MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR HELICOBACTER PYLORI TREATMENT
POLICY NUMBER	MP 2.308

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**3/1/2024**

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 general conclusion concerning the health outcomes or benefits associated with this procedure.

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross. Please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO: Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies .

III. DESCRIPTION/BACKGROUND

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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.

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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 those results in a splice defect or a stop codon. (1)

Table 1. CYP2C19 polymorphisms**

Allele	Nucleotide Change	Predicted Enzyme Activity
*1	None	Normal
*2	681G>A	None
*3	636G>A	None

Table 2. CYP2C19 phenotypes**

Allele	1	2	3
1	EM	IM	IM
2		PM	PM
3			PM

EM: extensive metabolizers; IM: intermediate metabolizers; PM: poor metabolizers.
** Adapted from AmpliChip package insert

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).

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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.

The American Gastroenterological Association published a “Clinical Practice Update on the Management of Refractory *Helicobacter pylori* Infection: Expert Review” in January of 2021. The update outlines the importance of CYP2C19 polymorphisms in metabolism of PPIs and failure of eradication of *H. pylori*. Studies have been completed in Asian-Pacific populations, however the literature highlights that the lack of study in the US population is important, given the “substantive racial and ethnic differences in the prevalence of CYP2C19 variant alleles and genotypes in the United States.” The guideline goes on to state that “current data are insufficient to support genetic polymorphism testing for guiding therapeutic selection in refractory (or primary) eradication therapy. Given the high population prevalence of metabolism-enhancing phenotypes of *CYP2C19* at least in non-Asian groups, empiric selection of strategies that achieve greater intragastric acid suppression might be reasonable in the management of refractory *H pylori* infection.”

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.

IV. RATIONALE

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Summary

The scientific evidence does not permit conclusions on whether the use of a pharmacogenomics-based treatment regimen for *H pylori* improves eradication rates. In general, eradication rates of *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 *H pylori* eradication rates compared to a standard treatment regimen. Therefore, the use of genetic testing for *Helicobacter pylori* treatment is considered investigational.

V. DEFINITIONS

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GENOTYPE refers to the pair of genes present for a particular characteristic or protein.

POLYMORPHISM refers to the state or quality of existing or occurring in several different forms.

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross'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. If a provider or a member has a question concerning the application of this medical policy to a specific member's

plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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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:

Procedure Codes								
81225								

IX. REFERENCES

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1. *Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Pharmacogenomics-based treatment of Helicobacter pylori infection. TEC Assessments 2008; volume 23, tab 2.*
2. *Kang JM, Kim N, Lee DH et al. Effect of the CYP2C19 polymorphism on the eradication rate of Helicobacter pylori infection by 7-day triple therapy with regular proton pump inhibitor dosage. J Gastroenterol Hepatol 2008; 23(8 Pt 1):1287-91.*
3. *Miehlke S, Schneider-Brachert W, Kirsch C et al. One-week once-daily triple therapy with esomeprazole, moxifloxacin, and rifabutin for eradication of persistent Helicobacter pylori resistant to both metronidazole and clarithromycin. Helicobacter 2008; 13(1):69-74.*
4. *Sapone A, Vaira D, Trespidi S et al. The clinical role of cytochrome p450 genotypes in Helicobacter pylori management. Am J Gastroenterol 2003; 98(5):1010-5.*
5. *Schwab M, Schaeffeler E, Klotz U et al. CYP2C19 polymorphism is a major predictor of treatment failure in white patients by use of lansoprazole-based quadruple therapy for eradication of Helicobacter pylori. Clin Pharmacol Ther 2004; 76(3):201-9.*
6. *Sheu BS, Kao AW, Cheng HC et al. Esomeprazole 40 mg twice daily in triple therapy and the efficacy of Helicobacter pylori eradication related to CYP2C19 metabolism. Aliment Pharmacol Ther 2005; 21(3):283-8.*
7. *Furuta T, Shirai N, Takashima M et al. Effects of genotypic differences in CYP2C19 status on cure rates for Helicobacter pylori infection by dual therapy with rabeprazole plus amoxicillin. Pharmacogenetics 2001; 11(4):341-8.*
8. *Padol S, Yuan Y, Thabane M et al. The effect of CYP2C19 polymorphisms on H. pylori eradication rate in dual and triple first-line PPI therapies: a meta-analysis. Am J Gastroenterol 2006; 101(7):1467-75.*
9. *Zhao F, Wang J, Yang Y et al. Effect of CYP2C19 genetic polymorphisms on the efficacy of proton pump inhibitor-based triple therapy for Helicobacter pylori eradication: a meta-analysis. Helicobacter 2008; 13(6):532-41.*

10. *Furuta T, Shirai N, Kodaira M et al. Pharmacogenomics-based tailored versus standard therapeutic regimen for eradication of H. pylori. Clin Pharmacol Ther 2007; 81(4):521-8.*
11. *Kuo CH, Wang SS, Hsu WH et al. Rabeprazole can overcome the impact of CYP2C19 polymorphism on quadruple therapy. Helicobacter 2010; 15(4):265-72.*
12. *Ward MB, Foster DJ. CYP2C19-guided design of a proton pump inhibitor dose regimen to avoid the need for pharmacogenetic individualization in H. pylori eradication. Eur J Clin Pharmacol 2011; 67(3):261-6.*
13. *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 rabeprazole, amoxycillin and clarithromycin in Chinese people. J Clin Pharm Ther 2010; 35(6):713-22.*
14. *Mayerle, J, et al. Identification of genetic loci associated with helicobacter pylori serologic status. JAMA 2013: 309:1912-1920.*
15. *US Food and Drug Administration. Center for Devices and Radiological Health. AmpliChip CYP450 Clearance Letter. December 23, 2004. Available online at: Accessed July 29, 2022*
16. *Chey, William D MD, FACG1; Leontiadis, Grigorios I MD, PhD2; Howden, Colin W MD, FACG3; Moss, Steven F MD, FACG4. ACG Clinical Guideline: Treatment of Helicobacter pylori Infection. American Journal of Gastroenterology: February 2017 - Volume 112 - Issue 2 - p 212-239 doi: 10.1038/ajg.2016.563*
17. *Zihlif M, Bashaireh B, Rashid M, Almadani Z, Jarrar Y. Effect of major CYP2C19 genetic polymorphisms on Helicobacter pylori eradication based on different treatment regimens. Biomed Rep. 2022 Jan;16(1):2. doi: 10.3892/br.2021.1485. Epub 2021 Nov 8. PMID: 34820125; PMCID: PMC8609274.*
18. *Shah, S. C., Iyer, P. G., & Moss, S. F. (2021, January 28). AGA clinical practice update on the management of refractory Helicobacter pylori Infection: Expert Review. Gastroenterology.*
19. *Blue Cross Blue Shield Association Medical Policy Reference Manual.2.04.50, Genetic Testing for Helicobacter pylori Treatment (Archived) July 2012.*

X. POLICY HISTORY

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MP-2.308	**11/22/11 CAC** - **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
	7/15/13 Administrative update. Coding review complete.
	9/30/13 CAC Consensus review. References updated but no changes to the policy statements.
	7/22/14 CAC Consensus review. References updated. Rationale added. No changes to the policy statements.
	7/21/15 CAC Consensus review. No change to the policy statement. Reference update. No coding changes.
	7/26/16 CAC Consensus review. No changes to the policy statements. Coding reviewed.
	11/23/16 Admin update. Variation reformatting.

	9/26/17 CAC Consensus review. No change to the policy statement. References reviewed. Coding reviewed.
	5/31/18 Consensus review. No change to the policy statement. References reviewed. Rationale revised**.**
	4/1/19 Admin update. Code review, no changes
	5/21/19 Consensus review. No change to policy statements. References reviewed.
	5/22/20 Consensus Review. No change to policy statement. Variations updated. References reviewed with no changes. Coding reviewed with no changes.
	4/14/2021 Consensus Review. No change to policy statement. References updated and coding reviewed.
	7/29/2022 Consensus Review. No change to policy statement. FEP, references updated, coding reviewed.
	7/31/2023 Consensus Review. No change to policy statement. Updated background, references. Coding reviewed, no changes.
	1/19/2024 Administrative update. Clinical benefit added.

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