Clinical Policy Title: Fecal biomarkers in inflammatory bowel disease

Effective Date: April 1, 2017
Initial Review Date: October 19, 2016
Most Recent Review Date: November 16, 2016
Next Review Date: November 2017

Related policies:
CP# 01.01.03 Measurement of serum antibodies to infliximab and adalimumab

ABOUT THIS POLICY: AmeriHealth Caritas Pennsylvania has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas Pennsylvania when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Pennsylvania’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Pennsylvania’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania’s clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas Pennsylvania considers the use of fecal biomarker testing for the management of inflammatory bowel disease (IBD) to be investigational and, therefore, not medically necessary.

Limitations:
None.

Alternative covered services:
- Endoscopy.
- Histology.
- Radiologic testing (e.g., computed tomography or magnetic resonance enterography).
- Physician consultation.

Background
IBD is a group of intestinal disorders characterized by chronic relapsing inflammation of the digestive tract (Loddo 2015). An estimated 1.0 to 1.3 million Americans suffer from IBD; the prevalence of IBD in persons of Caucasian and Ashkenazi Jewish origin than other racial and ethnic subgroups (Centers for Disease Control and Prevention [CDC] 2016). Approximately 20–25 percent of patients with IBD are diagnosed before 16 years of age, although onset of IBD before 5 years is rare (Loddo 2015).

While the exact cause of IBD is unknown, genetic, environmental, and immune influences, and changes in microbiota have been implicated (Loddo 2015, Harlan 2016). IBD is believed to result from an inappropriate immune response to symbiotic microorganisms in genetically susceptible individuals. It can be painful and even life-threatening, marked by episodes of relapse and remission, and adversely affects quality of life. Severe forms can result in weight loss, nutritional deficiencies, growth failure (in children), and extra-intestinal manifestations such as arthritis, dermatologic symptoms, kidney stones, osteopenia, osteoporosis, vitamin deficiencies, and certain liver diseases (Harlan 2016). IBD is associated with a high socioeconomic burden and increased risk of colon cancer, and has no cure (CDC 2016).

The two most common subtypes are ulcerative colitis (UC) and Crohn’s disease (CD). Although UC and CD have overlapping characteristics, their clinical presentations, genetic associations, gene expression patterns, and immune responses differ (Loddo 2015). UC is characterized by diffuse mucosal inflammation involving primarily the colon and rectum, bloody diarrhea often with prominent symptoms of rectal urgency, and tenesmus (American College of Gastroenterology [ACG] 2010). CD typically involves the ileum and/or colon but can involve any part of the digestive tract from the mouth to the anus; presenting symptoms vary from abdominal pain and typically non-bloody diarrhea to more severe forms involving penetration through the bowel wall and formation of fistula, strictures, and abscesses (Harlan 2016). The most common complication of CD is intestinal blockage due to swelling and scar tissue (CDC 2016).

In pediatric patients, CD is more commonly associated with growth failure, higher rates of surgery and hospitalizations than UC or other non-IBD disorders (Abraham 2012). Growth improved after surgical resection in patients with CD. However, the risk of cancer and death is low in this population (Abraham 2012).

There is no gold standard for diagnosing IBD (Baumgart 2009). Diagnosis is based on clinical assessment supplemented with radiologic, endoscopic, and histologic criteria to: exclude other etiologies; define the extent and severity of inflammation; and assess the presence of strictures and fistulae. IBD can be confused with irritable bowel syndrome (IBS), which is a chronic non-inflammatory bowel disorder that does not result in changes in bowel tissue or increase risk of colorectal cancer. Further invasive diagnostic procedures may be required to obtain a diagnosis and formulate a treatment plan, as treatment for IBD subtypes and non-IBD conditions differ.

**Biomarkers in IBD:**
New biomarkers have the potential to improve the management of IBD in several ways by: providing object measurement of disease activity and severity; predicting disease course and treatment; monitoring treatment effectiveness; and optimizing drug dosing (Harlan 2016, Bonneau 2015). They may avoid unnecessary invasive procedures such as colonoscopies that often show no abnormality. Current biomarkers under consideration include (Harlan 2016, Bonneau 2015):

- Non-specific inflammatory markers (e.g., C-reactive protein [CRP], albumin, and erythrocyte sedimentation rate [ESR]).
- Fecal markers (e.g., fecal calprotectin [FC] and fecal lactoferrin [FL]).
- Antibodies (e.g., anti-Saccharomyces cerevisiae antibodies [ASCA], perinuclear anti-neutrophil cytoplasmic antibodies [pANCA], anti-outer membrane porin C antibodies [anti-OmpC], anti-chitobioside carbohydrate antibodies [ACCA], anti-laminaribioside carbohydrate antibodies [ALCA], anti-mannobioside carbohydrate antibodies [AMCA], antichitin antibodies [anti-C], and anti-laminarin antibodies [anti-L]).
- Novel genetic determinants.

**Searches**

AmeriHealth Caritas Pennsylvania searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on September 28, 2016. Search terms were: “Inflammatory Bowel Diseases” (Mesh), and free text terms “inflammatory bowel disease,” “Crohn’s disease,” “ulcerative colitis,” “biomarker,” and “diagnosis.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

We found eight systematic reviews and meta-analyses (Hayes 2013a [updated 2016], Holtman 2016, Menees 2015, Murdoch 2015, Wang 2015, Zhou 2014, Kostakis 2013, and Waugh 2013), four guidelines
and one economic analysis for this policy. Three guidelines addressed the management of persons with IBD (Dignass 2012, Lichtenstein 2009, Van Assche 2010). One guideline also included a cost-effectiveness analysis from the United Kingdom (UK) perspective (National Institute for Health and Care Excellence [NICE] 2013).

The purported clinical value of fecal biomarkers is in the primary care setting to differentiate IBD from non-inflammatory causes such as IBS. The results may help guide referral to specialty care for further evaluation, potentially avoiding unnecessary endoscopic procedures and delays in diagnosing IBD. To be clinically useful, fecal markers would need a high negative predictive value to confidently rule out IBD.

FC and FL were the most studied fecal biomarkers. The available evidence is of large quantity but low quality and insufficient to support the use of either FC or FL for routine clinical use.

- Studies of diagnostic performance enrolled a highly select group of patients referred to specialty clinics with suspected or known IBD, resulting in spectrum bias that could inflate estimates of diagnostic accuracy and may not be applicable to the patient mix seen in primary care. High quality studies in the primary care setting are lacking, as is evidence that fecal biomarkers improve patient outcomes in either the primary care or specialty setting.
- The optimal cutoff value used to define inflammatory or non-inflammatory disease or to predict relapse versus continued remission has not been determined. Failure to adopt a uniform cutoff value can alter relative test accuracy, and studies reported a wide range of results. Certain conditions and drugs can interfere with test interpretation. For example, FC levels may be elevated in non-IBD conditions such as infectious enterocolitis, colorectal cancer, or with use of nonsteroidal anti-inflammatory drugs. Additional high-quality studies (e.g., patients stratified by disease type, severity, and distribution) are required to confirm the predictive value of FL.
- There is a lack of consensus among professional guidelines regarding the clinical value of fecal biomarkers in IBD. Only NICE recommends FC testing as an option to assist primary care physicians with the differential diagnosis of IBD or IBS in adults with recent onset lower gastrointestinal symptoms prior to referral to a specialist if cancer is not suspected, or in children with suspected IBD who have been referred for specialist assessment. In both cases appropriate quality assurance processes and locally agreed care pathways must be in place for the testing. Their recommendations were based on a systematic review and economic modeling specific to the UK population (NICE 2013).

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td>Hayes (2013a, last updated 2016)</td>
<td>Key points:</td>
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<tr>
<td>FC assay for CD: disease detection or prediction of</td>
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<td></td>
<td>- Systematic review of nine cross-sectional studies (61 to 183 patients per study) and seven cohort studies (53 to 163 patients per study) with CD or in remission from CD.</td>
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<td></td>
<td>- Overall quality: low to moderate with high risk of bias.</td>
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| relapse. | • Active vs. inactive CD compared with endoscopic findings: Sensitivity (Se) 0.70 to 0.91; specificity (Sp) 0.38 to 0.92; FC cutoffs ranged from 50 to 270 µg/g.  
• Prediction of relapse vs. other inflammatory markers (e.g., FL, serum CRP, and ESR): Se 0.28 to 0.81; Sp 0.48 to 0.93; FC cutoffs ranged from 120 to 340 mg/g.  
• Statistically significant correlations between FC levels and occurrence of relapse.  
• Impact on clinical management unclear.  
• Update: 16 new studies, one new systematic review and economic evaluation, and two new meta-analyses. New applications include: quantitative point-of-care test (FC-QPOCT) to predict endoscopic remission and point of recurrence; combination of FC, serum MMP9, and serum interleukin-22 to detect CD activity; two small studies of pediatric patients. No change in conclusions. |
| Holtman (2016) Noninvasive testing for pediatric IBD | Key points:  
• Systematic review of 19 studies (2,806 referred patients).  
• Overall quality: Not reported. All subjects were symptomatic.  
• Clinical symptoms (abdominal pain, diarrhea, rectal bleeding, and weight loss): Se 0.48 to 0.82, Sp 0.17 to 0.78.  
• Best serologic test performers:  
  • CRP: Se 0.63 (0.51 to 0.73), Sp 0.88 (0.80 to 0.93) (nine studies).  
  • Albumin: Se 0.48 (0.31 to 0.66), Sp 0.94 (0.86 to 0.98) (six studies).  
• FC: Se 0.99 (0.92 to 1.00), Sp 0.65 (0.54 to 0.74) (10 studies). |
| Menees (2015) CRP, ESR, and FL in adults with IBS | Key points:  
• Meta-analysis of prospective cohort studies (four of CRP, four studies of ESR, eight studies of FC, and two studies of FL).  
• Quality assessment: Not reported. All studies were prospective, cohort.  
• No biomarker reliably distinguished between IBS and healthy controls.  
• At a CRP level of ≤0.5 or FC level of ≤40 µg/g, there was a ≤ 1% probability of IBD.  
• Individual analysis of ESR and FL had little clinical utility.  
• Authors’ conclusion: The addition of CRP and FC to symptom-based criteria may improve diagnostic confidence of IBS. |
| Murdoch (2015) for the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) program, sponsored by the International Organization for the Study of Inflammatory Bowel Diseases. Biomarkers as treatment targets in IBD | Key points:  
• Systematic review and consensus expert opinion of 50 studies. Best studied: CRP and FC.  
• In CD and UC, CRP, FC and FL have inadequate diagnostic characteristics to be safe surrogates for endoscopic, radiographic or clinical end points.  
• CRP and FC are adjunctive measures that help alert the clinician to pursue further investigation; evaluations of FL are very limited. |
| Wang (2015) Diagnostic accuracy of FL for IBD | Key points:  
• Meta-analysis of 14 studies (1,816 total patients). |
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<tr>
<th>Citation</th>
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<tr>
<td><strong>Zhou (2014)</strong></td>
<td>IBD versus IBS using FL</td>
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<tr>
<td><strong>Key points:</strong></td>
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<tr>
<td>Meta-analysis of seven studies (1,012 total patients): 609 patients with IBD, 381 with IBS and 22 healthy controls.</td>
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<tr>
<td>Quality assessment: low to moderate. Heterogeneous patient and test characteristics.</td>
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<tr>
<td>IBD versus IBS:</td>
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<td>- Se 0.78 (95% confidence interval [CI] 0.75 to 0.82); Sp 0.94 (95% CI 0.91 to 0.96).</td>
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<td>- Positive likelihood ratio (LR) 12.31 (95% CI 5.93 to 29.15); negative LR 0.23 (95% CI 0.18 to 0.29).</td>
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<td>- Area under the summary receiver-operating characteristic curve 0.94 (95% CI 0.90 to 0.98).</td>
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<td>- Diagnostic odds ratio 52.65 (95% CI 25.69 to 107.91).</td>
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<td>Data reliability depends on methodological quality of studies; optimal cut-off could not be determined.</td>
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<td><strong>Kostakis (2013)</strong></td>
<td>Diagnostic accuracy of FC for identifying and monitoring PIBD</td>
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<td><strong>Key points:</strong></td>
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<tr>
<td>Systematic review of 34 mostly case-control studies of children referred for IBD treatment.</td>
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<tr>
<td>Quality assessment: Not reported but high risk of bias. Reliability of results could not be determined, leading to potential over-estimations of test accuracy.</td>
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<td>Most commonly used cutoffs for FC were 50 and 100μg/g. Where reported, the mean/median FC level ranged from 214 to 32,450μg/g.</td>
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<td>FC levels in PIBD &gt; healthy controls or patients with functional disorders or other gastrointestinal diseases.</td>
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<td>FC with any type of IBD (2,570 children, range 17 to 626):</td>
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<td>- Se 0.125 to 1.00; Sp 0.583 to 1.00.</td>
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<td>- Positive LR 1.1 to 34.9; Negative LR 0 to 1.</td>
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<td>In newly diagnosed and/or active IBD, the results are more homogeneous with high Se and positive LR, low negative LR, but moderate Sp.</td>
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<td>Inconclusive evidence. Negative results cannot exclude disease. Limitations of the review and uncertainties about data reliability may over-estimate test accuracy.</td>
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<tr>
<td><strong>NICE (2013)</strong></td>
<td>Guidance: FC tests for IBD</td>
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<td><strong>Key points:</strong></td>
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<tr>
<td>Systematic review and cost-effectiveness analysis from the UK perspective.</td>
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<td>Recommends FC testing as an option to support clinicians with the differential diagnosis of IBD or IBS in adults with recent onset lower gastrointestinal symptoms for whom specialist assessment is being considered, if:</td>
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<td>- Cancer is not suspected, having considered the risk factors.</td>
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| Waugh (2013) for The National Institute for Health Research Health Technology Assessment Programme | - Appropriate quality assurance processes and locally agreed care pathways are in place for the testing.  
  - recommends FC as an option to support clinicians with the differential diagnosis of IBD or non-IBD (including IBS) in children with suspected IBD who have been referred for specialist assessment, if appropriate quality assurance processes and locally agreed care pathways are in place for the testing. |
| Dignass (2012) for European Crohn’s and Colitis Organisation (ECCO) Guideline: Diagnosis and management of UC | Key points:  
  - Systematic review and economic analysis of 28 studies.  
  - Overall quality: low with high risk of bias.  
  - Most studies used laboratory enzyme-linked immunosorbent assay (ELISA) tests and patients referred to GI specialty centers.  
  - IBD versus IBS in adults (FC cut-off 50 µg/g): Se 0.93 (range 0.83 to 1.00), Sp 0.94 (range 0.60 to 1.00).  
  - IBD versus non-IBD in pediatric populations (FC cut-off 50 µg/g): Se 0.95 to 1.00, Sp 0.44 to 0.93.  
  - Limited data suggest POC testing is comparable to ELISA, perhaps less specific.  
  - FC testing in primary care could reduce the need for referral and colonoscopies.  
  - Likely small gains in quality-adjusted life-years due to low prevalence of IBD and high Se of tests (few false negatives), but potential savings by avoiding endoscopies.  
  - Areas of uncertainty include interpreting borderline results (50-150 µg/g), most of whom do not have IBD. Repeat testing may be appropriate before referral. |
| Van Assche (2010) for ECCO Guideline: CD | Key points:  
  - Routine use of the most widely studied serologic markers, pANCA and ASCA, is not justified.  
  - FC has limited clinical use, but its high negative predictive value may have value in patients with a low likelihood of other pathology.  
  - Endoscopy and radiological procedures are recommended. |
| Lichtenstein (2009) for the ACG Guideline: Management of CD in adults | Key points:  
  - Genetic testing is currently not recommended.  
  - Serologic studies are not sufficiently sensitive or specific to recommend as screening tools.  
  - Presence of fecal leukocytes (i.e., abnormal FC or FL) can confirm intestinal inflammation or inflammation in general. |
Glossary

**Biomarker (biological markers)** — A measurable indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention.

**Crohn’s disease (CD)** — One type of IBD that can manifest anywhere in the gastrointestinal tract. CD most commonly affects the end of the small bowel (the ileum) and the beginning of the colon, involves the entire thickness of the bowel wall, and can “skip” areas of the colon—leaving patches of diseased intestine.

**Irritable bowel syndrome (IBS)** — A chronic non-inflammatory condition of the colon. Unlike IBD, IBS is not associated with changes in bowel tissue or an increased risk of colorectal cancer.

**Inflammatory Bowel Disease (IBD)** — A group of intestinal disorders characterized by chronic relapsing inflammation of the digestive tract resulting in changes in bowel tissue.

**Tenesmus** — A continual or recurrent inclination to evacuate the bowels, caused by disorder of the rectum or other illness.

**Tumor necrosis factor alpha (TNFa)** — A chemical produced by the immune system that causes inflammation in the body. TNFa blockers suppress the immune system by blocking the activity of TNFa.

**Ulcerative colitis (UC)** — One type of IBD that manifests as inflammation limited to the innermost lining of the colon producing tiny ulcers.

References

**Professional society guidelines/other:**


Peer-reviewed references:


Loddo I, Romano C. Inflammatory Bowel Disease: Genetics, epigenetics, and pathogenesis. Front Immunol. 2015; 6: 551.

Menees SB, Powell C, Kurlander J, Goel A, Chey WD. A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. Am J Gastroenterol. 2015; 110(3): 444 – 454.


**CMS National Coverage Determinations (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

No LCDs identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>83630</td>
<td>Lactoferrin, fecal; qualitative</td>
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<tr>
<td>83993</td>
<td>Calprotectin, fecal</td>
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<thead>
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<th>Description</th>
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<tbody>
<tr>
<td>K50.00</td>
<td>Crohn’s disease of small intestine</td>
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<tr>
<td>K50.10</td>
<td>Crohn’s disease of large intestine</td>
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<tr>
<td>K50.80</td>
<td>Crohn’s disease of both small and large intestine</td>
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<tr>
<td>K50.90</td>
<td>Crohn’s disease, unspecified</td>
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<tr>
<td>K51.90</td>
<td>Ulcerative colitis, unspecified</td>
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<tr>
<th>HCPCS Level II Code</th>
<th>Description</th>
<th>Comments</th>
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