Fecal Analysis in the Diagnosis of Intestinal Dysbiosis
Archived Medical Policy

Archived medical policies are no longer subject to periodic review, are maintained for reference, and may be returned to active status if the need is identified.

Policy # 00040
Original Effective Date: 06/05/2002
Archived Date: 12/20/2017

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-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
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,
Fecal Analysis in the Diagnosis of Intestinal Dysbiosis

Archived Medical Policy

Archived medical policies are no longer subject to periodic review, are maintained for reference, and may be returned to active status if the need is identified.

Policy # 00040
Original Effective Date: 06/05/2002
Archived Date: 12/20/2017

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.

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 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 Diagnostics\(^1\) 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>
</tr>
</thead>
<tbody>
<tr>
<td>Digestion</td>
<td>• Triglycerides</td>
</tr>
<tr>
<td></td>
<td>• Chymotrypsin</td>
</tr>
<tr>
<td></td>
<td>• Iso-butyrate, iso-valerate, and n-valerate</td>
</tr>
<tr>
<td></td>
<td>• Meat and vegetable fibers</td>
</tr>
<tr>
<td>Absorption</td>
<td>• Long-chain fatty acids</td>
</tr>
<tr>
<td></td>
<td>• Cholesterol</td>
</tr>
<tr>
<td></td>
<td>• Total fecal fat</td>
</tr>
<tr>
<td></td>
<td>• Total short-chain fatty acids</td>
</tr>
<tr>
<td>Microbiology</td>
<td>• Levels of Lactobacilli, bifidobacteria, and Escherichia coli and other “potential pathogens,” including Aeromonas, Bacillus cereus, Campylobacter, Citrobacter, Klebsiella, Proteus, Pseudomonas, Salmonella, Shigella, Staphylococcus aureus, and Vibrio</td>
</tr>
</tbody>
</table>

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.
Fecal Analysis in the Diagnosis of Intestinal Dysbiosis

Archived Medical Policy

Archived medical policies are no longer subject to periodic review, are maintained for reference, and may be returned to active status if the need is identified.

Policy # 00040
Original Effective Date: 06/05/2002
Archived Date: 12/20/2017

- Identification and quantitation of fecal yeast (including Candida albicans, Candida tropicalis, Rhodotorula, and Geotrichum)

**Metabolic**
- N-butyrate (considered key energy source for colonic epithelial cells)
- β-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 immunoglobulin A (as a measure of luminal immunologic function)
- Calprotectin

The comprehensive stool analysis package has an optional parasitology component.

FMT has been rigorously studied for the treatment of patients with recurrent Clostridium difficile infection (CDI). 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)
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.
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=0.010 vs p IBS-D).

A 2014 retrospective analysis of data from the Genova Diagnostics database on 2256 patients who underwent stool testing was published by Goepp et al. Patients had symptoms suggestive of IBS (eg, 48% had abdominal pain, 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 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 led to improved health outcomes. All were conducted outside of the United States and 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* and *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 sex-matched healthy individuals. Total bacteria levels did not
Fecal Analysis in the Diagnosis of Intestinal Dysbiosis

Archived Medical Policy

Archived medical policies are no longer subject to periodic review, are maintained for reference, and may be returned to active status if the need is identified.

Policy # 00040
Original Effective Date: 06/05/2002
Archived Date: 12/20/2017

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 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 patients who had ulcerative colitis or Crohn disease (all p<0.001). In the ulcerative colitis and Crohn disease groups, there were higher levels of all 3 markers in patients 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 assessed 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, reviewers identified few well-designed randomized controlled trials (RCTs) and only a limited number of trials suitable for meta-analysis. 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 37 RCTs evaluating probiotics for managing lower gastrointestinal symptoms. Reviewers 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 trials reported a statistically significant benefit of probiotics compared with placebo. Reviewers 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 OF EVIDENCE**
For individuals who have suspected intestinal dysbiosis, 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.

References

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.
Fecal Analysis in the Diagnosis of Intestinal Dysbiosis

Archived Medical Policy

Archived medical policies are no longer subject to periodic review, are maintained for reference, and may be returned to active status if the need is identified.

Policy # 00040
Original Effective Date: 06/05/2002
Archived Date: 12/20/2017

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>04/18/2002</td>
<td>Medical Policy Committee review</td>
</tr>
<tr>
<td>06/05/2002</td>
<td>Managed Care Advisory Council approval</td>
</tr>
<tr>
<td>05/04/2004</td>
<td>Medical Director review</td>
</tr>
<tr>
<td>05/18/2004</td>
<td>Medical Policy Committee. Format revision. No substance change to policy.</td>
</tr>
<tr>
<td>06/28/2004</td>
<td>Managed Care Advisory Council approval</td>
</tr>
<tr>
<td>07/07/2006</td>
<td>Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.</td>
</tr>
<tr>
<td>08/02/2006</td>
<td>Medical Director review</td>
</tr>
<tr>
<td>08/09/2006</td>
<td>Medical Policy Committee approval. Rationale/Source updated to reflect most recent literature review.</td>
</tr>
<tr>
<td>12/03/2008</td>
<td>Medical Director review</td>
</tr>
<tr>
<td>12/17/2008</td>
<td>Medical Policy Committee approval. No change to coverage.</td>
</tr>
<tr>
<td>10/14/2010</td>
<td>Medical Policy Committee review</td>
</tr>
<tr>
<td>10/06/2011</td>
<td>Medical Policy Committee review</td>
</tr>
<tr>
<td>10/11/2012</td>
<td>Medical Policy Committee review</td>
</tr>
<tr>
<td>10/31/2012</td>
<td>Medical Policy Implementation Committee approval. Coverage eligibility unchanged.</td>
</tr>
<tr>
<td>10/03/2013</td>
<td>Medical Policy Committee review</td>
</tr>
<tr>
<td>10/16/2013</td>
<td>Medical Policy Implementation Committee approval. Coverage eligibility unchanged.</td>
</tr>
<tr>
<td>10/02/2014</td>
<td>Medical Policy Committee review</td>
</tr>
<tr>
<td>12/03/2015</td>
<td>Medical Policy Committee review</td>
</tr>
<tr>
<td>12/16/2015</td>
<td>Medical Policy Implementation Committee approval. Coverage eligibility unchanged.</td>
</tr>
<tr>
<td>12/01/2016</td>
<td>Medical Policy Committee review</td>
</tr>
<tr>
<td>01/01/2017</td>
<td>Coding update: Removing ICD-9 Diagnosis Codes</td>
</tr>
<tr>
<td>12/07/2017</td>
<td>Medical Policy Committee review</td>
</tr>
<tr>
<td>12/20/2017</td>
<td>Medical Policy Implementation Committee approval. Archived.</td>
</tr>
</tbody>
</table>

Next Scheduled Review Date: Archived medical policy.

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®), copyright 2016 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.
Fecal Analysis in the Diagnosis of Intestinal Dysbiosis

Archived Medical Policy

Archived medical policies are no longer subject to periodic review, are maintained for reference, and may be returned to active status if the need is identified.

Policy # 00040
Original Effective Date: 06/05/2002
Archived Date: 12/20/2017

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable to related or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

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

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>82239, 82656, 82710, 82715, 82725, 83520, 83630, 83986, 83993, 84311, 87102, 87328, 87329, 87336, 89160</td>
</tr>
<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
</tr>
</tbody>
</table>

*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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.