Corporate Medical Policy

Fecal Analysis in the Diagnosis of Intestinal Dysbiosis AHS – G2060

File Name: fecal_analysis_in_the_diagnosis_of_intestinal_dysbiosis
Origination: 01/01/19
Last CAP Review: 05/2020
Next CAP Review: 05/2021
Last Review: 05/2020

Description of Procedure or Service

Intestinal dysbiosis is defined as a disruption or imbalance of the intestinal microbial ecology (Guinane & Cotter, 2013). Dysbiosis is associated with many diseases, including irritable bowel syndrome (IBS), inflammatory bowel diseases (IBD), obesity, allergy, and diabetes (Carding, Verbeke, Vipond, Corfe, & Owen, 2015).

Related Policies
Diagnosis of Idiopathic Environmental Intolerance AHS – G2056
Fecal Calprotectin Testing AHS – G2061
Laboratory Testing for the Diagnosis of Inflammatory Bowel Disease AHS – G2121

Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

Fecal analysis as a diagnostic test for the evaluation of intestinal dysbiosis, irritable bowel syndrome, malabsorption or small intestinal overgrowth of bacteria is not covered.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Fecal Analysis in the Diagnosis of Intestinal Dysbiosis is covered

Not applicable.

When Fecal Analysis in the Diagnosis of Intestinal Dysbiosis is not covered

Reimbursement is not allowed for 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:

a. Triglycerides
b. Chymotrypsin
c. Iso-butyrate, iso-valerate, and n-valerate
d. Meat and vegetable fibers

e. Long chain fatty acids
f. Cholesterol
g. Total short chain fatty acids
h. 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
i. Identification and quantitation of fecal yeast (including C. albicans, C. tropicalis, Rhodoptorul and Geotrichum)
j. N-butyrate
k. Beta-glucoronidase
l. pH
m. Short chain fatty acid distribution (adequate amount and proportions of the different short chain fatty acids reflect the basic status of intestinal metabolism)
n. Fecal secretory IgA

Policy Guidelines

Background

The human intestinal tract has a diverse and complex microbial community necessary for health and nutrition. The gut microbiome is estimated to consist of upwards of 1000 bacterial species (Guinane & Cotter, 2013; Ley, Peterson, & Gordon, 2006; Qin et al., 2010). The microbiota functions with the immune system to protect against pathogens. It also performs essential metabolic functions, extracting certain forms of energy and nutrients from food and providing a source of other essential nutrients and vitamins (Carding et al., 2015).

The gut is colonized at birth, but the intestinal microbiome changes rapidly during the first year of life. In adults, each individual's unique population of gut microbiota is fairly stable over time; however, alterations in the microbiota can result from exposure to various environmental factors, including diet, toxins, drugs, and pathogens (Carding et al., 2015; Lozupone, Stombaugh, Gordon, Jansson, & Knight, 2012; Snapper & Abraham, 2019). This change in an individual's normal microbiota is called "dysbiosis" (Johnston, 2017). Dysbiosis has been associated with obesity (Ley, Turnbaugh, Klein, & Gordon, 2006; Zhang et al., 2009) malnutrition (Kau, Ahern, Griffin, Goodman, & Gordon, 2011), systematic diseases such as diabetes (Qin et al., 2012) and chronic inflammatory diseases such as inflammatory bowel disease (IBD) (Frank et al., 2007; Guinane & Cotter, 2013). Both direct assessment of the gut microbiota (examination of bacteria levels) and indirect assessment (measurement of non-living markers such as pH or beta-glucoronidase) have been proposed for investigation of intestinal dysbiosis.

Microbial or microbial-derived components have also been cited as potential representations of dysbiosis. For example, short-chain fatty acids have been identified as a mechanism to regulate intestinal processes and, as such, may represent dysbiosis (Johnston, 2017). These fatty acids are the products of bacterial fermentation of fiber, and the concentrations of these fatty acids have been noted to decrease in IBD cases. Some fatty acids, especially butyrate, have been demonstrated to factor in signaling cascades that control immune function, which indicates a role in controlling intestinal inflammation (Parada Venegas et al., 2019). Ongoing research has uncovered many other potential links between intestinal metabolism and gut microbiota so many markers have been suggested as potential indicators of dysbiosis.

Many tests exist for the assessment of the gut microbiome. Due to the amount of conditions associated (or proposed to be associated) with gut microbiome balance, there are many corresponding tests, including screening measures intended for completely healthy individuals. These tests primarily revolve around nucleic acid amplification; microbial DNA or RNA is obtained from the sample, unique sequences are identified, and the nucleic acid is quantified (Raby, 2019). For instance, Viome offers a comprehensive screening panel that measures "all

microorganisms" in the gut (including viruses, archaea, yeast, fungi, parasites, and bacteriophages). Those measurements are combined into a score for various issues, such as inflammatory activity, digestive efficiency, methane gas production, overall gas production, and more (Viome, 2019a). Viome also provides a list of nutritional recommendations, broken down into individual foods. Viome performs RNA sequencing with Illumina NextSeq and uses bioinformatics algorithms to classify taxonomic data (Viome, 2019b).

Some companies may offer companion products with their gut microbiome tests. BioHM provides a similar assessment of bacterial and fungal species in an individual's gastrointestinal tract, but the company also offers a series of probiotics. These probiotics are intended for various purposes, such as colon cleansing or immunity (BioHM, 2018). Other companies offering a gut microbiome test include Thryve, GenCove, DayTwo, American Gut, and Genova (DNATestingChoice, 2019; Genova, 2019).

The potential clinical impact of imbalance in the intestinal microbiota suggests a need for standardized diagnostic methods to facilitate microbiome profiling. Documenting dysbiosis has traditionally relied on classical microbiological techniques and the ability to culture pure isolates for identification and classification; however, the ability to classify bacteria and archaea according to individual 16S rRNA sequences can now possibly provide a rapid and detailed means of profiling complex communities of microorganisms (Casen et al., 2015; Zoetendal, Akkermans, & De Vos, 1998). Laboratory analysis of various fecal biomarkers have also been proposed as a method of identifying individuals with intestinal dysbiosis and may be useful in providing insight into the role of intestinal health and disease, and the development of non-gastrointestinal conditions associated with intestinal dysbiosis. However, there is a current lack of literature on the normal ranges of these biomarkers, which limit the applicability of these analyses in a general clinical setting (Bäckhed et al., 2012; Berry & Reinisch, 2013; Pang, Leach, Katz, Day, & Ooi, 2014).

Falony et al analyzed "two independent, extensively phenotyped cohorts: the Belgian Flemish Gut Flora Project (FGFP; discovery cohort; N = 1106) and the Dutch LifeLines-DEEP study (LLDeep; replication; N = 1135)." These two sets were integrated with global data sets, combining to yield 3948 items. A "core" set of 14 genera was identified. 69 clinical and questionnaire-based covariates were found to be associated with microbiota compositional variation with a 92% replication rate. The authors noted that "stool consistency showed the largest effect size, whereas medication explained largest total variance and interacted with other covariate-microbiota associations, but early-life events such as birth mode were not reflected in adult microbiota composition" (Falony et al., 2016)

Zhernakova et al sequenced the gut microbiomes of 1,135 participants from a Dutch population-based cohort. The authors identified relations between the microbiome and "126 exogenous and intrinsic host factors, including 31 intrinsic factors, 12 diseases, 19 drug groups, 4 smoking categories, and 60 dietary factors". "Significant" associations were found between the gut microbiome and various intrinsic, environmental, dietary, medication parameters, and disease phenotypes. The authors calculated that 18.7% of variation in microbial composition could be explained by these factors, and they observed that fecal chromogranin A was exclusively associated with 61 microbial species, totaling 53% of the microbial composition. A more diverse microbiome was associated with low CgA concentrations. The authors concluded that "these results are an important step toward a better understanding of environment-diet-microbe-host interactions" (Zhernakova et al., 2016).

Lo Presti et al profiled the fecal and mucosal microbiota of IBD and IBS patients. 38 IBD patients, 44 IBS patients, and 47 healthy controls were included, and overall, 107 fecal samples were provided. The authors found that "*Anaerostipes* and *Ruminococcaceae* were identified as the most differentially abundant bacterial taxa in controls, *Erysipelotrichi* was identified as [a] potential biomarker for IBS, while *Gammaproteobacteria*, *Enterococcus*, and *Enterococcaceae* [were identified] for IBD" (Lo Presti et al., 2019).

Malham et al investigated the microbiotic profile of pediatric IBD. 143 IBD patients and 34 healthy controls were included. A reduced "richness" in microbiotic profile was observed in IBD patients compared to healthy controls. In ulcerative colitis (UC), that reduced richness was associated with high intestinal inflammation and extensive disease. Nine species were "significantly" associated with a healthy microbiome, and three species were associated with IBD. The authors remarked that the microbiome composition could differentiate between Crohn's Disease, UC, and healthy controls (Malham et al., 2019).

Danilova et al compared the gut microbiome composition of IBD patients to healthy controls. 95 IBD patients and 96 healthy controls were included. The authors noted an increase of Proteobacteria and Bacteroidetes bacteria and decrease of Firmicutes bacteria and Euryarchaeota archaea in IBD patients. Butyrate-producing and hydrogen-utilizing bacteria were observed to have lower representation in IBD patients. Short-chain fatty acids (SCFA) were also found to have a lower absolute content in IBD patients. The authors suggested that this finding may "indicate inhibition of functional activity and number of anaerobic microflora and/or an [*sic*] change in SCFA utilization by colonocytes" (Danilova et al., 2019).

Vaughn et al in reviewing the current status of intestinal dysbiosis and fecal transplantation found that "it is hypothesized that intestinal dysbiosis may contribute to the pathogenesis of many diseases, especially those involving the gastrointestinal tract. Therefore, fecal microbiota transplantation (FMT) is increasingly being explored as a potential treatment that aims to optimize microbiota composition and functionality (Vaughn, Rank, & Khoruts, 2018)." Holleran et al also found that fecal transplant is not recommended for use outside of *Clostridium difficile* infection (CDI) due to concerns regarding outcome and safety; however, several case series and randomized controlled trials have described its use in a research environment for a few gastrointestinal conditions related to intestinal dysbiosis, including ulcerative colitis (UC), Crohn's disease (CD) and irritable bowel syndrome (IBS). The most successful reports of the clinical efficacy of FMT in gastrointestinal conditions outside of CDI have been in treating UC (Holleran et al., 2018).

Guidelines and Recommendations

2015 World Gastroenterology Organization (WGO) (Bernstein et al., 2016)

The WGO released their global guidelines for Inflammatory Bowel Disease in 2015 (published in 2016). Their recommendations concerning stool examination and testing are as follows:

- "Routine fecal examinations and cultures should be carried out to eliminate bacterial, viral, or parasitic causes of diarrhea.
- Testing for *Clostridium difficile* (should be considered even in the absence of antecedent antibiotics) — should be carried out within 2 hours of passage of stools.
- A check for occult blood or fecal leukocytes should be carried out if a patient presents without a history of blood in the stool, as this can strengthen the indication for lower endoscopy. Where lower endoscopy is readily available, these tests are rarely indicated.
- Lactoferrin, α1-antitrypsin. The main reason for listing this test is to rule out intestinal inflammation, rather than using it as a positive diagnostic test. It may not be available in developing countries, but it can be undertaken relatively inexpensively and easily with rapid-turnaround slide-based enzyme-linked immunoassay (ELISA) tests.
- Calprotectin — a simple, reliable, and readily available test for measuring IBD activity — may be better for UC than CD; the rapid fecal calprotectin

tests could be very helpful in developing countries. If available, a home test may be useful as a routine for follow-up.”

2012 Rome Foundation Report (Simren et al., 2013)

An international Working Group convened in 2012 “to provide clinical guidance on modulation of gut microbiota in IBS” and released their findings Intestinal microbiota in functional bowel disorders: a Rome foundation report in 2013. They state the following “Diagnostic and therapeutic general recommendations”:

- “There is currently no clinically useful way of identifying whether the microbiota are disturbed in particular patients with irritable bowel syndrome (IBS).
- Dietary evaluation and exclusion of possible sources of unabsorbable carbohydrates including fermentable oligo-, di- and mono-saccharides and polyols and excessive fibre could be beneficial in select patients.
- Probiotics have a reasonable evidence base and should be tried, for a period of at least 1 month, at adequate doses before a judgement is made about the response to treatment.
- The utility of testing for small intestinal bacterial overgrowth (SIBO) in the setting of IBS remains an area of uncertainty.
- If SIBO is strongly suspected based on clinical presentation and testing is being considered, using stringent criteria for the glucose breath test or jejunal aspirate appear to be the best tests.
- Consideration should be given to discontinuing proton pump inhibitors in those with SIBO.
- There is emerging evidence that non-absorbable antibiotics may have the potential to reduce symptoms in some patients with IBS.

European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Pediatric Infectious Diseases (ESPGHAN/ESPID)

These joint guidelines reviewed management of acute gastroenteritis (AGE) in children. In it, they note that AGE does not require a specific diagnostic workup and that “microbiological investigation is not helpful in most cases”. Fecal markers are also not recommended for differentiating viral and bacterial AGE. However, the guidelines observe that “microbiological investigations may be considered in children with underlying chronic conditions (eg, oncologic diseases, IBDs, etc), in those in extremely severe conditions, or in those with prolonged symptoms in whom specific treatment is considered” (Guarino et al., 2014).

World Gastroenterology Organisation Global Guidelines (WGO, 2013)

The WGO published guidelines on functional gastrointestinal (GI) symptoms. In it, they identify diagnostic tests for these symptoms. The basic diagnostic tests are as follows:

- Complete blood cell count (CBC)
- Erythrocyte sedimentation rate (ESR) / C-reactive protein (CRP)
- Biochemistry panel
- Fecal occult blood (patient aged > 50 y)
- Pregnancy test
- Liver function tests
- Calprotectin or other fecal test to detect inflammatory bowel disease in patients thought to have IBS, but in whom inflammatory bowel disease (IBD) is a possibility; now routine in many primary care settings (in the United Kingdom)

- Celiac serology; considered routine in areas with a high prevalence of celiac disease
- Stool testing for ova and parasites

National Institute for Health and Care Excellence (NICE, 2017)

NICE updated their IBS guidelines in 2017. In it, they list the following items about diagnostic tests:

"In people who meet the IBS diagnostic criteria, the following tests should be undertaken to exclude other diagnoses:

- full blood count (FBC)
- erythrocyte sedimentation rate (ESR) or plasma viscosity
- c-reactive protein (CRP)
- antibody testing for coeliac disease (endomysial antibodies [EMA] or tissue transglutaminase [TTG]).

The following tests are not necessary to confirm diagnosis in people who meet the IBS diagnostic criteria:
- ultrasound
- rigid/flexible sigmoidoscopy
- colonoscopy; barium enema
- thyroid function test
- faecal ova and parasite test
- faecal occult blood
- hydrogen breath test (for lactose intolerance and bacterial overgrowth)" (NICE, 2017).

Infectious Diseases Society of America/American College of Gastroenterology/American Society for Gastrointestinal Endoscopy/American Gastroenterological Association/North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (IDSA/ACG/ASGE/AGA/NASPGHAN)

These joint guidelines were sent to the FDA regarding recurrent Clostridium difficile infection (CDI). In it, the guidelines recommend screening donors for fecal microbiota transplantation (FMT) for C. difficile toxin B and performing a culture for enteric pathogens (IDSA/ACG/ASGE/AGA/NASPGHAN, 2013).

NASPGHAN published an FMT guideline for children in 2019, and the same analytes for screening (C difficile toxin B, culture for enteric pathogens) were recommended (Davidovics et al., 2019).

Food and Drug Administration (FDA)

The FDA has issued a guidance statement for fecal microbiota transplant (FMT) stating that it will exercise enforcement discretion regarding the investigational new drug (IND) requirements for the use of fecal microbiota for transplantation. In 2019, the FDA updated their guidance on FMT, stating that "FMT donor stool testing must include MDRO testing to exclude use of stool that tests positive for MDRO. The MDRO tests should at minimum include extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, vancomycin-resistant enterococci (VRE), carbapenem-resistant Enterobacteriaceae (CRE), and methicillin-resistant Staphylococcus aureus (MRSA). Culture of nasal or peri-rectal swabs is an acceptable alternative to stool testing for MRSA only. Bookend testing (no more than 60 days apart) before and after multiple stool donations is acceptable if stool samples are quarantined until the post-donation MDRO tests are confirmed negative (FDA, 2019)."

Fecal Microbiota Transplantation Workgroup (2011)

This Working Group published guidelines on FMT. Fecal donor screening recommendations were included. The following analytes were recommended to be screened:

- "C difficile toxin B by PCR; if unavailable, then evaluation for toxins A and B by enzyme immunoassay (EIA)
- Routine bacterial culture for enteric pathogens
- Fecal Giardia antigen
- Fecal Cryptosporidium antigen
- Acid-fast stain for Cyclospora, Isospora, and, if antigen testing unavailable, Cryptosporidium
- Ova and parasites
- Helicobacter pylori fecal antigen (for upper gastrointestinal [GI] routes of FMT administration)" (Bakken et al., 2011).

American Gastroenterological Association (AGA, 2015)

The AGA published guidelines on FMT, including information on donor pathogen screening. *C. difficile* toxin B and culture for enteric pathogens were "suggested" to be screened for, *Giardia*, *Cryptosporidium*, *Isospora* and *Cyclospora*, *Listeria*, *E. coli* O157, *Vibrio*, and *Norovirus* should be "considered", and Cytomegalovirus, Human T-cell lymphoma virus, Epstein–Barr virus, *Dientamoeba fragilis*, *Blastocystis hominis*, *Strongyloides stercoralis*, *Entamoeba histolytica*, *H. pylori*, *Schistosoma*, JC virus, Vancomycin-resistant *enterococci*, and Methicillin-resistant *Staphylococcus aureus* should "maybe" [term used by authors] be screened (Kelly et al., 2015).

Applicable Federal Regulations

Searches for "dysbiosis" and "microbiome" on the FDA website on August 19, 2019, yielded no results. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 82239, 82542, 82710, 82715, 82725, 83520, 83630, 83986, 84311, 87045, 87046, 87075, 87102, 87177, 87209, 87623, 87328, 87329, 87336

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Specialty Matched Consultant Advisory Panel review 5/2020.

Medical Director review 5/2020.

Policy Implementation/Update Information

1/1/2019   BCBSNC will not provide coverage for fecal analysis as a diagnostic test for the evaluation of intestinal dysbiosis, irritable bowel syndrome, malabsorption or small intestinal overgrowth of bacteria because it is considered investigational. BCBSNC does not provide coverage for investigational services or procedures. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

10/1/19   Policy statement is revised to read: Fecal analysis as a diagnostic test for the evaluation of intestinal dysbiosis, irritable bowel syndrome, malabsorption or small intestinal overgrowth of bacteria is not covered. Wording revised in the Not Covered section. "Investigational" changed to read "Reimbursement is not allowed…" Deleted coding grid. Notification given 10/1/2019 for effective date 12/2/2019. (an)

12/10/19   Reviewed by Avalon 3rd Quarter 2019 CAB. No changes to policy. Medical Director review 12/2019. (jd)

06/09/20   Related Policies section added. Policy Guidelines updated. Specialty Matched Consultant Advisory Panel review 5/2020. Medical Director review 5/2020. (jd)