

Corporate Medical Policy

Genetic Testing for Helicobacter pylori Treatment

File Name: genetic_testing_for_helicobacter_pylori_treatment
Origination: 4/2011
Last CAP Review: 4/2012
Next CAP Review: 4/2013
Last Review: 4/2012

Description of Procedure or Service

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.

Table 1. CYP2C19 Polymorphisms**			Table 2. CYP2C19 Phenotypes**			
Allele	Nucleotide Change	Predicted Enzyme Activity	Allele	1	2	3
*1	None	Normal	1	EM	IM	IM
*2	681G>A	None	2		PM	PM
*3	636G>A	None	3			PM

**Adapted from AmpliChip package insert

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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 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 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

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

Genotyping to determine cytochrome p450 (CYP2C19) genetic polymorphisms is considered investigational for the purpose of managing the treatment of H.pylori infection. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

Genetic Testing for Helicobacter pylori Treatment

When genetic testing for helicobacter pylori treatment is covered

Not applicable

When genetic testing for helicobacter pylori treatment is not covered

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

Policy Guidelines

The scientific evidence does not permit conclusions on whether the use of a pharmacogenomics-based treatment regimen for *H. pylori* improves eradication rates. 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. 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 *H. pylori* eradication rates compared to a standard treatment regimen.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81225

There are specific CPT codes for array-based evaluation of multiple molecular markers: 88384, 88385, 88386

When fewer than 11 probes are prepared and evaluated, the services are coded using CPT codes 83890-83914 as appropriate.

There is also a CPT genetic testing modifier that is specific to CYP2 genes: -9B

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

AmpliChip CYP450 test package insert. Roche Diagnostics/Roche Molecular Systems. Indianapolis, IN; July 2006. Available online at: http://www.amplichip.us/documents/CYP450_P.I._US-

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IVD_Sept_15_2006.pdf.

Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Pharmacogenomics-based treatment of *Helicobacter pylori* infection. TEC Assessments 2008; vol. 23, tab 2.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.50, 7/8/10

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.50, 11/10/11

Specialty Matched Consultant Advisory Panel 4/18/12

Policy Implementation/Update Information

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| 5/10/11 | New policy developed. Genotyping to determine cytochrome p450 (CYP2C19) genetic polymorphisms is considered investigational for the purpose of managing the treatment of H.pylori infection. Specialty Matched Consultant Advisory Panel review 4/27/2011. (adn) |
| 1/1/12 | CPT code 81225 added to Billing/Coding section. (adn) |
| 5/1/12 | Specialty Matched Consultant Advisory Panel review 4/18/12. No change to policy statement or criteria. (sk) |

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.