Fecal Analysis in the Diagnosis of Intestinal Dysbiosis

Policy Number: 2.04.26
Origination: 7/2006
Last Review: 7/2019
Next Review: 7/2020

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for fecal analysis in the diagnosis of intestinal dysbiosis. This is considered investigational.

When Policy Topic is covered
Not Applicable

When Policy Topic is not covered
Fecal analysis of the following components is considered investigational 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 E. coli and other “potential pathogens,” including Aeromona, Bacillus cereus, Campylobacter, Citrobacter, Klebsiella, Proteus, Pseudomonas, Salmonella, Shigells, 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
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.

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. The relevant outcomes are test 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 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.

**Background**

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 (eg, irritable bowel syndrome [IBS], inflammatory or autoimmune disorders, food allergy, atopic eczema, unexplained fatigue, arthritis, ankylosing spondylitis), malnutrition, or neuropsychiatric symptoms (eg, 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

<table>
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<th>Description of Procedure or Service</th>
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<td><strong>Populations</strong></td>
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<td>• With suspected intestinal dysbiosis, irritable bowel syndrome, malabsorption or small intestinal bacterial overgrowth</td>
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<td><strong>Interventions</strong></td>
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<td>• Interventions of interest are:</td>
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<td>• Fecal analysis testing</td>
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<td><strong>Comparators</strong></td>
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<td>• Comparators of interest are:</td>
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<td>• Standard approach to diagnosing specific conditions</td>
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<td><strong>Outcomes</strong></td>
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<td>• Relevant outcomes include:</td>
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<td>• Test accuracy</td>
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<td>• Test validity</td>
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<td>• Symptoms</td>
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<td>• Functional outcomes</td>
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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. 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 Comprehensive Digestive Stool Analysis 2.0 Test**

<table>
<thead>
<tr>
<th>Markers</th>
<th>Analytes</th>
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<td><strong>Digestion</strong></td>
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<td>Triglycerides</td>
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<td>Chymotrypsin</td>
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<td>Iso-butyrate, iso-valerate, and n-valerate</td>
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<td></td>
<td>Meat and vegetable fibers</td>
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<td><strong>Absorption</strong></td>
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<td></td>
<td>Long-chain fatty acids</td>
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<td></td>
<td>Cholesterol</td>
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<td></td>
<td>Total fecal fat</td>
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<td></td>
<td>Total short-chain fatty acids</td>
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<td><strong>Microbiology</strong></td>
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<td>Levels of Lactobacilli, bifidobacteria, and <em>Escherichia coli</em> and other &quot;potential pathogens,&quot; including <em>Aeromonas</em>, <em>Bacillus cereus</em>, <em>Campylobacter</em>, <em>Citrobacter</em>, <em>Klebsiella</em>, <em>Proteus</em>, <em>Pseudomonas</em>, <em>Salmonella</em>, <em>Shigella</em>, <em>Staphylococcus aureus</em>, and <em>Vibrio</em></td>
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<td>Identification and quantitation of fecal yeast (including <em>Candida albicans</em>, <em>Candida tropicalis</em>, <em>Rhodotorula</em>, and <em>Geotrichum</em>) (optional viral and/or parasitology components)</td>
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<tr>
<td><strong>Metabolic</strong></td>
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<td></td>
<td>N-butyrate (considered key energy source for colonic epithelial cells)</td>
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<tr>
<td></td>
<td>β-glucuronidase</td>
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<td></td>
<td>pH</td>
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<td></td>
<td>Short-chain fatty acid distribution (adequate amount and proportions of the different short-chain fatty acids reflect the basic status of intestinal metabolism)</td>
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<tr>
<td><strong>Immunology</strong></td>
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<td>Fecal secretory immunoglobulin A (as a measure of luminal immunologic function)</td>
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<td></td>
<td>Calprotectin</td>
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</table>

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). No specific stool testing, other than the identification of CDI, is currently recommended.

**Regulatory Status**

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 Amendments (CLIA). The Genova Diagnostics test is available under the auspices of CLIA. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

**Rationale**

This evidence review was created in November 2001 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through October 4, 2018.

Evidence reviews 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. Evidence reviews assess 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**

**Clinical Context and Test Purpose**

The purpose of fecal analysis in patients who have various gastrointestinal conditions is to differentiate intestinal microflora and related immunologic responses that may be related to those conditions.

The question addressed in this evidence review is: Does fecal dysbiosis testing used in individuals who have gastrointestinal conditions such as suspected intestinal dysbiosis, irritable bowel syndrome (IBS), malabsorption, or small intestinal bacterial overgrowth improve the net health outcome?

The following PICOTS were used to select literature to inform this review.
Patients
The relevant populations of interest are those with gastrointestinal conditions such as 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 (eg, 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: the standard approach to diagnosing specific intestinal conditions, which can include using 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.

Timing
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.

Setting
The setting is ambulatory primary care or gastroenterology consultation.

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

For the evaluation of clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- 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 development cohort.

Technical Reliability
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of
specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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 outcome in patients with gastrointestinal tract symptoms as compared to current clinical pathways. No studies were identified in the initial literature review or during the literature searches for evidence review 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 vs 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.

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. 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. Of the 3553 patient samples included, 13.6%, 27.5%, and 58.1%, respectively, reported having constipation-predominant IBS, 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 constipation-predominant IBS 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). Patients had symptoms suggestive of IBS (eg, 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. 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.

**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.

Andoh et al (2012) reported on fecal microbiota profiles of 161 Japanese 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*.

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. 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 Crohn disease, 84 unaffected relatives, and 55 matched controls in Belgium. When samples from patients who had Crohn disease were compared with all unaffected controls, significant differences were found in the concentration of five 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* 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 Crohn disease, 42 ulcerative colitis) undergoing diagnostic ileocolonoscopy, who provided fecal samples. 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 Crohn disease (all p<0.001). In the ulcerative colitis and Crohn disease 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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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.

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 on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

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. The relevant outcomes are test 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 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.

**SUPPLEMENTAL INFORMATION**

**Practice Guidelines and Position Statements**
No guidelines or statements were identified.

**U.S. Preventive Services Task Force Recommendations**
Not applicable.
**Medicare National Coverage**
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing and Unpublished Clinical Trials**
A search of ClinicalTrials.gov in October 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

**REFERENCES**

**Billing Coding/Physician Documentation Information**

82270  Blood, occult, by peroxidase activity (eg, guaiac), qualitative; feces, consecutive collected specimens with single determination, for colorectal neoplasm screening (ie, patient was provided three cards or single triple card for consecutive collection)

82272  Blood, occult, by peroxidase activity (eg, guaiac), qualitative, feces, 1-3 simultaneous determinations, performed for other than colorectal neoplasm screening

82274  Blood, occult, by fecal hemoglobin determination by immunoassay, qualitative, feces, 1-3 simultaneous determinations

82239  Bile acids; total

82542  Column chromatography, includes mass spectrometry, if performed (eg, HPLC, LC, LC/MS, LC/MS-MS, GC, GC/MS-MS, GC/MS, HPLC/MS), non-drug analyte(s) not elsewhere specified, qualitative or quantitative, each specimen

82656  Elastase, pancreatic (EL-1), fecal, qualitative or semi-quantitative

82710  Fat or lipids, feces; quantitative

82715  Fat differential, feces, quantitative

82725  Fatty acids, nonesterified

83520  Immunoassay for analyte other than infectious agent antibody or
infectious agent antigen; quantitative, not otherwise specified
83630 Lactoferrin, fecal; qualitative
83631 Lactoferrin, fecal; quantitative
83986 pH, body fluid, except blood
83993 Calprotectin, fecal
84311 Spectrophotometry, analyte not elsewhere specified
86403 Particle agglutination; screen, each antibody
87045 Culture, bacterial; stool, aerobic, with isolation and preliminary examination (eg, KIA, LIA), Salmonella and Shigella species
87046 Culture, bacterial; stool, aerobic, additional pathogens, isolation and presumptive identification of isolates, each plate
87075 Culture, bacterial; any source, except blood, anaerobic with isolation and presumptive identification of isolates
87102 Culture, fungi (mold or yeast) isolation, with presumptive identification of isolates; other source (except blood)
87177 Ova and parasites, direct smears, concentration and identification
87209 Smear, primary source with interpretation; complex special stain (eg, trichrome, iron hematoxylin) for ova and parasites
87328 Infectious agent antigen detection by enzyme immunoassay technique, qualitative or semiquantitative, multiple-step method; cryptosporidium
87329 Infectious agent antigen detection by enzyme immunoassay technique, qualitative or semiquantitative, multiple-step method; giardia
87336 Infectious agent antigen detection by enzyme immunoassay technique, qualitative or semiquantitative, multiple-step method; Entamoeba histolytica dispar group
89160 Meat fibers, feces

CPT Codes 82491, 82492 were deleted 1/1/2016

Additional Policy Key Words
N/A

Policy Implementation/Update Information
7/1/06 New policy, considered investigational.
7/1/07 No policy statement changes.
7/1/08 No policy statement changes.
7/1/09 No policy statement changes.
7/1/10 No policy statement changes.
7/1/11 No policy statement changes.
7/1/12 No policy statement changes.
7/1/13 No policy statement changes.
7/1/14 No policy statement changes.
7/1/15 No policy statement changes.
7/1/16 Added CPT code 82542. No policy statement changes.
7/1/17 No policy statement changes.
7/1/18 No policy statement changes.
7/1/19 No policy statement changes.
State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.