Helicobacter pylori Testing

Policy Number: AHS – G2044 – *Helicobacter pylori* Testing	Prior Policy Name and Number, as applicable:
Effective Date: 09/01/2022	

I. Policy Description

Helicobacter pylori (*H. pylori*) is a spiral-shaped, gram negative bacteria that has thrived to live in acidic environments and grows in close association with the stomach lining; therefore, H. *pylori* infection causes chronic inflammation (infection) in the stomach and is associated with conditions such as peptic ulcer disease, chronic gastritis, gastric adenocarcinoma, and gastric mucosa associated lymphoid tissue (MALT) lymphoma (Lamont, 2020).

II. Related Policies

Policy Number	Policy Title
	Not applicable

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Medical Policy Statements do not ensure an authorization or payment of services. Please refer to the plan contract (often referred to as the Evidence of Coverage) for the service(s) referenced in the Medical Policy Statement. If there is a conflict between the Medical Policy Statement and the plan contract (i.e., Evidence of Coverage), then the plan contract (i.e., Evidence of Coverage) will be the controlling document used to make the determination.

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. If there is a conflict between this Policy and any relevant, applicable government policy [e.g. National Coverage Determinations (NCDs) for Medicare] for a particular member, then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coveragedatabase/overview-and-quick-search.aspx?from2=search1.asp& or the manual website.

Specifications pertaining to Medicare and Medicaid can be found in Section VII of this policy document.

1) Urea Breath testing OR stool antigen testing for *H. pylori* infection **MEETS COVERAGE CRITERIA** for adult patients (>18y) in the following situations:

   a) In the evaluation of a patient with suspected *H. pylori* infection and the following situations:

      i) dyspeptic symptoms, or

      ii) active peptic ulcer disease (PUD), or

      iii) past PUD without *H. pylori* history, or

      iv) low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma, or

      v) a history of endoscopic resection of early gastric cancer (EGC), or

      vi) in patients with gastric intestinal metaplasia (GIM), or

      vii) patients with uninvestigated dyspepsia who are under the age of 60 years and without alarm features, or

      viii) Patients initiating chronic treatment with a non-steroidal anti-inflammatory drug (NSAID), or

      ix) Patients with unexplained iron deficiency anemia, or

      x) In the evaluation of a patient with chronic immune thrombocytopenic purpura (ITP) and suspected *H. pylori* infection, or

      xi) In patients with family history of gastric cancer, or

      xii) In patients who are first-generation immigrants from high prevalence areas.

   b) Re-evaluation to measure success of eradication of *H. pylori* infection, at least 4 weeks post-treatment.

      i) Any patient with an *H. pylori*-associated ulcer, or

      ii) As part of the follow-up of patients with persistent symptoms of dyspepsia following appropriate antibiotic treatment for *H. pylori*, or

      iii) In patients with Gastric MALT Lymphoma, or

      iv) In individuals who have undergone resection of early gastric cancer.

2) Urea Breath testing OR stool antigen testing for *H. pylori* infection **MEETS COVERAGE CRITERIA** for pediatric patients (<18y) in the following situations:

   a) In the evaluation of a patient with chronic immune thrombocytopenic purpura (ITP) and suspected *H. pylori* infection.

   b) Re-evaluation to measure success of eradication of *H. pylori* infection, at least 4 weeks post-treatment.

3) Biopsy-based endoscopic histology test and either Rapid Urease Test or culture with susceptibility testing **MEETS COVERAGE CRITERIA** in pediatric patients (<18y) for the diagnosis of *H. pylori* infection in following situations:

   a) Children with gastric or duodenal ulcers, or

   b) Children with refractory iron deficiency anemia (IDA) in which other causes have been ruled out.

4) Biopsy-based endoscopic histology test and Rapid Urease Test or culture with susceptibility testing **MEETS COVERAGE CRITERIA** in adult patients (>18 y) undergoing endoscopic examination or in those with alarm symptoms for the diagnosis of *H. pylori* infection.

5) Urea Breath testing OR stool antigen testing for *H. pylori* infection **DOES NOT MEET COVERAGE CRITERIA** for asymptomatic pediatric (<18y) and asymptomatic adult (>18y) patients in all other situations and adult patients with typical symptoms of gastroesophageal reflux disease (GERD) who do not have a history of peptic ulcer disease (PUD).

6) Serologic testing for *H. pylori* infection **DOES NOT MEET COVERAGE CRITERIA** in adult and pediatric patients as it does not distinguish between currently active infection with past exposure and an infection that has been cured.

7) Biopsy-based endoscopic histology test and Rapid Urease Test or culture with susceptibility testing **DOES NOT MEET COVERAGE CRITERIA** in pediatric patients (<18y) for the diagnosis of *H. pylori* infection in following situations:

   a) Children with functional abdominal pain, or

   b) As part of initial investigation in children with iron deficiency anemia, or

   c) When investigating causes of short stature.

8) Testing with the Urea Breath test and/or stool antigen and/or biopsy-based testing **DOES NOT MEET COVERAGE CRITERIA** in patients with recent use of antibiotics, proton pump inhibitors (PPIs) or bismuth.

9) Concurrent testing with the Urea Breath test and/or stool antigen testing and/or biopsy-based testing **DOES NOT MEET COVERAGE CRITERIA** as simultaneous use of both methods does not improve clinical understanding.

10) The use of nucleic acid testing for *H. pylori*, including polymerase chain reaction (PCR), 16S rRNA, 23S rRNA, and next-generation sequencing (NGS) of *H. pylori*, **DOES NOT MEET COVERAGE CRITERIA** as it is not practical for routine diagnosis.

IV. Table of Terminology

Term	Definition
ACG	American College of Gastroenterology
AGA	American Gastroenterological Association
ASCP	American Society for Clinical Pathology
ASH	American Society of Hematology
CAG	Canadian Association of Gastroenterology
CLIA ’88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid
DNA	Deoxyribonucleic acid
EAGEN	European Association for Gastroenterology, Endoscopy and Nutrition
EGC	Early gastric cancer

EIA	Enzyme immunoassay
ELISA	Enzyme-linked immunosorbent assay
ESNM	European Society of Neurogastroenterology and Motility
ESPGHAN	European Society for Pediatric Gastroenterology Hepatology and Nutrition
FDA	Food and Drug Administration
FIA	Fluorescence immunoassay
GERD	Gastroesophageal reflux disease
GIM	Gastric intestinal metaplasia
gyrA	Deoxyribonucleic acid gyrase subunit A
HpSA-LFIA	*H. pylori* stool antigen lateral flow immunochromatography assay
H. pylori	*Helicobacter pylori*
HP	*Helicobacter pylori*
ID	Iron deficiency
IDA	Iron deficiency anemia
IgG	Immunoglobulin G
ITP	Immune thrombocytopenic purpura
LDTs	Laboratory-developed tests
MALT	Mucosa associated lymphoid tissue
NAFLD	Non-alcoholic fatty liver disease
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology and Nutrition
NGS	Next-generation sequencing
NICE	National Institute for Health and Care Excellence
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
PCR	Polymerase chain reaction
Pg	Pepsinogen
PLA	Proprietary laboratory analyses
PPI	Proton pump inhibitor
PUD	Peptic ulcer disease
qPCR	Quantitative polymerase chain reaction
RNA	Ribonucleic acid
rRNA	Ribosomal ribonucleic acid
RUT	Rapid urease test
SA	Stool antigen
SAT	Stool antigen test
UBT	Urea breath test
USS	Updated Sydney system

V. Scientific Background

Infection with *H. pylori* is common, with conservative estimates at 50% of the world's population affected. Prevalence in the United States is significant, estimated to be 30 – 40% in the general

population (Siao & Somsouk, 2014). *H. pylori* is associated with many conditions, such as peptic ulcer disease, chronic gastritis, and gastric mucosa associated lymphoid tissue (MALT) lymphoma. Other conditions such as dyspepsia have been attributed to *H. pylori* as well (Lamont, 2020). Common symptoms of these conditions include gastritis, dyspepsia, heartburn, and stomach pain (Jensen, 2019; Longstreth, 2017).

Identification of *H. pylori* infection is accomplished with one or more of the several tests available. The choice of test is guided by the reason for the test, cost and availability of the test, the patient's age and clinical presentation, prevalence in a population, and the patient's use of certain medications. Testing for *H. pylori* infection is done for two main reasons; to detect an active infection that will be treated and to confirm eradication of the infection post-treatment. Invasive and non-invasive approaches have been used. Endoscopy and collection of biopsy specimens for evaluation of *H. pylori* infection and early gastric cancer detection typically is done in older individuals and those with "alarm" symptoms, including bleeding, unexplained anemia, unexplained weight loss, progressing dysphagia, recurrent vomiting, a family history of gastrointestinal cancer, or a personal history of esophagogastric malignancy. Tissue samples can be tested for *H. pylori* via methods such as a rapid urease test, culture, or staining. Molecular methods include PCR and next-generation sequencing, and serological methods include ELISA, immunoassays, and dried blood spots. Other non-invasive methods include urea breath test and stool antigen test. Testing for eradication of infection may be performed with the same tests used for diagnosis (Lamont, 2020).

Analytical Validity

Non-invasive options for detection of active *H. pylori* infection include urea breath tests and stool antigen testing. The stool antigen test is an immunoassay that detects the presence of *H. pylori* in a stool sample. The test is reported to have greater than 90% sensitivity and specificity for detection of active *H. pylori* infection, and its use has been FDA cleared for all ages. This test may be used for initial diagnostic purposes and for post-treatment testing. Urea breath tests, which take advantage of the bacteria's urease activity, may also be used to detect active *H. pylori* infection. The patient ingests a solution containing either ^{13}C or ^{14}C labeled urea, after a set amount of time, the patient's breath is collected and analyzed for the presence of ^{13}C or ^{14}C labeled CO_2. If *H. pylori* is present, it will have metabolized the labeled urea and labeled CO_2 will be detected, thus indicating infection with *H. pylori*. This test takes approximately 15-20 minutes (Lamont, 2020).

ELISA-based serological tests are also available for detection of *H. pylori*. However, serological tests often need validation at the local level, which may not be practical in routine practice. Furthermore, serological tests do not distinguish between past and present infections. Serological tests also have a very low positive predictive value in populations with low or average prevalence, as the antibodies will be detected even after an infection has been treated or naturally resolved. In these low-prevalence areas, a positive serological test is more likely to be a false positive (Lamont, 2020).

Other tests such as PCR-based tests are infrequently used. The PCR test, despite its high accuracy, is often too expensive for routine use. In fact, nested PCR tests have approached 100% sensitivity and 100% specificity for detection of *H. pylori* (Singh et al., 2008), but the test may not be widely available and may be of limited use due to high cost (Lamont, 2020; Patel et al., 2014). PCR tests have been used for diagnostic purposes as well as identifying genetic variants of the bacteria and pathogenic genes present in a patient. A variety of body fluids, such as stool and saliva, have been used in PCR tests for this bacterial species (Patel et al., 2014).

Some medications are known to inhibit the growth or urease activity of *H. pylori* and can cause a false negative *H. pylori* test result. Proton pump inhibitors, antibiotics, and bismuth-containing medications may decrease sensitivity of tests, thereby increasing rates of a false negative. Eradication testing is often done weeks after treatment is completed (Lamont, 2020).

Dechant et al. (2020) evaluated the accuracy of various rapid urease tests (RUTs) and compared it with histopathology results. No differences were detected in the sensitivity or specificity of the various RUTs and RUTs had comparable results to histology; however, in patients treated with proton pump inhibitors and antibiotics. RUTs seemed to be more sensitive compared to histology. Pohl et al. (2019) discuss the drawbacks of RUTs, including false negative test results if the bacterial load is less than 10^4 in the gastric biopsy and false positive test results with some urease positive bacteria, affecting the sensitivity and specificity of RUTs. Commercially available RUTs, such as HpFast, CLOTest, and HpOne, have reported specificities ranging from 95% to 100%, but their sensitivity is moderate (85% to 95%) (Pohl et al., 2019).

Hussein et al. (2021) compared the sensitivity, specificity, positive, and negative predictive values of invasive tests (RUT and gastric tissue culture) and noninvasive tests (^{14}C-Urea breath test (^{14}C-UBT), stool antigen test, and CagA-IgG serology) to the gold standard quantitative PCR (qPCR) tests for *H. pylori* in Iraq. 115 participants strongly suspected of *H. pylori* infection were tested. Overall, the prevalence rates ranged from 47.8% to 70.4% depending on the test method. "The ^{14}C-UBT showed the highest overall performance with 97.5% sensitivity, 97% specificity, and total accuracy of 97.3% followed by SAT, RUT, Cag-IgG, and culture method." SAT had a sensitivity of 95.0% and a specificity of 91.2%. RUT had a sensitivity of 93.8% and a specificity of 94.1%. CagA-IgG had a sensitivity of 75.3% and a specificity of 85.3%. Gastric tissue culture had a sensitivity of 67.9% and a specificity of 79.4%. The authors conclude that ^{14}C-UBT "may be recommended as first choice due to its higher performance compared to other methods" (Hussein et al., 2021). Hassan et al. (2021) compared the accuracy, specificity, and sensitivity of the stool antigen test and the urea breath test in 45 children who underwent osophagogastroduodenoscopy between 2013 and 2019 in Sulaymaniyah City, Iraq. Histopathological findings from biopsies were used as a confirmatory diagnosis tool. The authors found that "UBT has a statistical significant correlation with result of biopsy, also it is more accurate and more sensitive than SAT, but they share same positive predictive value and same specificity." The authors conclude that UBT is preferred over SAT in children above 6 years (Hassan et al., 2021).

Abdelmalek et al. (2021) evaluated the accuracy and utility assurance of *H. pylori* stool antigen lateral flow immunochromatography assay (HpSA-LFIA) in Egypt. The study used stool samples from 200 gastric patients and compared HpSA-LFIA results to the monoclonal antibody-based ELISA kit. The authors report that HpSA-LFIA achieved sensitivity of 93.75%, specificity of 59.76%, a negative predictive value of 98.00%, positive predictive value of 31.25%, and accuracy of 65.31%. The authors conclude that "HpSA-LFIA was not accurate enough to be the sole test for diagnosis and needs other confirmatory tests in case of positive conditions" (Abdelmalek et al., 2021).

Clinical Utility and Validity

The stool antigen test has been shown to have strong accuracy. A meta-analysis by Gisbert et al. (2006) focusing on 2499 patients of 22 studies found the diagnostic test to have a sensitivity of 0.94 and a specificity of 0.97. The monoclonal version of the test was shown to be more sensitive than the polyclonal one (0.95 vs 0.83). The authors also evaluated the diagnostic test after eradication of the bacteria in 957 patients of 12 studies. The authors evaluated the antigen test at 0.93 sensitivity and 0.96 specificity post-eradication (Gisbert et al., 2006).

A new automated LIAISON® Meridian *H. pylori* SA assay, a chemiluminescent immunoassay that uses novel monoclonal antibodies for capture and detection of the *H. pylori* stool antigen, was evaluated for its clinical performance. Opekun et al. (2020) studied the utility of this assay on 277 patients who tested positive for H. pylori infection from an endoscopy. Comparing histology, culture, and rapid urease test results, the assay delivered a sensitivity of 95.5% and specificity of 97.6%. The authors conclude that LIAISON® "brings reliable noninvasive testing for *H. pylori* to the laboratory that is in very good agreement with the current, more invasive biopsy-based methods such as histology, culture, or rapid urease test" (Opekun et al., 2020).

The rapid in-office, monoclonal test is widely used and provides significant benefit in terms of availability and speed. However, a study using the test as a reference to compare against a new test found the in-office test to only have a 0.50 sensitivity and 0.96 specificity out of 162 patients (Korkmaz et al., 2015).

The UBT has also been well-validated. A meta-analysis by Ferwana et al. (2015) including 3999 patients of 23 studies found the diagnostic test to have a pooled sensitivity of 0.96 and a pooled specificity of 0.93. The authors noted that their populations had significant heterogeneity but concluded that the UBT had high diagnostic accuracy for detecting an *H. pylori* infection (Ferwana et al., 2015). This test is often considered the gold standard for diagnosing an *H. pylori* infection (Patel et al., 2014).

Serological tests to assess infection have also been used. A meta-analysis by Loy et al. focused on commercial serological kits assessing *H. pylori*. Loy et al. found these kits to have a pooled sensitivity of 0.85 and specificity of 0.79. The authors concluded that there was no major difference in accuracy between any of the kits tested (Loy et al., 1996).

As costs of sequencing decreases, use of Next Generation Sequencing (NGS) to detect *H. pylori* infection and its antibiotic resistance has increased. In a study by Nezami et al. (2019), 133 H. *pylori* positive specimens from histological evaluation were analyzed by NGS to detect mutations in gyrA, 23S rRNA, and 16s rRNA genes. NGS detected H. *pylori* in 126/133 cases (95% sensitivity). NGS also detected multiple mutations associated with resistance in 92 cases (73%), one mutation in 63 cases (50%), and mutations in several genes in 29 cases (23%). In the 58 cases where treatment history was available, therapy failure was observed in cases where the number of mutated genes was high. Therapy failed in 11/16 cases with multiple gene mutations and 5/27 cases with one gene mutation (Nezami et al., 2019).

Yang et al. (2019) performed a meta-analysis investigating the association between *H. pylori* and colorectal cancer. 27 studies encompassing 14357 cases were included. The authors found an increased rate of colorectal cancer with *H. pylori* infection (odds ratio [OR] = 1.27). The authors also identified odds ratios for certain subgroups, such as Western countries (OR = 1.34), serological testing (OR = 1.20), multiple methods of testing (OR = 2.63), and cross-sectional studies (OR = 1.92) (Yang et al., 2019).

Wang et al. (2019) performed a meta-analysis assessing the association between *H. pylori* and osteoporosis. 21 studies totaling 9655 patients were analyzed. The authors found that *H. pylori* infection was associated with an increased risk of osteoporosis with an odds ratio of 1.39. However, the decrease of bone mineral density in *H. pylori* positive patients was not found to be significant compared to *H. pylori* negative patients (Wang et al., 2019).

Zhou et al. (2019) investigated the association between *H. pylori* infection and non-alcoholic fatty liver disease (NAFLD). 15 studies including 97228 patients were evaluated. The authors identified an increased risk of NAFLD in *H. pylori* positive patients compared to *H. pylori* negative patients by an odds ratio of 1.19. Similar results were found despite differing subgroups, such as geographical locations.

Testing method did not significantly change the results, and there was no significant difference when using multiple detection methods (Zhou et al., 2019).

Halland et al. (2021) assessed two novel enzyme assays (EIA), H. PYLORI QUIK CHEK™ and H. PYLORI CHEK™, for the detection of *H. pylori* antigen in stool from 271 patients in America, Germany, and Bangladesh. The EIA results were compared to clinical diagnosis, which included histological analysis and rapid urease test. H. PYLORI QUIK CHEK™ had a sensitivity of 92% and a specificity of 91%. H. PYLORI CHEK™ had a sensitivity of 91% and a specificity of 100%. The authors concluded that "the H. PYLORI QUIK CHEK™ and H. PYLORI CHEK™ assays demonstrate excellent clinical performance compared the composite reference method" (Halland et al., 2021). Rolon et al. (2021) have developed and tested a real-time PCR assay to simultaneously detect *H. pylori* infection and genotypic markers of clarithromycin resistance. *H. pylori* infection can be treated with clarithromycin-based therapy; The American College of Gastroenterology (ACG) recommends clarithromycin-based triple therapy as first-line treatment in regions where clarithromycin resistance is known to be below 15% in patients with no history of macrolide exposure. "Clarithromycin resistance is most commonly caused by point mutations in the 23S rRNA (rRNA) gene, including A2143G, A2142G, and A2142C, which result in decreased macrolide binding to the 23S rRNA ribosomal subunit; clarithromycin resistance is considered the main cause of clarithromycin therapy failure." The authors tested 524 stool samples. *H. pylori* stool antigen tests were used as a control test for *H. pylori* detection. Sanger sequencing was used as control tests for genetic susceptibility. PCR results were positive for 98% of positive antigen stool tests. "The clarithromycin-based triple therapy success was lower when resistance was predicted by PCR (41%) than when no resistance was predicted (70%; P = 0.03)." The authors conclude that the PCR assay can diagnose *H. pylori* infection and provide genetic susceptibility information. The authors suggest the need for susceptibility-guided therapy when clarithromycin-based therapy is considered (Marrero Rolon et al., 2021).

VI. Guidelines and Recommendations

American Gastroenterological Association (AGA)

The AGA recommends that "patients 55 years or younger without alarm features should receive *H. pylori* test and treat followed by acid suppression if symptoms remain" and note that "*H. pylori* testing is optimally performed by a 13C-urea breath test or stool antigen test." Alarm features include symptoms such as recurrent vomiting and weight loss. Additionally, the AGA indicates that "although the yield of endoscopy is low, it is recommended for patients older than 55 years of age and for younger patients…presenting with new-onset dyspepsia." They reason that endoscopy with biopsy is the preferred test for this age group because upper gastrointestinal malignancy becomes more common after age 55 years (Talley, 2005).

In 2015 the AGA published a technical review on Upper Gastrointestinal biopsy to evaluate dyspepsia in the absence of visible mucosal lesions and found that:

- In the defined population, biopsy of normal-appearing gastric mucosa can detect HP [*H. pylori*] infection that would be missed on the exam without biopsies. The quality of evidence is very low, and there are noninvasive methods to detect HP infection.
- "Detection of HP infection with tissue biopsy and its eradication in patients with dyspepsia is associated with symptom improvement and reduction of risk for HP-related comorbidities,

including gastric cancer compared with no biopsy (or no eradication). The quality of evidence is moderate. The effect on symptom resolution is not universal and it does not appear to improve well-being. Quality of evidence for this statement is low" (Allen et al., 2015).

The AGA also released guidelines focusing on gastric intestinal metaplasia. In it, they recommend testing for *H. pylori* (followed by eradication) over no testing and eradication (Gupta et al., 2020).

The AGA released guidelines on gastrointestinal evaluation of iron deficiency anemia. AGA recommends that patients with iron deficiency anemia, without other identifiable etiology after bidirectional endoscopy, should undergo noninvasive testing for H. *pylori* over no testing at all to reduce the incidence of gastric cancer (Ko et al., 2020).

American College of Gastroenterology/Canadian Association of Gastroenterology

The ACG and CAG have released guidelines on testing for *H. pylori*:

- All patients with active peptic ulcer disease (PUD), a past history of PUD (unless previous cure of *H. pylori* infection has been documented), low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma, or a history of endoscopic resection of early gastric cancer (EGC) should be tested for *H. pylori* infection. Those who test positive should be offered treatment for the infection.
- In patients with uninvestigated dyspepsia who are under the age of 60 years and without alarm features, non-endoscopic testing for *H. pylori* infection is a consideration. Those who test positive should be offered eradication therapy.
- When upper endoscopy is undertaken in patients with dyspepsia, gastric biopsies should be taken to evaluate for *H. pylori* infection. Infected patients should be offered eradication therapy.
- Patients with typical symptoms of gastroesophageal reflux disease (GERD) without history of PUD need not be tested for *H. pylori* infection. For those who are found to be infected, treatment should be offered, acknowledging that effects on GERD symptoms are unpredictable.
- In patients taking long-term low-dose aspirin, testing for *H. pylori* infection could be considered.
- Patients initiating chronic treatment with a non-steroidal anti-inflammatory drug (NSAID) should be tested for *H. pylori* infection. Those who test positive should be offered eradication therapy.
- Patients with unexplained iron deficiency (ID) anemia despite an appropriate evaluation or idiopathic thrombocytopenic purpura should be tested for *H. pylori* infection.
- There is insufficient evidence to support routine testing and treating of *H. pylori* in asymptomatic individuals with a family history of "gastric cancer or patients with lymphocytic gastritis, hyperplastic gastric polyps and hyperemesis gravidarum".
- The ACG recommends the breath test and fecal stool antigen test as eradication tests, supported by moderate evidence (Chey et al., 2017).

Another set of joint guidelines from the ACG and Canadian Association of Gastroenterology (CAG) noted that dyspepsia patients under 60 should be tested for *H. pylori* (Moayyedi et al., 2017).

National Institute for Health and Care Excellence

NICE recommends testing for *H. pylori* with a carbon-13 urea breath test or a stool antigen test. A re-test should be with a breath test. Office-based serological tests are not recommended. NICE recommends a "2-week washout period after proton pump inhibitor (PPI) use before testing for *Helicobacter pylori.*" NICE recommends that individuals with positive *H. pylori* tests be offered therapy to eradicate the bacteria; however, they note that re-testing to confirm eradication should not be routinely offered. NICE limits the recommendation for post-treatment testing to **"**people with peptic ulcer (gastric or duodenal)…6 to 8 weeks after beginning treatment, depending on the size of the lesion (NICE, 2019).

NICE released further guidelines in 2015 reaffirming the carbon-13 urea breath test and the stool antigen test to test for *H. pylori*. A locally validated lab-based serology test may also be used to assess *H. pylori*. NICE reaffirms the 2 week washout period before testing for *H. pylori* if the patient is on PPIs as well as the 4 week washout period if the patient is on antibiotics (NICE, 2015).

This guideline was reaffirmed in 2020 (NICE, 2020).

American College of Cardiology

The American College of Cardiology recommends testing for and eradicating *H. pylori* in patients with a history of ulcer disease before starting chronic antiplatelet therapy (Bhatt et al., 2008).

World Gastroenterology Organization

The World Gastroenterology Organization Global Guidelines on *Helicobacter pylori* recommends testing for *H. pylori* based on evidence-based indications, noting that these indications may differ in different regions of the world based on prevalence, resources, competing needs, and individual patient factors. The guidelines state that "peptic ulcer disease is the prime indication in most of the world." The guidelines list other indications for the treatment of *H. pylori* as: past or present duodenal and/or gastric ulcer, gastric MALT lymphoma, gastric mucosal atrophy and/or intestinal metaplasia, resection of gastric cancer, first-degree relatives with gastric cancer, functional dyspepsia, NSAID use, before long-term aspirin therapy in patients at high risk of ulcers and ulcer-related complications, during long-term low-dose aspirin therapy in patients with a history of upper gastrointestinal bleeding and perforation, patients with gastroesophageal reflux disease who require long-term proton-pump inhibitors, as a strategy for gastric cancer prevention in communities with a high incidence, unexplained iron-deficiency anemia or idiopathic thrombocytopenic purpura, and patients' wishes after a full consultation with their physician (Katelaris et al., 2021).

European Association for Gastroenterology, Endoscopy and Nutrition (EAGEN), European Society of Neurogastroenterology and Motility (ESNM), and European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)

The pan-European guideline recommends the use of ^{13}C -urea breath tests as a noninvasive alternative for testing for "all indications of *Helicobacter pylori* testing if endoscopy is not required or if biopsies are contraindicated" and as "a preferred option for conformation of *Helicobacter pylori* eradication in adults and children." Alternatively, when there is indication for endoscopy and no contraindication for biopsy, the guidelines recommend RUT as the first-line diagnostic tests (Keller et al., 2021).

The European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN)

The ESPGHAN and NASPGHAN have issued updated guidelines for management of *H. pylori* in children and adolescents. They have proposed recommendations for diagnosis and management of *H. pylori* infection in pediatric patients. They have defined pediatric patients as children and adolescents below 18 years of age. The following recommendations were stated:

The guidelines recommend biopsies for rapid urease test and other cultures should only be taken if treatment is likely to be offered in the case of a confirmed infection. Treatment may be considered if *H. pylori* is an incidental finding at endoscopy.

The guidelines recommend against a "test and treat" strategy for *H. pylori* infection in children. The panelists explained that performing a noninvasive test to detect infection and treat is not needed because *H. pylori* infection usually does not cause any symptoms in the absence of peptic ulcer disease (PUD).

The guidelines recommend that "testing for *H. pylori* be performed in children with gastric or duodenal PUD."

The guidelines recommend against diagnostic testing for *H. pylori* infection in children with functional abdominal pain, iron deficiency anemia, and when investigating causes of short stature. Serology-based testing was also not recommended.

PPIs should be stopped 2 weeks before *H. pylori* testing, and antibiotics should be stopped 4 weeks before *H. pylori* testing. Diagnosis should be based on either: "positive culture or *H. pylori* gastritis on histopathology with at least 1 other positive biopsy-based test".

The non-invasive diagnostic testing was indicated in children when investigating causes of chronic immune thrombocytopenic purpura or for the assessment of anti-*H. pylori* therapy at least after 4 weeks of therapy (L. Jones et al., 2017).

Japanese Society for Pediatric Gastroenterology, Hepatology and Nutrition (JSPGHAN)

The JSPGHAN have updated their guidelines for *H. pylori* testing in pediatrics, including recommendations for diagnostic methods in children.

For diagnosis using endoscopic biopsy specimens, the guidelines recommend considering the performance and accuracy of the rapid urease test, recommending an additional urea breath test or stool antigen test when there is inconsistency between histopathology and the rapid urease test. The guidelines further recommend histological examination of gastric biopsies, and culture diagnostic tests to diagnose active *H. pylori* infection (Kato et al., 2020).

For diagnosis without endoscopic biopsy specimens, the guidelines recommend ^{13}C-urea breath test and stool antigen tests. To increase the diagnosis accuracy, the guidelines recommend more than two tests (two noninvasive tests or a biopsy-based and a noninvasive test) be completed. The guidelines recommend urea breath test or stool antigen test four or more weeks after treatment to confirm eradication of *H. pylori*, and recommend against using endoscopic biopsy methods and single serological tests to confirm eradication. The guidelines also recommend against anti-*H. pylori* antibody tests as a single test to diagnose *H. pylori* in a clinical setting (Kato et al., 2020).

Maastricht V/Florence Consensus Report

This report was published in 2017 on behalf of the European Helicobacter and Microbiota Study Group and Consensus panel. The panel reports that UBT is "the most investigated and best recommended non-invasive test in the context of a 'test-and-treat strategy". The panel also notes that monoclonal tests can be used and that serological tests can be used only after validation. However, rapid "office" serology tests are not recommended and "should be avoided". The guidelines recommend the rapid urease test (RUT) as a first line diagnostic test if there is an indication for endoscopy and no contraindication for biopsy. The guideline state that *H. pylori* is linked to "unexplained iron deficiency anaemia (IDA), idiopathic thrombocytopenic purpura , and vitamin B12 deficiency", and in these disorders, an *H. pylori* infection should be "sought and eradicated". The guidelines state that PPIs should be stopped 2 weeks and antibiotics and other bismuth compounds should be stopped 4 weeks before testing for *H. pylori*. In cases of chronic (active) gastritis in which *H. pylori* is not detected by histochemistry, immunohistochemical testing of *H. pylori* can be used as an ancillary test. If histology is normal, no immunohistochemical staining should be performed. It is recommended to perform clarithromycin susceptibility testing when a standard clarithromycin-based treatment is considered as the first-line therapy, except in populations or regions with well documented low clarithromycin resistance (<15%). Pepsinogen (Pg) serology is considered the most useful non-invasive test to explore gastric mucosa status (non-atrophic vs atrophic). The PgI/PgII ratio can never be assumed as a biomarker of gastric neoplasia. UBT is the best option for confirmation of *H. pylori* eradication and monoclonal SAT is an alternative. It should be performed at least 4 weeks after completion of therapy (Malfertheiner et al., 2017).

The Maastricht IV from 2012 also addressed testing for the cagA and vacA variants, stating that no specific genetic or virulence markers can be recommended at this time (Malfertheiner et al., 2012).

American Society for Clinical Pathology

The ASCP recommends against using the serological tests for *H. pylori* and recommends the stool antigen and breath tests instead. The ASCP states that serological evaluation is no longer clinically useful and the stool and breath tests have superior statistical power (ASCP, 2016).

American Society of Hematology (ASH)

ASH published an update to the immune thrombocytopenic purpura guidelines in 2019. In it, they "suggest" that "Screening for *H pylori* be considered for patients with ITP in whom eradication therapy would be used if testing is positive". However, ASH still recommends against "routine testing for *H pylori* in children with chronic ITP" (Neunert et al., 2019).

Houston Consensus Conference

This conference included 11 experts on "management of adult and pediatric patients with *H. pylori*, from different geographic regions of the United States" and was convened to "discuss key factors in diagnosis of *H. pylori* infection, including identification of appropriate patients for testing, effects of antibiotic susceptibility on testing and treatment, appropriate methods for confirmation of infection and eradication, and relevant health system considerations". Two cohorts of approval were present: one of the 11 experts, and another consisting of a selected group of United States-based gastroenterologists. These recommendations were intended to provide practical advice for US practitioners, and also guidelines to be adopted by US health care systems.

Recommendations approved by both groups are listed below:

- "Statement 1: We recommend that all patients with active *H pylori* infection be treated (100% agree/strongly agree, Grade 1A).
- Statement 2: All patients with current or past gastric or duodenal ulcers should be tested for *H pylori* infection (100% agree/strongly agree; Grade 1A).
- Statement 3: We recommend that all patients with uninvestigated dyspepsia be tested for *H pylori* infection (100% agree/strongly agree, Grade 1A).
- Statement 4: We recommend routine testing for *H pylori* infection in patients with reflux symptoms only if they are at high risk for *H pylori*-related disease (91% agree/strongly agree, Grade 1C).
- Statement 5: We recommend that patients with gastric mucosa-associated lymphoid tissue (MALT) lymphoma be tested for *H pylori* infection (100% agree/strongly agree, Grade 1B).
- Statement 6: We recommend that individuals with family history of gastric cancer be tested for *H pylori* infection (100% agree/strongly agree, Grade 1B).
- Statement 7: We recommend that patients who are first-generation immigrants from high prevalence areas be tested for *H pylori* infection (82% agree/strongly agree, Grade 1B).
- Statement 8: We suggest that patients of Latino and African American racial or ethnic groups may be considered for *H pylori* testing due to their high risk of infection (91% agree/strongly agree, Grade 2C)."
- Statement 17: We recommend that validated diagnostic testing of stool or gastric mucosal biopsy by culture and susceptibility, or molecular analysis be universally available (100% agree/strongly agree, Grade 1)
- Statement 18: We suggest that antibiotics that may be routinely evaluated for susceptibility include amoxicillin, clarithromycin, levofloxacin, metronidazole, and tetracycline (100% agree/strongly agree, Grade 2C).
- Statement 20: We recommend the use of tests for active *H pylori* infection (ie, UBT, HpSAg testing) for the initial diagnosis (100% agree/strongly agree, Grade 1A).
- Statement 22: We recommend that serology not be utilized for detection of active *H pylori* infection (100% agree/strongly agree, Grade 1A).
- Statement 23: We recommend that bismuth and antibiotics be stopped at least 4 weeks before *H pylori* testing with tests for active infection (ie, UBT, and HpSAg testing and histology; 100% agree/strongly agree, Grade 1C).
- Statement 27: We recommend that all patients receiving treatment for *H pylori* receive posttreatment confirmation of eradication. We recommend that only tests that evaluate for active infection, such as UBT, HpSAg test, or histology (if endoscopy is required for other reasons), are utilized for this purpose (100% agree/strongly agree, Grade 1A).
- Statement 28: Once appropriate testing has confirmed eradication, we recommend against further *H pylori* testing, (100% agree/strongly agree, Grade 1C)"

The following recommendations reached a consensus by the expert panel, but not the external group:

- "Statement 9: We recommend that patients with idiopathic thrombocytopenia be tested for *H pylori* infection (experts vs survey: 100% vs 68% agree/strongly agree, Expert Grade 1B)
- Statement 10: We suggest that patients receiving long-term PPIs (>1 month) be tested for *H pylori* infection (experts vs survey: 82% vs 68% agree/strongly agree, Expert Grade 2C)

- Statement 11: We recommend that family members residing in the same household of patients with proven active *H pylori* infections undergo *H pylori* testing (experts vs survey: 91% vs 78% agree/strongly agree, Expert Grade 1B)
- Statement 12: We recommend that individuals with a family history of peptic ulcer disease be tested for *H pylori* infection (experts vs survey: 91% vs (73% agree/strongly agree, Expert Grade 1B)" (El-Serag et al., 2018).

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

A search for "*pylori*" yielded 57 results on January 04, 2022, which encompasses various immunoassays and breath tests (FDA, 2022).

On Feb 22, 2012, the FDA approved the BreathTek UBT for *H. pylori* Kit created by Otsuka America Pharmaceutical, Inc. TheBreathTek UBT for *H. pylori* Kit (BreathTek UBT Kit) is intended for use in the qualitative detection of urease associated with *H. pylori* in the human stomach and is indicated as an aid in the initial diagnosis and post-treatment monitoring of *H. pylori* infection in adults, and pediatric patients 3 to 17 years old. The test may be used for monitoring treatment if used at 4 weeks following completion of therapy. The FDA notes its sensitivity and specificity to be 0.958 and 0.992 respectively (FDA, 2012).

On Jan 17, 2002, the FDA approved the BreathTek UBiT for *H. pylori* created by Meretek Diagnostics Inc. The scientific basis underlying the BreathTek UBT and the BreathTek UBiT UBT kit is identical. The urea breath test is FDA cleared for use in individuals 18 years of age and older (FDA, 2002).

On February 18, 2020, the FDA approved the PyloPlus UBT System created by ARJ Medical Inc. PyloPlus detects urease associated with *H. pylori* in the stomach and is indicated as an aid in the initial diagnosis of H. pylori infection in adults 18 years and older (FDA, 2020).

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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VIII. Applicable CPT/HCPCS Procedure Codes

Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all inclusive and is subject to updates. In addition, codes listed are not a guarantee of payment.

Code Number	Code Description
83009	Helicobacter pylori, blood test analysis for urease activity, non-radioactive isotope (eg, C-13)
83013	Helicobacter pylori; breath test analysis for urease activity, non-radioactive isotope (eg, C-13)
83014	Helicobacter pylori; drug administration
86318	Immunoassay for infectious agent antibody(ies), qualitative or semiquantitative, single step-method (eg, reagent strip);
86677	Antibody; Helicobacter pylori
87070	Culture, bacterial; any other source except urine, blood or stool, aerobic, with isolation and presumptive identification of isolates
87077	Culture, bacterial; aerobic isolate, additional methods required for definitive identification, each isolate
87081	Culture, presumptive, pathogenic organisms, screening only;
87149	Culture, typing; identification by nucleic acid (DNA or RNA) probe, direct probe technique, per culture or isolate, each organism probed
87150	Culture, typing; identification by nucleic acid (DNA or RNA) probe, amplified probe technique, per culture or isolate, each organism probed
87153	Culture, typing; identification by nucleic acid sequencing method, each isolate (eg, sequencing of the 16S rRNA gene)
87181	Susceptibility studies, antimicrobial agent; agar dilution method, per agent (eg, antibiotic gradient strip)
87186	Susceptibility studies, antimicrobial agent; microdilution or agar dilution (minimum inhibitory concentration [MIC] or breakpoint), each multi-antimicrobial, per plate
87205	Smear, primary source with interpretation; Gram or Giemsa stain for bacteria, fungi, or cell types
87338	Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative; Helicobacter pylori, stool
87339	Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative; Helicobacter pylori
88305	Level IV - Surgical pathology, gross and microscopic examination - Stomach biopsy
0008U	Helicobacter pylori detection and antibiotic resistance, DNA, 16S and 23S rRNA, gyrA, pbp1, rdxA and rpoB, next generation sequencing, formalin-fixed paraffin-embedded or fresh tissue or fecal sample, predictive, reported as positive or negative for resistance to clarithromycin, fluoroquinolones, metronidazole, amoxicillin, tetracycline, and rifabutin

	Proprietary test: AmHPR H. Antibiotic Resistance Panel Lab/Manufacturer: American Molecular Laboratories, Inc

IX. Evidence-based Scientific References

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X. Revision History

Revision Date	Summary of Changes
01/01/2022	Initial Effective Date
07/19/2022	Updated background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate modification to coverage criteria. Addition of "or" to several coverage criteria for clarity. Revised code disclaimer statement