I. Policy

Genotyping to determine cytochrome p450 (CYP2C19) genetic polymorphisms is considered investigational for the purpose of managing the treatment of *H. pylori* infection. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

II. Product Variations

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

FEP PPO*

*The FEP program dictates that all drugs, devices or biological products approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational. Therefore, FDA-approved drugs, devices or biological products may be assessed on the basis of medical necessity.

III. Description/Background

*Helicobacter pylori* infection of the gastrointestinal (GI) tract is treated with a combination of antibiotics and proton-pump inhibitors (PPI). Genetic factors may influence the success of *H pylori* treatment through effects on PPI metabolism. Individuals with polymorphisms in the *CYP2C19* gene metabolize PPIs more rapidly than normal and may have a reduced therapeutic effect. Therefore, individualized treatment regimens based on genetic testing may improve eradication rates.
*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 (PPI), 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>
<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>
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<tr>
<td>*1</td>
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<td></td>
<td></td>
<td>PM</td>
<td>PM</td>
</tr>
<tr>
<td>*3</td>
<td>636G&gt;A</td>
<td>None</td>
<td></td>
<td></td>
<td>PM</td>
<td></td>
</tr>
</tbody>
</table>
Polymorphisms of the \textit{CYP2C19} gene are relatively common and vary by ethnicity. Patients with no polymorphisms of CYP2C19 have 2 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 \textit{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 \textit{H pylori}. \textit{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 \textit{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 \textit{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 \textit{H pylori} could lead to improved health outcomes by reducing the need for retreatment following treatment failure, reducing recurrences of \textit{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.

\textbf{IV. RATIONALE}

Validation of genotyping to improve pharmacologic treatment outcomes is a multistep process. In general, important steps in the validation process address the following:

- **Analytic validity**: measures technical performance, i.e., whether the test accurately and reproducibly detects the gene markers of interest.
- **Clinical validity**: measures the strength of the associations between the selected genetic markers and dose, therapeutic efficacy, and/or adverse events.
- **Clinical utility**: determines whether the use of genotyping for specific genetic markers to guide prescribing and/or dosing improves patient outcomes such as therapeutic effect, time to effective dose, and/or adverse event rate compared to standard treatment without genotyping.

The AmpliChip Cytochrome P450® Genotyping test tests for known polymorphisms of 2 isoenzymes of the cytochrome p450 system, CYP2D6 and CYP2C19. This system uses DNA extracted from whole blood and a polymerase chain reaction (PCR)-based GeneChip Microarray Instrumentation system to determine the presence or absence of genetic polymorphisms. (1)

For the **CYP2C19** gene, the test examines for the 2 common polymorphisms associated with enzymatic activity (Table 1). Information from the manufacturer claims greater than 99% accuracy in detecting these common polymorphisms. (2) However, a number of rare polymorphisms that have been identified are not tested for by the AmpliChip system. The results of the test are included in a report to the ordering physician that includes potential clinical implications of the result.

**Literature review**

*Is there a correlation between CYP2C19 genetic status and *H pylori* eradication rates?*

Numerous case series and re-analysis of clinical trials completed for other reasons have suggested that there is a correlation between CYP2C19 status and success rates for eradication of *H pylori*. For the most part, these are studies in which a single treatment regimen was used and in which patients were tested for CYP2C19 status. These studies then report eradication rates for *H pylori* according to CYP2C19 status. (3-7)

The majority of studies that did not use rabeprazole reported lower eradication rates in extensive metabolizer (EM) patients compared with poor metabolizer (PM) patients. Rabeprazole is the only proton pump inhibitor (PPI) that is not metabolized by the CYP2C19 enzyme, and therefore eradication rates with regimens including rabeprazole may not vary according to CYP2C19 status. For studies not using rabeprazole, eradication rates in PM patients are consistently in the 95–100% range. The eradication rates for EM patients are substantially lower, ranging from 29–80%, with eradication rates for intermediate metabolizer (IM) patients generally intermediate between the two. For trials that used rabeprazole, eradication rates according to CYP2C19 group were generally similar, although at least one study did report lower eradication rates for EM patients. (8)

A meta-analysis from 2006 (9) confirmed these findings. This analysis included clinical trials of *H pylori* eradication that used dual or triple therapy antibiotic regimens, reported eradication rates.
by CYP2C19 status, and had a Jadad quality score of 2 or greater. The authors identified 19 trials that met their inclusion criteria and reported pooled eradication rates by genetic status and specific PPI agent. For all PPIs, the pooled eradication rate was highest in the PM group (89%), intermediate in the IM group (83%), and lowest in the EM group (71%), with the difference between these groups significant at the p<0.0001 level. The difference in eradication rates by CYP2C19 status also appeared to vary by the specific PPI used. The greatest difference in eradication rates between EM groups and PM groups was seen for omeprazole (93% vs. 63%, respectively). The difference in eradication rates was less pronounced for lansoprazole (88% vs. 74%, respectively), and least evident for rabeprazole (81% vs. 77%, respectively).

A second meta-analysis reported similar findings. This study (10) reviewed 20 studies that evaluated the relationship between CYP2C19 genetic status and H. pylori eradication rates. Poor metabolizers had the highest rates of eradication when compared to either heterozygous EMs (odds ratio [OR]: 1.73, p=0.002) or homozygous EMs (OR: 2.79, p<0.001). Among the individual PPIs included in these studies, CYP2C19 status was associated with eradication rates for treatment regimens using omeprazole and lansoprazole but not for regimens using rabeprazole.

Conclusions. Numerous observational studies and meta-analyses have established that the eradication rate for H. pylori is dependent on CYP2C19 genetic status. Poor metabolizers have the highest rates of eradication, at approximately 90% or higher. Intermediate metabolizers and PMs have lower eradication rates, with reported rates in the literature ranging from 60-90%.

Does genetic testing for CYP2C19 variants improve eradication rates in individuals with Helicobacter pylori infection?

A single randomized, controlled trial (RCT) was identified for use of genetic testing in selecting the treatment regimen for H. pylori infection. (11) This study randomly assigned 300 Japanese patients to a pharmacogenomics-based treatment regimen versus a standard treatment regimen. The pharmacogenomics regimen included testing for CYP2C19 genetic status, esophagogastroduodenoscopy (EGD), and H. pylori culture with sensitivity testing to clarithromycin. In the pharmacogenomics group, the dose of PPI was adjusted according to CYP2C19 genetic status, and the antibiotic regimen was adjusted according to H. pylori sensitivity to clarithromycin.

Eradication rates following initial treatment were 96% (95% confidence interval [CI]: 91.5–98.2%) in the pharmacogenomics-based treatment group versus 70.0% (95% CI: 62.2–77.2%) in the standard therapy group (p<0.001). When analyzed according to genetic status, the improvement in eradication rates in the pharmacogenomics group was greater for EM patients (100% vs. 58%, respectively) and IM patients (95% vs. 72%, respectively), compared to PM patients (91% vs. 91%, respectively). Eradication rates also varied by clarithromycin-resistant status, with particularly low eradication rates occurring in the standard treatment group for EM
patients with clarithromycin resistance (0%) and IM patients with clarithromycin resistance (48%).

Patients who failed eradication following first-line treatment were re-treated. By intent-to-treat analysis, eradication rates following re-treatment were 97.8% (95% CI: 94.3–99.6%) for the pharmacogenomics group compared to 88.0% (95% CI: 81.7–92.7%) for the standard regimen group (p<0.001). When analyzed by per-protocol, the eradication rates were 99.3% (95% CI: 96.3–100%) for the pharmacogenomics group compared to 95.7% (95% CI: 90.8–98.4%) for the standard treatment group (p=NS).

Alternative regimens, involving higher PPI doses and/or PPI medications that are not metabolized by cytochrome P450, have been tested as another option to genetic testing.(12-14) Several more recent trials have directly compared the eradication rates of a treatment regimen containing rabeprazole to a treatment regimen containing an alternative PPI in Asian populations. (12, 14) Kuo et al. (12) enrolled 195 patients who had previously failed initial treatment and reported an eradication rate of 78.7% (95% CI: 72.5-84.9%) for the rabeprazole regimen compared to 72.9% (95% CI: 64.9-80.9%, p=0.05) for the esomeprazole-based regimen group. These results remained significant after controlling for the effect of antibiotic resistance. Zhang et al. (14) studied 240 Chinese patients with peptic ulcer disease and compared eradication rates for rabeprazole-based regimens compared with omeprazole-based regimens. The eradication rates were significantly higher for the rabeprazole-based regimens among EMs but not among patients with wild-type CYP2C19 (p=0.01).

Conclusions. While the single available RCT reports an increased rate of H pylori eradication in the pharmacogenomics strategy compared with a standard approach, this study does not provide definitive evidence that use of a pharmacogenomics-based treatment regimen improves health outcomes. There are numerous variations in the treatment regimen within the experimental group that make it difficult to determine which specific aspects of the treatment regimen may have led to benefit. In particular, it appears that clarithromycin resistance is an important factor in treatment success and that there may be an interaction between clarithromycin resistance and CYP2C19 status.

Alternative treatment strategies exist for eradicating H pylori that address some of the issues raised by CYP2C19 variability but do not rely on testing for CYP2C19 status. For example, empiric treatment with higher-dose PPI for all patients might be reasonable, particularly for non-Asian populations in which CYP2C19 mutation rates are lower. This approach may be as effective as regimens tailored by pharmacogenomics, with little additional risk. The use of a PPI that is less susceptible to CYP2C19 status, such as rabeprazole, has been associated with higher eradication rates compared to other PPIs. This may be the preferred regimen, given that there is no reason to suspect other advantages to use of omeprazole or lansoprazole. Ideally, a clinical trial will evaluate whether a tailored pharmacogenomics approach is superior to other empiric approaches such as these.
Summary

The scientific evidence does not permit conclusions on whether the use of a pharmacogenomics-based treatment regimen for \textit{H pylori} improves eradication rates. In general, eradication rates of \textit{H pylori} vary by CYP2C19 status, with the highest rates found in patients who are poor metabolizers of PPIs. In the single randomized controlled trial comparing a pharmacogenomics-based treatment regimen with a standard regimen, eradication rates after first-line treatment were higher for the pharmacogenomics group compared with the standard treatment group. However, because of numerous variations in treatment protocol within the pharmacogenomics group, it is not possible to determine whether the improvement resulted from the tailored PPI dosages according to CYP2C19 genetic status or due to other variations in the treatment protocol unrelated to CYP2C19 status. It is possible that other clinical factors, such as clarithromycin resistance, or other treatment factors, such as length of antibiotic treatment, may have influenced eradication rates. The use of a PPI that is less susceptible to CYP2C19 status, such as rabeprazole, has been associated with higher eradication rates compared to other PPIs. Therefore, additional trials are needed to address the issues noted above, including alternative treatment regimens, before conclusions can be made on whether a pharmacogenomics-based treatment regimen improves \textit{H pylori} eradication rates compared to a standard treatment regimen. Therefore, the use of genetic testing for \textit{Helicobacter pylori} treatment is considered investigational.

2016

Review of the literature revealed no new information that would alter the conclusions reached above. Therefore, the policy statement is unchanged.

Practice Guidelines and Position Statements
None

Medicare National Coverage
None

V. DEFINITIONS

\textbf{Genotype} refers to the pair of genes present for a particular characteristic or protein.

\textbf{Polymorphism} refers to the state or quality of existing or occurring in several different forms.
VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member’s contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore not covered, genetic testing for the purpose of managing the treatment of helicobacter pylori infection:

| CPT Codes® | 81225 |

IX. REFERENCES

14. Zhang L, Mei Q, Li QS et al. The effect of cytochrome P2C19 and interleukin-1 polymorphisms on H. pylori eradication rate of 1-week triple therapy with omeprazole or

X. POLICY HISTORY

<table>
<thead>
<tr>
<th>MP-2.308</th>
<th>CAC 11/22/11 - Adopt BCBSA. The information related to Helicobacter pylori treatment was extracted from Cytochrome p450 Genotyping (formerly Drug Metabolism Genetic and Pharmacogenomic Testing) and a separate policy was created. Policy statement unchanged, remains investigational. Administrative Coding review complete 7/15/13 RSB</th>
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