Fecal Analysis in the Diagnosis of Intestinal Dysbiosis

Policy # 00040
Original Effective Date: 06/05/2002
Current Effective Date: 10/16/2013

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, 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-glucoronidase
- 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
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 4 patterns of dysbiosis:

- Putrefaction
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- **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 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*).
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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.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
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).

Centers for Medicare and Medicaid Services (CMS)
No national coverage determination.

Rationale/Source
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 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 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. 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. 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. 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 prausnitzii* and *Bifidobacterium adolescentis* and an increase in *Ruminococcus gnavus*. 
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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 and colleagues in Germany evaluated 139 patients (54 IBS, 43 Crohn’s 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 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. 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. Most recently, in 2012, Jonkers and colleagues conducted a systematic review of studies evaluating probiotics in the management of IBS. 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.

References
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Coding

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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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Policy History

Original Effective Date:  06/05/2002
Current Effective Date:  10/16/2013
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.

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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.

Next Scheduled Review Date: 10/2014

*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. Food and Drug Administration (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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