Genetic Testing for Helicobacter pylori Treatment

The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Preauthorization is not required but is recommended if, despite this Protocol position, you feel this service is medically necessary; supporting documentation must be submitted to Use Management.* Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

Description

*Helicobacter pylori* (*H. pylori*) is a bacterium associated with a range of gastrointestinal (GI) disorders, such as peptic ulcer disease, chronic gastritis, and gastric malignancy. Eradication of *H. pylori* has been proven beneficial for a number of indications.

Currently, multiple regimens are available for treating *H. pylori* infection. These include proton pump inhibitors (PPIs), as well as similar medication(s), to suppress acid production in combination with antibiotic treatment, consisting of one or more agents such as amoxicillin, clarithromycin, or metronidazole. These first-line regimens generally achieve eradication rates in the 70–90% range. Differences in eradication rates are dependent on the regimen used and the population being treated. Treatment failures are most often attributed to antibiotic resistance or poor patient compliance. Resistance to clarithromycin is an important factor associated with treatment failure, with high rates of treatment failure for standard first-line regimens in patients infected with clarithromycin-resistant strains of *H. pylori*. A 2002 survey from the U.S. estimated that 13% of *H. pylori* strains are resistant to clarithromycin and that the rate of resistance was rising in comparison to earlier studies.

Genetic factors may influence the success of *H. pylori* treatment through effects on PPI metabolism. Individuals with polymorphisms in the CYP2C19 gene, a component of the cytochrome p450 (CYP450) system, metabolize PPIs more slowly than normal. Genetic variation in the CYP450 enzyme system is one of the most extensively studied in the field of pharmacogenomics. This family of enzymes is found in the liver and is important for metabolizing and eliminating a large number of pharmacologic agents. Differences in PPI metabolism lead to variability in gastric acid suppression, with associated variability in gastric pH and potential impact on the efficacy of *H. pylori* treatment. Observational research suggests that patients who are extensive metabolizers of PPIs have lower eradication rates following standard treatment for *H. pylori*, compared with poor metabolizers.

Three major CYP2C19 alleles determine enzymatic activity, as shown in Table 1. The *1* allele is the wild-type found in most individuals, while the *2* and *3* alleles are the most common polymorphisms that are known to impact enzymatic activity. Both the *2* and *3* alleles are examples of “null” alleles, which have no enzymatic activity. Each null allele is caused by a single nucleotide change that results in a splice defect or a stop codon. (1)

Table 1. CYP2C19 polymorphisms**            Table 2. CYP2C19 phenotypes**

<table>
<thead>
<tr>
<th>Allele</th>
<th>Nucleotide Change</th>
<th>Predicted Enzyme Activity</th>
<th>Allele</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1</td>
<td>None</td>
<td>Normal</td>
<td>1</td>
<td>EM</td>
<td>IM</td>
<td>IM</td>
</tr>
<tr>
<td>*2</td>
<td>681G&gt;A</td>
<td>None</td>
<td>2</td>
<td>PM</td>
<td>PM</td>
<td></td>
</tr>
<tr>
<td>*3</td>
<td>636G&gt;A</td>
<td>None</td>
<td>3</td>
<td></td>
<td></td>
<td>PM</td>
</tr>
</tbody>
</table>

(1)
**Adapted from AmpliChip package insert**

EM extensive metabolizers

IM intermediate metabolizers

PM poor metabolizers

Polymorphisms of the CYP2C19 gene are relatively common and vary by ethnicity. Patients with no polymorphisms of CYP2C19 have two wild-type alleles and no reduction in their ability to metabolize PPIs. These patients are typically called extensive metabolizers (EM) (Table 2). Heterozygous polymorphisms are found in 27–37% of the Caucasian population and 46–50% of the Asian population. These patients have a minor reduction in their ability to eliminate PPIs and are called intermediate metabolizers (IM). Homozygous polymorphisms of the CYP2C19 gene are found in 3–6% of Caucasians and in 12–20% of Asians. These patients eliminate PPIs from the circulation substantially more slowly than unaffected patients and are termed poor metabolizers (PM).

In patients treated with PPIs, intragastric pH has been shown to correlate with CYP2C19 status. Patients homozygous for a CYP2C19 mutation (PM) exhibit a less acidic pH when compared to patients without a CYP2C19 mutation, with heterozygous patients exhibiting intermediate values. Intragastric pH has important implications for treating *H. pylori*. *H. pylori* is more sensitive to antibiotics at less acidic pH levels. Less acidic pH levels also lead to greater stability and bioavailability of antibiotics. Therefore, it is expected that treatment of *H. pylori* will be more successful if there is maximal suppression of gastric acid production and higher intragastric pH levels.

Therefore, it has been proposed that a pharmacogenomics-based treatment regimen individualized by CYP2C19 status may improve the success rate of treatment for *H. pylori*. If CYP2C19 status is known prior to treatment, adjustments can be made in the selection of PPI and/or the dosing schedule to achieve optimal acid suppression in all patients. Improved eradication rates for *H. pylori* could lead to improved health outcomes by reducing the need for retreatment following treatment failure, reducing recurrences of *H. pylori*-associated disorders and reducing the morbidity and mortality associated with disease recurrence.

At least one commercially available genetic test, the Roche AmpliChip Cytochrome P450® Genotyping test, has been approved by the U.S. Food and Drug Administration (FDA) as a class II medical device. This test examines polymorphisms in CYP2D6 and CYP2C19 isoenzymes of the cytochrome p450 enzyme system. Approval for this device was originally granted in December 2004 as an aid in determining treatment choice and individualizing treatment dose for therapeutics that are primarily metabolized by the CYP2D6 enzyme. The use of information on CYP2C19 polymorphisms was not addressed as part of the FDA approval process.

**Corporate Medical Guideline**

Genotyping to determine cytochrome p450 (CYP2C19) genetic polymorphisms is considered *investigational* for the purpose of managing the treatment of *H. pylori* infection.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced
procedures. Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.