Fecal Analysis in the Diagnosis of Intestinal Dysbiosis

Policy # 00040
Original Effective Date: 06/05/2002
Current Effective Date: 12/21/2016

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers fecal analysis of the following components, as a diagnostic test for the evaluation of intestinal dysbiosis, irritable bowel syndrome (IBS), malabsorption or small intestinal overgrowth of bacteria to be investigational:*

- 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 Aeromona, Bacillus cereus, Campylobacter, Citrobacter, Klebsiella, Proteus, Pseudomonas, Salmonella, Shigella, S. aureus, Vibrio
- Identification and quantitation of fecal yeast (including C. albicans, C. tropicalis, Rhodoptorul 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

Background/Overview
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 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.

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 offers a “Comprehensive Digestive Stool Analysis 2.0” that evaluates a stool sample for the following components:
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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. Fecal calprotectin as a stand-alone test is addressed in a separate policy.

A related topic, fecal microbiota transplantation (FMT), the infusion of intestinal microorganisms to restore normal intestinal flora is addressed in a separate policy. 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.

**FDA or Other Governmental Regulatory Approval**
U.S. Food and Drug Administration (FDA)
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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. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**Rationale/Source**
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 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 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 and 14%, 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 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 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
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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.

Summary of Evidence
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.

References
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04/18/2002 Medical Policy Committee review
06/05/2002 Managed Care Advisory Council approval
05/04/2004 Medical Director review
05/18/2004 Medical Policy Committee. Format revision. No substance change to policy.
06/28/2004 Managed Care Advisory Council approval
07/07/2006 Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
08/02/2006 Medical Director review
08/09/2006 Medical Policy Committee approval. Rationale/Source updated to reflect most recent literature review.
12/03/2008 Medical Director review
12/17/2008 Medical Policy Committee approval. No change to coverage.
10/14/2010 Medical Policy Committee review
10/06/2011 Medical Policy Committee review
10/11/2012 Medical Policy Committee review
10/31/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/03/2013 Medical Policy Committee review
10/16/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/02/2014 Medical Policy Committee review
12/03/2015 Medical Policy Committee review
12/16/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/01/2016 Medical Policy Committee review
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes

Next Scheduled Review Date: 12/2017

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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<tr>
<td>HCPCS</td>
<td>No codes</td>
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<td>ICD-10 Diagnosis</td>
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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:
  A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
  B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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