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Fecal Analysis in the Diagnosis of Intestinal Dysbiosis

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Related Policies (if applicable)
SUR703.049: Fecal Microbiota Transplantation

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

Fecal analysis of the following components **is considered experimental, investigational and/or unproven** 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 *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;

- 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);
- Fecal secretory Immunoglobulin A.

Policy Guidelines

CPT codes might be reported to identify individual components of fecal analysis of intestinal dysbiosis.

Fecal analysis may also include other standard components such as stool culture, stool parasitology and fecal occult blood.

Description

Intestinal dysbiosis may be defined as a state of disordered microbial ecology that is believed to cause disease. Laboratory analysis of fecal samples is proposed as a method of identifying individuals with intestinal dysbiosis and other gastrointestinal disorders.

Fecal Markers of Dysbiosis
Laboratory analysis of both stool and urine has been investigated as markers of dysbiosis. Commercial laboratories may offer testing for comprehensive panels or individual components of various aspects of digestion, absorption, microbiology, and metabolic markers. Representative components of fecal dysbiosis testing are summarized in Table 1.

Table 1. Components of the Fecal Dysbiosis Marker Analysis

Markers	Analytes
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 *Escherichia 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	*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[a]

[a]Fecal calprotectin as a stand-alone test is not addressed in this medical policy.

A related topic is fecal microbiota transplantation, the infusion of intestinal microorganisms to restore normal intestinal flora; that is addressed in SUR703.049 Fecal Microbiota Transplantation. Fecal microbiota transplantation has been rigorously studied for the treatment of patients with recurrent *Clostridium difficile* infection.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of comprehensive testing for fecal dysbiosis.

Some U.S. commercially available fecal dysbiosis tests are listed in Table 2 below.

Table 2. Commercially Available Fecal Dysbiosis Tests by CLIA Certified Laboratories

Device	Manufacturer	Indications
GI Effects	Genova Diagnostics	Assessment of complete gut health, assessing the root cause of many GI complaints; includes the utilization of stool profiles

CLIA: Clinical Laboratory Improvement Amendments.

Rationale

Medical policies assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. The policy assesses the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources. The following is a summary of the literature to date.

Fecal Testing for Intestinal Dysbiosis

The gastrointestinal tract is colonized by a large number and a 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 in addition to gastrointestinal disorders 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 or neurodevelopmental conditions (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 (SIBO) 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 the 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 small intestinal bacterial overgrowth.

<u>Clinical Context and Test Purpose</u>

The purpose of fecal analysis in individuals who have various gastrointestinal conditions is to differentiate intestinal microflora and related immunologic markers that can be used to assist in the diagnosis of those conditions.

The following PICO was used to select literature to inform this policy.

Populations

The relevant populations of interest are those with suspected intestinal dysbiosis, IBS, malabsorption, or small intestinal bacterial overgrowth.

Interventions
The intervention of interest is the use of fecal dysbiosis testing. The rationale for intestinal dysbiosis testing is that alterations in intestinal flora (e.g., overgrowth of some commonly found microorganisms) and related immunologic responses have an impact on human health and disease. The further assumption is that therapeutic (antibiotics, prebiotic, probiotic, or fecal microbiota transplantation) or lifestyle management interventions can be made to address the alterations.

Comparators
The following practices are currently being used to manage various gastrointestinal conditions: laboratory tests, imaging, and endoscopy as indicated.

Outcomes
The general outcomes of interest are the correct diagnosis of gastrointestinal conditions potentially associated with alterations in intestinal microflora and initiation of appropriate treatment.

These tests might be used during the evaluation and treatment of acute and chronic intestinal disorders. The duration of follow-up is condition-specific and is expected to be weeks to months later.

Study Selection Criteria
For the evaluation of clinical validity of fecal dysbiosis testing, methodologically credible studies were selected using the following principles:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard.
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.
- Included a validation cohort separate from the development cohort.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Establishing that fecal analysis to identify intestinal dysbiosis is beneficial would involve evidence that the fecal dysbiosis testing provides an incremental benefit to net health outcomes in patients with gastrointestinal tract symptoms as compared to current clinical pathways. No studies were identified 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, SIBO, or other conditions. Additionally, no studies were identified establishing diagnostic criteria for intestinal dysbiosis as a disorder.

Retrospective Studies

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. (1) Records were identified from samples sent to Genova 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 24258 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. The Genova Comprehensive Digestive Stool Analysis evaluates digestion/absorption markers, gut metabolic markers, and gut microbiology markers. (2) Of the 3553 patient samples included, 13.6%, 27.5%, and 58.1%, respectively, reported having constipation-predominant IBS (IBS-C), diarrhea-predominant (IBS-D), and mixed subtypes 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 mixed subtypes of IBS 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 retrospective analysis of data from the Genova Diagnostics database for 2256 patients who underwent stool testing was published by Goepp et al. (2014). (3) Patients had symptoms suggestive of IBS (e.g., 48% had abdominal pain, 14% had diarrhea). Eighty-three percent of patients had at least one abnormal test result. The most common abnormal result, occurring in 73% of cases, was low growth in the beneficial bacteria *lactobacillus* and/or *bifidobacterium*. The 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 (i.e., using Rome criteria) and thus the accuracy of the Genova tests compared with clinical diagnosis could not be determined.

Nonrandomized Observational Studies

Studies using quantitative real-time polymerase chain reaction analysis have compared microbiota in patients who had known disease with healthy controls in an attempt to identify a microbiotic profile associated with a particular disease. None of these studies evaluated whether the fecal analysis in patients with IBS or other conditions led to improved health outcomes.

Jeffrey et al. (2020) evaluated fecal samples of 80 patients with IBS and 65 healthy controls. (4) *Ruminococcus gnavus* and *Lachnospiraceae* species were significantly elevated in patients with IBS, while *Barnesiellaintestinihominis* and *Coprococcus catus* amounts were found to be significantly lower. Additionally, in IBS patients, galactose degradation, sulfate reduction and assimilation, and cysteine biosynthesis were all reduced, indicating a decrease in sulfur metabolism compared to controls. No differences were noted in fecal microbiota across IBS subtypes. In patients screened for bile acid malabsorption (n=45), 40% tested positive to varying degrees. Only patients with positive screening results in the severe bile acid malabsorption (BAM) category showed significant differences in their fecal microbiome

compared to borderline, mild, and moderate cases. Elevated glycerophospholipids and oligopeptides were considered predictive for BAM.

Andoh et al. (2012) reported on fecal microbiota profiles of 161 Japanese patients with Crohn disease (CD) and 121 healthy controls. (5) Healthy individuals tended to have a different distribution of fecal microbiota than CD patients. For example, compared with controls, CD patients had significantly lower levels of *Faecalibacterium* and *Eubacterium* and significantly higher levels of *Streptococcus*.

Sobhani et al. (2011) evaluated fecal microbiota samples taken before colonoscopy from 60 patients with colorectal cancer and 119 sex-matched healthy individuals in France. (6) Total bacteria levels did not differ significantly between colorectal cancer and non-colorectal cancer groups. There were significant elevations of the *Bacteroides/Prevotella* group in the colorectal cancer population.

Joossens et al. (2011) published a study comparing fecal microbiota in 68 patients with CD, 84 unaffected relatives, and 55 matched controls in Belgium. (7) When samples from patients who had CD were compared with all unaffected controls, significant differences were found in the concentration of five bacterial species. Compared with controls, CD patients had lower levels of *Dialister invisus*, an uncharacterized species of *Clostridium* cluster XIVa, *Faecalibacterium prausnitzii*, and *Bifidobacterium adolescentis* as well as an increase in *Ruminococcus gnavus*.

Fecal markers in addition to microbiology profiles have been evaluated whether the testing can distinguish between individuals with various gastrointestinal diseases. Langhorst et al. (2008) in Germany evaluated 139 patients (54 with IBS, 43 CD, 42 ulcerative colitis) undergoing diagnostic ileocolonoscopy, who provided fecal samples. (8) Samples were analyzed with enzyme-linked immunosorbent assay. Patients with IBS had significantly higher levels of lactoferrin, calprotectin, and polymorphonuclear-elastase than patients who had ulcerative colitis or CD (all $p<0.001$). In the ulcerative colitis and CD groups, there were higher levels of all three markers in patients who had inflammation compared with those who did not.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No randomized or comparative intervention studies supporting the clinical utility of fecal testing were identified.

Chain of Evidence
Indirect evidence of clinical utility rests on clinical validity. It is not possible to construct a chain of evidence because there is insufficient evidence of clinical validity to draw conclusions on clinical utility.

Summary of Evidence
For individuals who have gastrointestinal conditions such as suspected intestinal dysbiosis, irritable bowel syndrome, 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 who had a known disease with 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 the fecal microbiome and inflammatory markers may differ across patients with irritable bowel syndrome subtypes. No studies were identified on the diagnostic accuracy of fecal analysis vs another diagnostic approach or that 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 that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements
American Gastroenterological Association
The American Gastroenterological Association (AGA) published clinical practice guidelines (2019) on laboratory evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome (IBS) in adults. (9) Related to fecal analysis, the AGA suggests the use of fecal calprotectin or fecal lactoferrin to screen for IBS in individuals presenting with chronic diarrhea (conditional recommendation; low-quality evidence).

In 2020, the AGA published a clinical practice update on small intestinal bacterial overgrowth (SIBO). (10) On the topic of fecal analysis, the guideline states, "there is insufficient evidence to support the use of inflammatory markers, such as fecal calprotectin to detect SIBO." No other fecal markers are explicitly mentioned.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this policy are listed in Table 3.

Table 3. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02839317	Comparison of Fecal MicroBiota Between Patients With Early and Late Crohn's Disease	300	May 2024

	and Relationship with Different Genetic and Serological Profiles		
NCT05619055	Intestinal Dysbacteriosis in the Pathogenesis of Necrotizing Enterocolitis	30	Mar 2025

NCT: national clinical trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
04/01/2025	Reviewed. No changes.
12/15/2024	Document updated with literature review. Coverage unchanged. References 9 and 10 added.
12/01/2023	Reviewed. No changes.
07/15/2022	Document updated with literature review. Coverage unchanged. Reference 4 added.
04/01/2021	Review only. No changes.
05/15/2020	Document updated with literature review. Coverage unchanged. Two references updated; other references removed.
04/15/2019	Reviewed. No changes.
04/15/2018	Document updated with literature review. Coverage unchanged. Reference number 2 was added.
04/15/2017	Reviewed. No changes.
04/15/2016	Document updated with literature review. Coverage unchanged.
06/01/2015	Reviewed. No changes.
03/01/2014	Document updated with literature review. Coverage unchanged.
02/15/2008	Revised/Updated Entire Document.
08/15/2003	New Medical Document