Clinical Policy Title: Noninvasive testing for H. pylori

Clinical Policy Number: 08.01.04

Effective Date: January 1, 2016
Initial Review Date: August 19, 2015
Most Recent Review Date: August 17, 2016
Next Review Date: August 2017

Policy contains:
- Helicobacter pylori (H. pylori) infection.
- Urea breath testing (UBT).
- Stool antigen testing (SAT) or fecal antigen testing (FAT).

Related policies:
None.

ABOUT THIS POLICY: Keystone First has developed clinical policies to assist with making coverage determinations. Keystone First’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 Keystone First 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. Keystone First’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. Keystone First’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First will update its clinical policies as necessary. Keystone First’s clinical policies are not guarantees of payment.

Coverage policy

Keystone First considers the use of noninvasive diagnostic testing for H. pylori infection including serology, urea breath testing (UBT) or stool antigen testing (SAT) to be clinically proven and, therefore, medically necessary when any of the following criteria are met:

- Evaluation of new onset dyspepsia in the following groups:
  - Those less than 55 years of age without “alarm features,” including bleeding, anemia, early satiety, unexplained weight loss, progressive dysphagia, odynophagia, persistent vomiting or family history of gastrointestinal cancers.
  - Active peptic ulcer disease (PUD).
  - Past history of peptic ulcers.
  - Gastric mucosa-associate tissue lymphoma (MALT).

- Recurrent dyspeptic symptoms despite two weeks of antibiotic treatment.

- Recurrent dyspeptic symptoms suggestive of reinfection with H. pylori.

- Post-treatment eradication evaluation (no sooner than four weeks after completion of treatment and using either UBT or SAT) is only required in patients with:
  - PUD.
  - Persistent dyspeptic symptoms.
  - H. pylori-associated MALT lymphoma.
  - Previously resected early gastric cancers.
Limitations:

All other uses of non-invasive diagnostic testing for H. pylori are not medically necessary, including any of the following:

- Screening individuals without documented upper gastrointestinal symptoms.
- Screening individuals with non-invasive techniques who have documented “alarm features” or are greater than 55 years of age, with new onset dyspepsia (upper gastrointestinal endoscopy is indicated).
- Screening individuals with non-invasive techniques who have had upper gastrointestinal endoscopy, with testing for H. pylori within preceding six weeks.
- Screening individuals without dyspeptic symptoms post-treatment (other than groups listed above).
- Screening using UBT or SAT for those without a two-week washout period of proton pump inhibitors (PPIs).
- Using UBT with carbon-14 in pregnant women or children.
- Using serologic testing as an eradication evaluation measure post-antibiotic treatment.
- Simultaneous testing using UBT and SAT concurrently.

Note: The following CPT/HCPCS codes are not listed in the Pennsylvania Medicaid fee schedule:

83013 - Helicobacter pylori; breath test analysis for urease activity, non-radioactive isotope

87338 - Helicobacter pylori, stool

Alternative covered services:

Clinical evaluation by physicians and appropriate standard diagnostic procedures.

Background

H. pylori is a gram-negative bacterium found in the luminal surface of the gastric epithelium and responsible for the inflammation of the underlying mucosa of the gastric epithelium. This bacterium is unique in its ability to survive in the acidic environment of the stomach because of its high urease enzyme that converts the urea of gastric juice to basic ammonia and carbon dioxide activity. H. pylori infection can be a cause of chronic gastritis, peptic ulcer disease and gastric malignancy.

Estimates of the prevalence of H. pylori infection indicate that at least 50 percent of the world’s population is affected (Tonkic 2012). Within the United States, prevalence estimates range from 30 percent to 40 percent of the general public. The likelihood of infection increases with age, lower socioeconomic status and male gender (Tonkic 2012).

Acquisition of the infection occurs mostly during childhood, due to poor living conditions. In the U.S., falling prevalence rates among children correlate with improved living conditions. The majority of individuals infected with H. pylori does not display clinically significant complications and will not require treatment (Tonkic 2012).
Signs, symptoms, and conditions associated with H. pylori:

Recognition, testing, and treatment for H. pylori can be difficult because of the variety of non-specific gastrointestinal signs and symptoms at presentation. H. pylori causes many symptoms of indigestion or dyspepsia defined as “long-term pain in the upper abdomen,” which can also be linked to non-ulcer dyspepsia or gastroesophageal reflux disease (GERD). The most frequent features reported in patients with H. pylori are heartburn or epigastric pain, burping, bloating or post-prandial fullness, nausea, vomiting, slow digestion or delayed gastric emptying and acid hyper secretion.

H. pylori bacteria inflame the mucosa lining triggering an increase in gastrin, a hormone that stimulates stomach acid release. Elevated levels of gastrin cause excess acid secretion from all areas of the stomach (even those areas not infected). In turn, the high acidity, which further damages the mucosa lining of the stomach, causes ulceration and metaplasia and increases the risk for additional infection by the H. pylori bacteria. There is a strong association between the H. pylori infection, gastric cancer and gastric MALT lymphomas. Eradication of the infection provides a cure to 80 percent of duodenal ulcers unrelated to non-steroidal anti-inflammatory drugs (NSAIDs) and reduces progression of atrophic gastritis and localized gastric MALT lymphoma.

Diagnosis of H. pylori:

Proper eradication treatment can resolve symptoms of dyspepsia, if it is related to an underlying ulcer disease caused by H. pylori. However, screening is not recommended in all patients with symptoms of dyspepsia, as empiric treatment with acid suppression is effective among some populations. Further, many conditions, including GERD and non-ulcer dyspepsia, are not associated with H. pylori.

There are numerous different diagnosis tests for H. pylori including endoscopy, serology, UBT and SAT. These tests are used for diagnosis and evaluation of eradication after treatment. The most invasive diagnostic tool is endoscopy, which entails a biopsy of cells from the pre-pyloric region or fundic region. Endoscopy is not required for diagnosis and is not often the test of choice to confirm diagnosis.

Serologic tests identify the immunoglobulin G (IgG) antibodies response to H. pylori bacteria within an individual’s blood. This type of testing has lower sensitivity at 85 percent and specificity at 79 percent. The results can be reported as equivocal. It is not useful in testing for eradication of the bacteria, as antibodies may persist for months beyond treatment despite eradication of the bacteria.

A common noninvasive test is UBT; this test relies on the bacteria’s ability to convert carbon dioxide to urea. UBT centers on labeling isotopes of carbon dioxide urea ingested by the patient. The test compares a baseline sample with the post administration level of carbon dioxide using a mass spectrometer or infrared spectrophotometer. This test is commonly used to measure the success of treatment and is widely used, as the samples are easy to collect and can be sent to central laboratories. This reduces the need for expensive equipment at individual providers.

Confirmation of diagnosis and eradication is also possible with SAT (or FAT). Identifying H. pylori-specific antigens using either monoclonal or polyclonal antibodies detects the presence of H. pylori. Compared to UBT, monoclonal testing is more sensitive and specific, less expensive, less affected by PPI use, and requires less equipment.
Keystone First 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 July 11, 2016. Search terms were: “Helicobacter Infections/diagnosis” (Mesh), “diagnostic test,” “stool antigen” and “urea breath test.”

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**

Table 1 summarizes the findings from four systematic reviews of the clinical validity of multiple types of non-invasive H. pylori diagnostic tests. The second table summarizes the results of four systematic reviews of non-invasive testing, one randomized control trial (RCT) comparing diagnostic tests and four professional guidelines related to diagnosis and treatment of H. pylori.

**Serologic testing for H. pylori:**

The results from available systematic reviews listed in the two tables indicate that serologic testing for antibodies linked to H. pylori infections demonstrate high sensitivity and specificity for initial diagnosis. These tests are especially useful in areas with high prevalence of the infection, but antibodies specifying this infection can differ locally, and the accuracy of this test can range (Childs 2000). Because of the cost effectiveness and ease of blood tests, this is a first line diagnostic measure in some places, but confirmation requires additional testing if the area has a low prevalence (Ling 2013, Chey 2007). Further serologic testing is unreliable for post-treatment eradication verification, as antibodies for H. pylori may remain in the blood for six to 12 months after eradication (Childs 2000).

**UBT testing:**

The evidence for UBT testing for screening for H. pylori in a test-and-treat strategy is based on three systematic reviews (Ling 2013, Ferwana 2015, Childs 2006) and professional guidelines. As shown in Table 1, UBT has high sensitivity and specificity, both > 90 percent and can also be used to evaluate if eradication treatments were successful. UBT is considered the gold standard for post-treatment testing (Childs 2000). This test can be prohibitively expensive and some facilities may not have the materials on-site to perform. UBT testing in women and children should only use carbon-13 isotopes, as they provide lower doses of radiation.
Table 1. Pooled estimates of sensitivity and specificity of non-invasive tests for H. pylori diagnosis.

<table>
<thead>
<tr>
<th>Type of Test</th>
<th>Source</th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serological</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Childs 2000</td>
<td>90 – 95</td>
<td>85 – 95</td>
</tr>
<tr>
<td></td>
<td>Ling 2013</td>
<td>92.2 (82.6 – 97.3)</td>
<td>71.7 (63.8 – 77.5)</td>
</tr>
<tr>
<td></td>
<td>ICSI 2004</td>
<td>88 – 94</td>
<td>74 – 88</td>
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<tr>
<td><strong>UBT</strong></td>
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<td></td>
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<tr>
<td></td>
<td>Childs 2000</td>
<td>90 – 98</td>
<td>90 – 98</td>
</tr>
<tr>
<td></td>
<td>Calvet 2009</td>
<td>90.3 (83 – 95)</td>
<td>89.5 (81 – 95)</td>
</tr>
<tr>
<td></td>
<td>Ling 2013</td>
<td>95 (90.1 – 97.5)</td>
<td>91.6 (81.3 – 96.4)</td>
</tr>
<tr>
<td></td>
<td>Ferwana 2015</td>
<td>96 (95 – 97)</td>
<td>93 (91 – 94)</td>
</tr>
<tr>
<td></td>
<td>ICSI 2004</td>
<td>90 – 96</td>
<td>88 – 98</td>
</tr>
<tr>
<td><strong>Monoclonal Stool</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>NICE 2009</td>
<td>68 – 100</td>
<td>89 – 100</td>
</tr>
<tr>
<td></td>
<td>Chey 2007</td>
<td>96</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>Gisbert 2006</td>
<td>95 (93 – 96)</td>
<td>97 (94 – 98)</td>
</tr>
<tr>
<td></td>
<td>MAS 2010</td>
<td>85.1 (79.5 – 94.4)</td>
<td>90.1 – 98.7 depending on test</td>
</tr>
<tr>
<td><strong>Polyclonal stool</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Calvet 2009</td>
<td>90.3 (83 – 95)</td>
<td>93 (84 – 97)</td>
</tr>
<tr>
<td></td>
<td>Chey 2007</td>
<td>91</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>Gisbert 2006</td>
<td>83 (80 – 85)</td>
<td>96 (94 – 97)</td>
</tr>
<tr>
<td><strong>Stool testing (with no differentiation to type)</strong></td>
<td>ICSI 2004</td>
<td>86 – 94</td>
<td>86 – 95</td>
</tr>
</tbody>
</table>

95% CI, 95% confidence interval

**Policy updates:**

We identified two new professional guidelines from the American Gastroenterological Association (Yang 2015) and the American Society for Gastrointestinal Endoscopy (Shaukat 2015). Both addressed the role of endoscopy in managing dyspepsia. Their recommendations are consistent with the original policy. Therefore, no changes to the policy are warranted.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, methods, recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferwana (2015)</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td><strong>UBT</strong></td>
<td>• Systematic review of 3,999 patients for the accuracy of UBT (Level B).</td>
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<tr>
<td></td>
<td>• Twenty-three studies pooled found UBT testing of Se = 96% and Sp = 93%.</td>
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<td></td>
<td>• UBT showed “significant discrimination” ability between infected and non-infected states.</td>
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<td>• May provide better comprehensive results than endoscopy because eliminate error with endoscopic biopsy when H. pylori has inconsistent distribution and does not rely on pathologist.</td>
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<td>• Oral flora’s urease activity may impact accuracy of results.</td>
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<tr>
<td>Shaukat (2015)</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td>Citation</td>
<td>Content, methods, recommendations</td>
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</tbody>
</table>
| ASGE The role of endoscopy in dyspepsia | • Recommend initial endoscopy for new-onset dyspepsia in patients age ≥ 50 or those with alarm features (moderate quality evidence).  
• Recommend dyspeptic patients age < 50 and without alarm features undergo either initial “test and treat” approach for H pylori or empiric therapy with a PPI, depending on the prevalence of H pylori infection in their population (moderate quality evidence).  
• Recommend “test and treat” for H pylori prevalence > 20%.  
• Recommend offering a trial of PPI acid suppression to dyspeptics age < 50, lack alarm features and H pylori negative (low quality evidence).  
• Recommend performing endoscopy if H pylori negative and nonresponsive to empiric PPI (low quality evidence). |
| Yang (2015) for the AGA Guidelines for Upper Gastrointestinal Biopsy to Evaluate Dyspepsia in the Absence of Mucosal Lesions | Key points:  
• Guidelines generally support test-and-treat approach to managing dyspepsia.  
• Alternative non-endoscopic tests are available for the diagnosis of H. pylori, but a patient who is already undergoing an esophagogastroduodenoscopy would likely prefer not having to take additional time to undergo one of the alternative H. pylori tests. Cost of these alternative tests would offset the cost of diagnosing H. pylori infection endoscopically. |
| National Institute for Health and Care Excellence (2014) Dyspepsia and GERD | Key points:  
• Recommendations (Level C).  
• Serological testing is not a viable option for post-treatment/eradication evaluation.  
• Dyspepsia and acute gastrointestinal bleeding require same day referral to endoscopic procedure.  
• Prior to UBT or SAT testing, patient must undergo two week washout out of PPIs, as they can affect results. |
| Ling (2013) Carbon-13 UBT in uninvestigated dyspepsia | Key points:  
• Systematic review of 21 studies with 4,536 patients (Level A).  
• Serology and UBT are comparable sensitive, but UBT is more sensitive.  
• Clinically, serological is a first-line diagnostic test in the United States; UBT or SAT is also considered first-line diagnostic methods.  
• Lack of standards in processing of UBT creates variability in results. |
| Calvet (2009) SAT | Key points:  
• SAT is most accurate non-invasive test (Level B).  
• One RCT (n = 199) found among patients with dyspepsia, SAT demonstrated the most accurate alternative to endoscopy compared to UBT. |
| Chey (2007) for the American College of Gastroenterology (ACG) Guidelines for management of helicobacter infection | Key points:  
• Level C evidence.  
• Testing for proof of eradication post-treatment is required for those with PUD with persistent dyspeptic symptoms, H. pylori MALT lymphoma, and resected early gastric cancers.  
• Test and treat in those with active PUD, past history of peptic ulcers, and gastric MALT, or those greater than 55 years of age without alarm symptoms.  
• UBT is the most reliable method to test for post-treatment eradication.  
• Post-treatment eradication testing should be at least four weeks after antibiotic regimen completion.  
• Carbon-13 is preferred method of UBT in children and pregnant women, as lower doses of radiation. |
<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, methods, recommendations</th>
</tr>
</thead>
</table>
|          | • Cost of UBT testing is driven by expensive and rare equipment and costly labeled isotopes.  
|          | • SAT and UBT are interchangeable diagnostic methods.  
|          | • Use of serological testing for specific antibodies is acceptable in areas of high prevalence (including urban or immigrant areas) as the positive predictive value is good. In low prevalence areas (~20%), avoid relying on antibody or confirm with SAT or UBT before treatment. |
| Gisbert (2006) | **Key points:**  
| FAT | • Systematic review of 2,499 patients (Level A).  
| | • Pre-treatment pooled Se = 94%, Sp = 97%, monoclonal FAT had higher sensitivity (Se = 95%, Sp = 96%) versus polyclonal test (Se = 83%, Sp = 96%).  
| | • Post-treatment evaluation shows distinct difference between monoclonal (Se=91%, Sp=95%) and polyclonal (Se = 76%, SP = 95%), as monoclonal is more sensitive.  
| | • Monoclonal testing shows better distinction between infection and non-infection, with no equivocal response. |
| Talley (2005) for the ACG Guidelines on management of dyspepsia | **Key points:**  
| | • Level C evidence.  
| | • Those greater than 55 years of age, with alarm signs (bleeding, anemia, early satiety, unexplained weight loss, progressive dysphagia, odynophagia, persistent vomiting, and family history of gastrointestinal cancers) should be examined with endoscopy.  
| | • When prevalence is greater than 10%, use test and treat strategy using non-invasive diagnostic methods; when prevalence is less than 10%, initiate empiric PPI treatment and revert to test and treat for H. pylori, if PPI therapy is unsuccessful.  
| | • Serological tests require local validation; sensitivity and specificity can range depending on geography. |
| Institute for Clinical Systems Improvement (ICSI, 2004) Algorithm annotations for dyspepsia and GERD | **Key points:**  
| | • Level C evidence.  
| | • Symptoms persisting after four weeks of treatment require additional screening with endoscopy.  
| | • Prior PUD is a predictor of recurrent ulcers; 30-95% of PUD are due to H. pylori, so testing is required for those with past medical history.  
| | • Most cost effective first line test is serological. |
| Childs (2000) Noninvasive and post treatment testing | **Key points:**  
| | • Systematic review.  
| | • Serology is not accurate for all patient populations and requires local validation; can have six to 12-month lag time in detecting changes in infection status, although may be the cheapest option.  
| | • UBT is non-invasive test of choice.  
| | • Post-treatment testing is required in those with severe or complicated DU or GU, MALT lymphoma, and early gastric cancer.  
| | • H. pylori treatment guided by testing is preferred choice, although cost savings are slow to see. Can lower cost of treatment further by using empiric treatment where there is high prevalence of infection and DU. |

**Glossary**

**Dyspepsia** — General discomfort of the upper gastrointestinal tract, including upper abdominal pain, heartburn, acid reflux, nausea or vomiting.
**Endoscopy** — A non-surgical procedure to enable providers to examine interior structures, such as organs or joints using an endoscope, a flexible tube with a light and camera. Samples can be taken during this procedure.

**Gastric MALT lymphoma** — A cancer involving the mucosa-associated lymphoid tissue of the stomach that originates in B cells and is related to inflammation.

**Gastritis** — Inflammation of the lining of the stomach. May cause symptoms including upper abdominal pain, vomiting, nausea, bloating, loss of appetite or heart burn.

**Gastroesophageal reflux disease (GERD)** — A disease caused by chronic back-flow of acid from the stomach into the esophagus, causing heartburn and leading to irritation and possible damage to the lining of the esophagus.

**Histology** — The study of the anatomy of cells and tissues. In medicine, this microscopic study is performed by pathologists to correctly diagnose certain cancers and other diseases.

**Non-steroidal anti-inflammatory drugs (NSAIDs)** — A class of drugs with both analgesic and anti-inflammatory effects.

**Serology** — Testing of blood serum for the presence of specific products that can serve as indicators of disease.

**References**

**Professional society guidelines/other:**


**Peer-reviewed references:**


**Clinical trials:**

Searched clinicaltrials.gov on July 11, 2016 using terms: helicobacter pylori diagnosis | Open Studies. 31 studies found, one relevant.


**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.

<table>
<thead>
<tr>
<th>CPT codes</th>
<th>Description</th>
<th>Comment</th>
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<tr>
<td>83013</td>
<td>Helicobacter pylori; breath test analysis for urease activity, non-radioactive isotope</td>
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<tr>
<td>87338</td>
<td>Helicobacter pylori, stool</td>
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<tr>
<th>ICD-10 Code</th>
<th>Description</th>
<th>Comment</th>
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<tbody>
<tr>
<td>A04.8</td>
<td>Helicobacter pylori (H. pylori)</td>
<td></td>
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<tr>
<td>B96.81</td>
<td>H. pylori as the cause of diseases classified elsewhere</td>
<td></td>
</tr>
<tr>
<td>C88.4</td>
<td>MALT lymphoma</td>
<td></td>
</tr>
<tr>
<td>K27.9</td>
<td>Peptic ulcer, site unspecified</td>
<td></td>
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<tr>
<td>R10.13</td>
<td>Dyspepsia</td>
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<th>HCPCS Level II</th>
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