
<tr>
<td>June 2014</td>
<td>Update Policy</td>
<td>Policy updated with literature review, adding reference 2. No changes to policy statement.</td>
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### Keywords

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

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This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 17, 2017 and is effective April 17, 2017.

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