

Pharmacogenomics-Based Treatment of *Helicobacter pylori* Infection



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Executive Summary

Background

Helicobacter pylori infection is endemic worldwide, and eradication of *H. pylori* is an important component of treatment for peptic ulcer disease and other gastrointestinal disorders. Genetic factors may influence the success of *H. pylori* treatment through effects on proton pump inhibitor (PPI) metabolism. PPIs are metabolized primarily by the CYP2C19 enzyme, and polymorphisms in this enzyme result in altered pharmacokinetics for PPIs. This, in turn, leads to variability in gastric acid suppression and gastric pH, potentially having an impact on the efficacy of *H. pylori* eradication.

Objective

To determine whether a pharmacogenomics-based treatment regimen is superior to a standard treatment regimen for the eradication of *H. pylori*, and whether the use of a pharmacogenomics-based treatment regimen improves health outcomes compared to standard treatment.

Search Strategy

MEDLINE[®] was searched (via PubMed) using the terms “*Helicobacter pylori*” OR “*H. pylori*” cross-referenced with the terms “pharmacogenetics” OR “pharmacogenomics,” and the term “CYP2C19,” for the time period from 1990 through December 2007, limited to English-language articles on human subjects. Electronic searches were supplemented with the “related articles” function on PubMed for key studies, and with a hand-search of bibliographies from recent review articles and clinical studies.

Selection Criteria

Studies were selected for inclusion in this Assessment that 1) included patients with documented *H. pylori* infection and an indication for eradication of *H. pylori*; 2) was a clinical trial comparing a pharmacogenomics-based treatment regimen for *H. pylori* with a standard treatment regimen; and 3) reported on one or more relevant clinical outcomes.

Main Results

A single randomized, controlled trial was identified that met the inclusion criteria. This study randomized 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% CI: 91.5–98.2%) in the pharmacogenomics-based treatment 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

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pharmacogenomics group was greater for extensive metabolizer (EM) patients (100% vs. 58%) and intermediate metabolizer (IM) patients (95% vs. 72%), compared to poor metabolizer (PM) patients (91% vs. 91%). Eradication rates also varied by clarithromycin-resistance status, with particularly low eradication rates occurring in the standard treatment group for patients with clarithromycin resistance (0%) and IM patients with clarithromycin resistance (48%).

Patients who failed eradication following first-line treatment were treated again. By intention-to-treat analysis, eradication rates following repeated 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 ($p = \text{NS}$).

Author's Conclusions and Comments

This study demonstrates how pharmacogenomics can be used to individualize medication regimens, and how a clinical trial can be constructed to evaluate the impact of a pharmacogenomics-based treatment approach. This study is also notable in that it addresses a common, real-life clinical problem, and uses commercially available technology for pharmacogenomics-based decision-making. The optimal clinical trial for evaluating the utility of a pharmacogenomics-based *H. pylori* treatment regimen would isolate the impact of treatment changes made as a result of genetic status. Ideally, such a trial would be done in the U.S. in a population with rates of CYP2C19 polymorphisms approximating that of the general U.S. population. Also, the ideal trial would use an approach to diagnosing *H. pylori* that reflects usual care in the U.S. and would use a standard treatment regimen recommended for U.S. patients.

While the single available randomized, controlled trial reports an increased rate of *H. pylori* eradication in the pharmacogenomics strategy compared with a standard approach, this study does not meet the parameters for an optimal trial. The protocol for this trial includes changes in treatment regimen that are unrelated to genetic status, particularly regarding clarithromycin resistance. In addition, the study was performed in a Japanese population and did not employ a diagnostic approach or a treatment regimen that is standard care in the U.S.

The numerous variations in treatment regimen within the experimental group make it difficult to isolate the impact of genetic status on outcome, apart from other modifications in the treatment regimen, that 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. From the data reported in the study, it is not possible to separate the potential impact of clarithromycin resistance on eradication rates from the impact of tailored PPI dosage schedules.

In addition to the limitations on internal validity, the clinical relevance of the study is also limited for several reasons. The treatment approach used was relatively intensive, including genetic testing for CYP2C19, EGD with biopsy for all patients, and testing of *H. pylori* isolates for clarithromycin resistance. This treatment approach is much more intensive than generally used in the U.S., where the diagnosis of *H. pylori* is usually made by noninvasive methods and initial empiric treatment is instituted without isolating *H. pylori* or testing for resistance. Furthermore, the patient population was from Japan, limiting the generalizability of the results, especially given the higher prevalence of CYP2C19 polymorphisms in the Asian population compared to that in Caucasian populations.

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, might also be justified given that there is no

reason to suspect that the use of omeprazole or lansoprazole offer other advantages. Ideally, a future clinical trial will evaluate whether a tailored pharmacogenomics approach is superior to other empiric approaches such as these.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether the use of a pharmacogenomics-based treatment regimen for *H. pylori* meets the Blue Cross and Blue Shield Association's Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

At least one commercially available genetic test, the Roche AmpliChip® CYP450 test, has been cleared for diagnostic use by the U.S. Food and Drug Administration (FDA). This test examines polymorphisms in CYP2D6 and CYP2C19 isoenzymes of the cytochrome P450 enzyme system. Clearance for this device was originally granted in December 2004 as an aid in determining treatment choice and individualizing treatment dose for therapeutics that are metabolized primarily by the CYP2D6 enzyme. Subsequent clearance for CYP2C19 testing was granted in January 2005.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

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 was 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.

3. The technology must improve the net health outcome; and

4. The technology must be as beneficial as any established alternatives.

It cannot be determined whether pharmacogenomics-based treatment of *H. pylori* improves the net health outcome, nor whether pharmacogenomics-based treatment of *H. pylori* is as beneficial as any established alternatives, since the evidence is not sufficient to permit conclusions on its effect on health outcomes.

5. The improvement must be attainable outside the investigational settings.

It cannot be determined whether improvement is attainable outside the investigational setting since the evidence is not sufficient to permit conclusions on the effect of pharmacogenomics-based treatment for *H. pylori* on health outcomes.

For the above reasons, the use of a pharmacogenomics-based treatment regimen for *H. pylori* does not meet the TEC criteria.

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Assessment Objective

The overall objective of this Assessment is to determine whether a pharmacogenomics-based treatment regimen is superior to a standard treatment regimen for the eradication of *Helicobacter pylori*, and whether the use of a pharmacogenomics-based treatment regimen improves health outcomes compared to standard treatment.

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. Eradication requires an intensive antibiotic regimen combined with a proton pump inhibitor (PPI), or similar medication(s), to suppress gastric acid production. Genetic factors may influence the success of *H. pylori* treatment through effects on PPI metabolism. PPIs are metabolized by CYP2C19, a member of the cytochrome P450 enzyme family. Individuals with polymorphisms in the CYP2C19 gene metabolize PPIs more slowly than normal. 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.

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 in order 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.

Background

Pharmacogenomics is the study of genetic influences on response to pharmacologic agents. Individual responses to drugs vary considerably. While there are large population differences in

response to pharmacologic agents, variability in metabolism of drugs within individuals are comparatively much smaller. This suggests a genetic basis underlying the variable response to drugs (Evans and McLeod 2003).

It has been estimated that between 20–95% of variability in drug pharmacokinetics and pharmacodynamics can be explained by genetics. The differences in response to drugs may involve variants in genes that code for the metabolism, transport and/or receptors for drugs (Evans and McLeod 2003). The clinical importance of genetic variations may be related to differences in the efficacy of an agent or differences in the susceptibility to adverse effects (Roden et al. 2006).

Pharmacogenomics, therefore, offers the opportunity to optimize and individualize pharmacologic treatment according to genetic parameters. The selection of a particular medication, and/or the dosing of a particular medication, can be potentially based on genetic information. Theoretically, pharmacogenomic-based prescribing can eventually lead to optimal efficacy for a drug and/or a reduced risk for serious adverse effects (Roden et al. 2006).

Helicobacter pylori Infection

H. pylori infection is endemic worldwide, with up to 50% of the world's population infected (Ables 2007). In North America, it is estimated that approximately 30% of adults are infected with *H. pylori*. Risk factors for infection include poor socioeconomic conditions, family overcrowding, and genetic/ethnic factors (Ables et al. 2007).

H. pylori has emerged over the last two decades as an important pathogen associated with a variety of medical disorders. First described as a causative agent in peptic ulcer disease, it has since been associated with a number of other GI disorders such as atrophic gastritis and GI malignancy. It has also been implicated in some non-GI disorders such as idiopathic thrombocytopenic purpura and iron deficiency anemia (Malfertheiner et al. 2007).

Diagnosis of *H. pylori* can be made by a variety of methods. The gold standard for diagnosing active infection is endoscopy with biopsy of the gastric mucosa. *H. pylori* can be identified on biopsy specimens by the rapid urease test, or by culture. However, there are also noninvasive methods of diagnosis, which are

more commonly used in the U.S. for establishing the diagnosis of *H. pylori* infection. Serum antibodies to *H. pylori* are a sensitive method of diagnosing exposure to *H. pylori*, but do not distinguish between past exposure and active infection. The ¹⁵C urea breath test detects metabolites of the *Helicobacter* bacterium, and can distinguish between past and current infection. Stool antigen testing for *H. pylori* is also available and is an alternative method for making the diagnosis in a noninvasive manner.

The eradication of *H. pylori* is an important component of treatment for peptic ulcer disease and other gastrointestinal disorders. The majority of patients with peptic ulcer disease in the U.S. are infected with *H. pylori*. Eradication of *H. pylori* leads to a lower incidence of recurrent ulcers and GI bleeding in patients with peptic ulcer disease and *H. pylori* infection. Eradication of *H. pylori* is also considered useful in a variety of other gastrointestinal disorders such as gastric lymphoma, and some non-GI disorders such as chronic urticaria and idiopathic thrombocytopenic purpura (Furuta et al. 2007).

There are currently multiple regimens for treating *H. pylori* infection. These include a PPI to suppress acid production, in combination with antibiotic treatment, consisting of one or more agents such as amoxicillin,

clarithromycin, or metronidazole (Table 1). 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* (Chey et al. 2007). 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 (Duck et al. 2004). Some experts believe that the increasing rate of clarithromycin resistance will reduce the success rates for current first-line regimens and may necessitate changes in treatment guidelines in the near future (Chey et al. 2007).

Second-line treatment regimens are successful in the majority of patients who fail to experience eradication of *H. pylori* after first-line treatment. The most common second-line regimens are quadruple therapy with bismuth subsalicylate, an acid blocker, and two antibiotics. A recent meta-analysis of 16 studies estimated

Table 1. First-Line Regimens for Eradication of *H. pylori* (adapted from Chey et al. 2007)

Medications	Duration	Eradication Rates	Comments
Standard dose PPI twice daily Clarithromycin 500 mg twice daily Amoxicillin 1,000 mg twice daily	10–14 days	70–85%	Targeted for patients who are not penicillin allergic and have not previously received a macrolide
Standard dose PPI twice daily Clarithromycin 500 mg twice daily Metronidazole 500 mg twice daily	10–14 days	70–85%	Targeted for patients who are CN allergic and have not previously received a macrolide, or who are unable to tolerate bismuth
Standard dose PPI daily or twice daily (or ranitidine 150 mg twice daily) Bismuth subsalicylate 525 mg daily Metronidazole 250 mg daily Tetracycline 500 mg daily	10–14 days	75–90%	Targeted for penicillin allergic patients who are able to tolerate bismuth
PPI Amoxicillin 1,000 mg twice daily followed by: PPI Clarithromycin 500 mg twice daily Tinidazole 500 mg twice daily	5 days 5 days	>90%	Newer regimen Not well validated in North American populations

that *H. pylori* was eradicated in 76% of patients treated with a second-line regimen (Hojo et al. 2001). Failure to respond to two or more treatment regimens is an indication for esophago-gastroduodenoscopy (EGD) with culture for *H. pylori*, and further treatment directed by antibiotic sensitivities.

Genetic Polymorphisms of CYP2C19

Genetic variation in the cytochrome P450 (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 (Roden et al. 2006). PPIs are metabolized by the CYP450 system, and the principal enzyme responsible for metabolism of PPIs is CYP2C19.

There are three major CYP2C19 alleles that determine enzymatic activity, as shown in Table 2. 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 that produce enzymes having no activity. Each null allele is caused by a single nucleotide change that results in a splice defect or an abnormally early stopping point during gene transcription into messenger RNA (mRNA). The protein translated from the abnormal mRNA lacks normal activity (AmpliChip® package insert 2006).

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 3). Heterozygous genotypes are found in 27–37% of the Caucasian population and 46–50% of the Asian population (Gillen 2005). These patients have a minor reduction in their ability to eliminate PPIs, and are called intermediate metabolizers (IM) (Table 3). Patients who are homozygous for null polymorphisms of the CYP2C19 gene are found in 3–6% of Caucasians and in 12–20% of Asians (Gillen 2005). These patients eliminate PPIs from the circulation much more slowly than EM or IM patients, and are termed poor metabolizers (PM) (Table 3).

In patients treated with PPIs, intragastric pH has been shown to correlate with CYP2C19 status. Patients homozygous for a CYP2C19 polymorphism (PM) exhibit a less acidic pH when compared to patients without a CYP2C19 mutation, or with heterozygous patients exhibiting intermediate metabolic capacity (Furuta et al. 2005). 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

Table 2. CYP2C19 Polymorphisms¹

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

Table 3. CYP2C19 Phenotypes¹

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

¹Adapted from AmpliChip® package insert

EM extensive metabolizers
IM intermediate metabolizers
PM poor metabolizers

more successful if there is maximal suppression of gastric acid production and higher intragastric pH levels (Furuta et al. 2005).

Observational research has suggested that there is a correlation between CYP2C19 status and success rates for eradication of *H. pylori*. Tables 4 and 5 show a representative sample of these types of studies. For the most part, they are clinical trials of different regimens for *H. pylori* eradication in which CYP2C19 status was evaluated as a secondary objective. The studies are separated into trials that did not use rabeprazole (Table 4) and trials that did use rabeprazole (Table 5), since rabeprazole is not metabolized by the CYP2C19 enzyme.

The majority of studies that did not use rabeprazole reported lower eradication rates in extensive metabolizers compared with poor metabolizers (Table 4). As shown in these trials, 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 IM patients generally intermediate between the two.

For trials that used rabeprazole (Table 5), eradication rates according to CYP2C19 group were generally similar, although at least one study did report lower eradication rates for EM patients (Furuta et al. 2001a). Rabeprazole is the only PPI that is not metabolized by the CYP2C19 enzyme, and therefore eradication rates with regimens including rabeprazole may not vary according to CYP2C19 status.

A recent meta-analysis (Padol et al. 2006) 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 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 (85%), 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%). The difference in eradication rates was less pronounced for lansoprazole (88% vs. 74%), and least evident for rabeprazole (81% vs. 77%).

Genetic Testing for CYP2C19 Status

A CYP2C19 genotype test has been commercially available since December 2004 through Roche Diagnostics. The AmpliChip® CYP450 test detects known polymorphisms of two isoenzymes of the CYP450 system, CYP2D6 and CYP2C19. This system uses DNA extracted from whole blood and a PCR-based GeneChip Microarray Instrumentation system to determine the presence or absence of genetic polymorphisms (AmpliChip® package insert 2006).

For the CYP2C19 gene, the test examines for the two common polymorphisms associated with enzymatic activity (Table 2). Information from the manufacturer claims greater than 99% accuracy in detecting these common polymorphisms (AmpliChip® package insert 2006). However, there are a number of rare polymorphisms that have been identified that are not detected by the AmpliChip® system (AmpliChip® package insert 2006). The results of the test are included in a report to the ordering physician that includes potential clinical implications of the result.

FDA Status. The Roche AmpliChip® CYP450 test has been cleared for marketing by the FDA via 510(k) (<http://www.fda.gov/cdrh/mda/docs/k042259.html>). This test examines polymorphisms in CYP2D6 and CYP2C19 isoenzymes of the cytochrome P450 enzyme system. Clearance for this device was originally granted in December 2004 as an aid in determining treatment choice and individualizing treatment dose for therapeutics that are metabolized primarily by the CYP2D6 enzyme. Subsequent clearance for CYP2C19 testing was granted in January 2005.

Methods

Search Methods

MEDLINE® was searched (via PubMed) using the terms “*Helicobacter pylori*” OR “*H. pylori*” cross-referenced with the terms “pharmacogenetics” OR “pharmacogenomics,” and the term “CYP2C19.” Search was performed for the time period from 1990 through December 2007, and was limited to English-language articles on human subjects. Electronic searches were

Table 4. Correlation of CYP2C19 Genetic Status with Eradication Rates for *H. pylori* (Studies not Using Rabeprazole)

Study/Year	Patient Population	Treatment Regimen	<i>H. pylori</i> Eradication Rates			Comments
			EM	IM	PM	
PPI Regimens not Containing Rabeprazole						
Sheu et al. 2005	93 Chinese patients with <i>H. pylori</i> infection and dyspepsia randomized to omeprazole arm of a randomized, controlled trial comparing different PPI doses	omeprazole 20 mg twice daily (7 days) clarithromycin 500 mg twice daily (7 days) amoxicillin 1000 mg twice daily (7 days)	63%	87%	100%	
Okudaira et al. 2005	87 Japanese patients with <i>H. pylori</i> infection and peptic ulcer disease or gastritis randomized to PPI only arm of PPI with or without famotidine	lansoprazole 30 mg twice daily (7 days) clarithromycin 200 mg three times daily amoxicillin 500 mg three times daily	76%	90%	96%	
Schwab et al. 2004	131 untreated <i>H. pylori</i> -positive patients from Germany enrolled in clinical trial of different treatment regimens; drawn from 243 total patients	Patients randomized to one of three different regimens for treatment of <i>H. pylori</i>	80.2%	*	98%*	* IM and EM groups combined for analysis due to small number of patients (n=3) in IM group p<0.01
Sapone et al. 2003	143 consecutive Italian patients with GI complaints referred for EGD and found to be <i>H. pylori</i> positive	omeprazole 20 mg twice daily (7 days) clarithromycin 500 mg twice daily (7 days) amoxicillin 1000 mg twice daily (7 days)	60% (70/116)	84% (21/25)	100% (2/2)	
Furuta et al. 2001b	271 patients with ulcers or gastritis and <i>H. pylori</i> positive, enrolled in a randomized, controlled trial comparing omeprazole and lansoprazole	omeprazole 20 mg twice daily (7 days); OR lansoprazole 30 mg twice daily (7 days) clarithromycin 200 mg three times daily amoxicillin 500 mg three times daily	73% (/88)	92% (/126) p<0.001	98% (/46) p<0.001	
Furuta et al. 1998	62 patients from Japan with peptic ulcer disease and <i>H. pylori</i> positive	omeprazole 20 mg daily (6 weeks) amoxicillin 500 mg four times daily (14 days)	29% (8/28)	60% (15/25) p=0.03	100% (9/9) p<0.001	

Table 5. Correlation of CYP2C19 Genetic Status with Eradication Rates for *H. pylori* (Studies Using Rabeprazole)

Study/Year	Patient Population	Treatment Regimen	<i>H. pylori</i> Eradication Rates			Comments
			EM	IM	PM	
PPI Regimens Containing Rabeprazole						
Kawabata et al. 2003	187 consecutive patients with peptic ulcer disease and <i>H. pylori</i> positive, enrolled in a randomized, controlled trial of lansoprazole vs. rabeprazole	lansoprazole 30 mg twice daily (7 days); OR rabeprazole 10 mg twice daily (7 days) clarithromycin 400 mg twice daily (7 days) amoxicillin 750 mg twice daily (7 days)	79% (50/63)	78% (69/88)	73% (16/22)	No difference in eradication rates between groups. Eradication better in clarithromycin-sensitive vs. -resistant strains (86% vs. 24%, p<0.05).
Miki et al. 2003	145 patients with peptic ulcer disease and <i>H. pylori</i> positive, enrolled in a randomized, controlled trial of lansoprazole vs. rabeprazole	lansoprazole 30 mg twice daily (7 days); OR rabeprazole 10–20 mg twice daily (7 days) clarithromycin 400 mg twice daily (7 days) amoxicillin 1000 mg twice daily (7 days)	89% (39/44)	89% (64/72)	77% (17/22)	No difference in eradication rates between groups. Eradication dependent on clarithromycin sensitivity with only 1/16 clarithromycin-resistant strains eradicated.
Furuta et al. 2001a	101 patients from Japan with gastritis and <i>H. pylori</i> positive	rabeprazole 10 mg twice daily (14 days) amoxicillin 500 mg three times daily (14 days)	61% (/33)	92% (/48)	93% (/16)	p value for differences between groups on ANOVA, p<0.001.
Miyoshi et al. 2001	199 patients with peptic ulcer disease and <i>H. pylori</i> positive, enrolled in a randomized, controlled trial of omeprazole vs. rabeprazole	omeprazole 20 mg twice daily; OR rabeprazole 10 mg twice daily amoxicillin 500 mg three times daily	72% (42/58)	72% (60/83)	79% (26/33)	No difference in eradication rates between groups. Smoking only independent predictor of treatment failure.

supplemented with the “related articles” function on PubMed for key studies, and with a hand-search of bibliographies from recent review articles and clinical studies. Searches for web-based information were initiated through the website, www.genetests.org.

Study Selection

Studies were selected for inclusion in this Assessment that met the following criteria:

- Full-length publications, published in a peer-reviewed journal in the English language.
- Included patients with documented *H. pylori* infection and an indication for eradication of *H. pylori*.
- Clinical trial comparing a pharmacogenomics-based treatment regimen for *H. pylori* with a standard treatment regimen.
- Reported on one or more relevant clinical outcomes:
 - *H. pylori* eradication rates
 - disease recurrence following treatment
 - morbidity and/or mortality of *H. pylori*-associated disorder
 - adverse effects of treatment for *H. pylori*

Study Quality Assessment

Study quality for clinical trials was formally assessed as per the approach outlined by the U.S. Preventive Services Task Force (USPSTF; Harris et al. 2001). In this approach, 5 quality indicators are assessed as met or not met. These are:

- Initial assembly of comparable groups (adequacy of randomization, allocation concealment, and equal distribution of confounders among groups);
- Maintenance of comparable groups (attrition, crossovers, contamination, non-adherence);
- Comparable performance of and clear definition of interventions with equivalent attention and quality of care;
- Comparable measurements: unbiased, reliable, and valid (includes masking of outcome assessment);
- Appropriate analysis of outcomes. Intent-to-treat analysis for randomized, controlled trials, consideration of confounding variables in nonrandomized studies. All important outcomes considered.

An overall level of quality of “good” (meets all criteria), “fair” (does not meet all criteria but no “fatal flaws”), or “poor” (has “fatal flaws”) is assigned based on these 5 parameters.

Medical Advisory Panel Review

This Assessment was reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on February 12, 2008. In order to maintain the timeliness of the scientific information in this Assessment, literature searches were performed subsequent to the Panel’s review (see “Search Methods”). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the tables and text where appropriate.

Formulation of the Assessment

Patient Indications

The relevant patient population is patients with active *H. pylori* infection and an indication for eradication of *H. pylori*. The distribution of *H. pylori*-associated disorders and indications for eradication will vary according to the patient population treated. In Caucasian patients from the U.S., the most common indications are peptic ulcer disease and chronic gastritis. In Asian populations, the prevalence of GI malignancy is higher. For the purpose of this Assessment, the relevant population will include individuals with *H. pylori* infection and at least one condition for which *H. pylori* eradication is indicated, and who have not previously been treated for *H. pylori*.

Technologies to be Compared

Pharmacogenomics-based treatment regimen(s) will be compared to standard treatment regimens for *H. pylori*. There are a number of standard treatment regimens that are commonly used in clinical practice; these include an intensive antibiotic regimen in combination with a PPI to suppress acid production.

Health Outcomes

The primary outcome to be evaluated will be successful eradication of *H. pylori*. Successful eradication of *H. pylori* has been proven to reduce the recurrence of gastritis and peptic ulcer disease and to reduce future GI bleeding associated with peptic ulcer disease. Improved rates of *H. pylori* eradication will therefore improve health outcomes by reducing disease recurrence and reducing the need for retreatment.

Specific Assessment Questions

Does use of a pharmacogenomics-based treatment regimen for *H. pylori* lead to improved eradication rates compared with a standard treatment regimen?

Does use of a pharmacogenomics-based treatment regimen for *H. pylori* improve overall health outcomes compared with a standard treatment regimen?

Review of Evidence

A single randomized, controlled trial (RCT) was identified that met the inclusion criteria (Furuta et al. 2007) (Table 6). This RCT compared a pharmacogenomics-based treatment regimen for *H. pylori* with a standard treatment regimen. Three hundred Japanese patients were enrolled into this study. Patients were older than 15 years of age with *H. pylori* infection and at least one documented *H. pylori*-associated GI disorder (gastritis (n=144); gastric ulcer (n=88); duodenal ulcer (n=60); or gastroduodenal ulcer (n=8)).

All patients underwent EGD and biopsy of the gastric mucosa for *H. pylori*. Genetic testing was performed on *H. pylori* isolates in order to determine sensitivity to clarithromycin. Genetic testing was also performed on DNA extracted from tissue samples obtained at EGD to determine CYP2C19 genetic status. Patients were classified into three genetic groups: extensive metabolizers (EM), intermediate metabolizers (IM), and poor metabolizers (PM).

Patients were randomized to a pharmacogenomics-based treatment regimen or to a standard treatment regimen for *H. pylori*. In the standard treatment group, patients were treated for one week with a regimen consisting of lansoprazole 30 mg twice daily, clarithromycin 400 mg twice daily, and amoxicillin 750 mg twice daily, regardless of genetic status. In the pharmacogenomics group, the treatment regimen was adjusted based on genetic status (Figure).

Three groups were defined by genetic status. Extensive metabolizers (EM) were patients with no mutation in the CYP2C19 gene, intermediate metabolizers (IM) were patients heterozygous for a CYP2C19 polymorphism, and poor metabolizers (PM) were homozygous for a CYP2C19 polymorphism. The dose of lanso-

prazole was adjusted according to the CYP2C19 status. EMs received a dose of 30 mg three times daily; IMs received 15 mg three times daily; and PMs received a dose of 15 mg twice daily. The antibiotic regimen was adjusted according to the genetic status for clarithromycin sensitivity. Patients with clarithromycin sensitivity received both clarithromycin 200 mg three times daily and amoxicillin 500 mg three times daily. Patients with genetic status indicating clarithromycin resistance received only amoxicillin at a dose of 500 mg four times daily. This resulted in six distinct treatment regimens that varied in the dose of PPI and the antibiotic regimen used (Figure).

The rationale for the specific adjustments made in PPI dosing by CYP2C19 status was partially based on empiric evidence from prior research and partially from a preliminary study performed prior to the RCT. From previous research, the authors determined that PPI regimens that resulted in intragastric pH in the 5.0-5.8 range were associated with high eradication rates. The authors then measured 24-hour intragastric pH according to lansoprazole dose and CYP2C19 genetic status, selecting doses of lansoprazole for each group that resulted in pH levels within the 5.0-6.0 range.

Evaluation of *H. pylori* eradication was performed one month following treatment. Repeat EGD with biopsy was performed to determine whether *H. pylori* was still present. A second test, the ¹⁵C-urea breath test was also used for detection of *H. pylori*. *H. pylori* was considered eradicated if both the biopsy specimen and the breath test were negative. If either test was positive, then *H. pylori* was considered to still be present.

Formal quality assessment was performed according to the methods of Harris et al. (2001; Table 7). A quality score of "fair" was assigned since the study did not meet all quality parameters, but did not contain any fatal flaws. The two quality parameters that were not met were maintenance of comparable groups and comparability of interventions. There were more patients lost to follow-up in the standard-therapy group, especially after retreatment of initial treatment failures (12/150 vs. 3/150). The treatment protocol in the experimental group contained numerous variations in medication protocol, including dose, interval, and length of antibiotic treatment. This created difficulties in isolating the effect of treatment decisions made

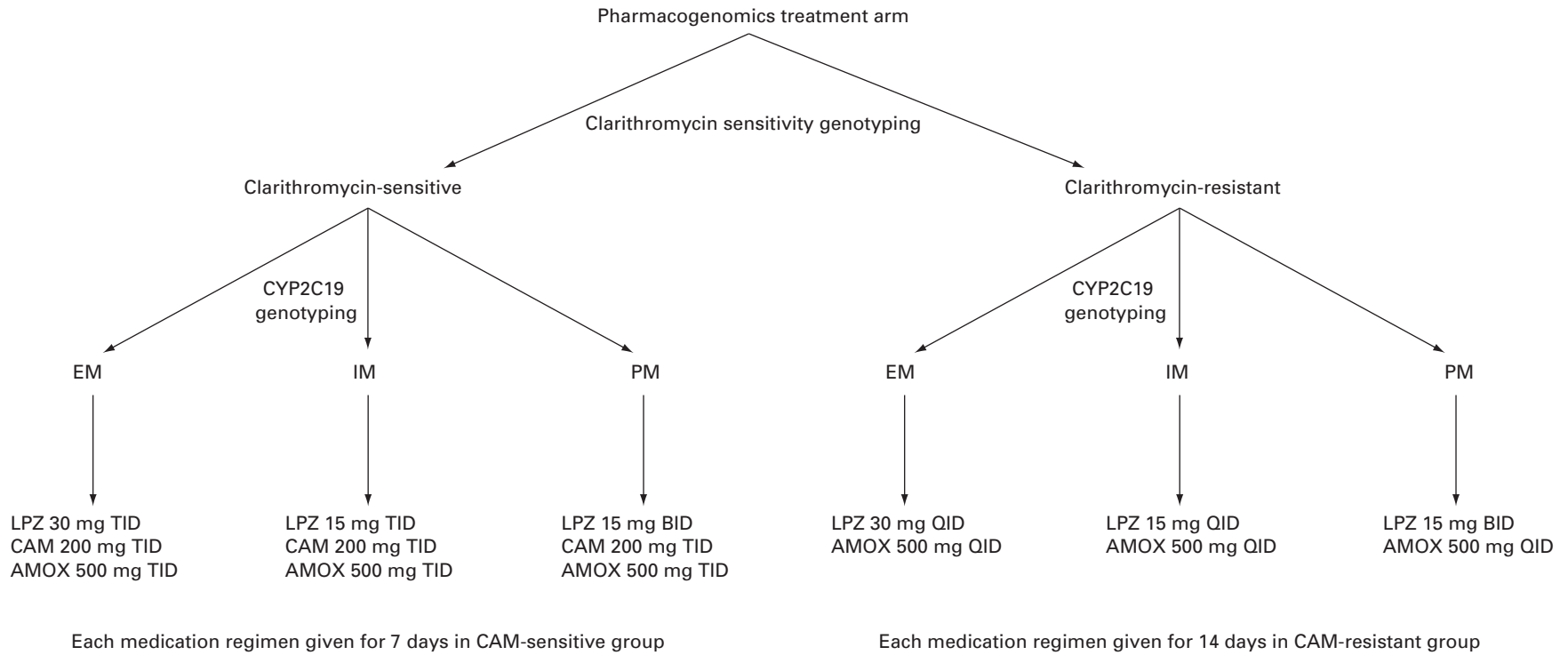
Table 6. Randomized, Controlled Trial Evaluating Pharmacogenomics-Based Treatment Regimen – Study Characteristics

Study/Yr	Patient Population	Treatment Groups	Treatment Regimen	Outcomes Reported
Furuta et al. 2007	300 Japanese patients seen at one medical center between 2003–2005 who were: – older than 15 years – <i>H. pylori</i> -positive by EGD and biopsy – At least one <i>H. pylori</i> -associated GI disorder (gastritis, n=144; gastric ulcer, n=88; duodenal ulcer, n=60; gastroduodenal ulcer, n=8)	Pharmacogenomics	Medication regimen adjusted for genetic status, resulting in six distinct treatment groups (see Figure)	<i>H. pylori</i> eradication rates (after initial treatment)
		Standard	lansoprazole 30 mg twice daily (7 days) clarithromycin 400 mg twice daily (7 days) amoxicillin 750 mg twice daily (7 days)	<i>H. pylori</i> eradication rates (after retreatment)

Abbreviations

EGD esophagogastroduodenoscopy

Figure. Treatment Algorithm for the Pharmacogenomics Treatment Arm



AMOX amoxicillin
 BID twice daily
 CAM clarithromycin
 EM extensive metabolizers
 IM intermediate metabolizers
 LPZ lansoprazole
 PM poor metabolizers
 QID four times daily
 TID three times daily

Table 7. Quality Assessment for Furuta et al. 2007

Study/Year	Initial Assembly of Comparable Groups	Maintenance of Comparable Groups	Comparable Intervention(s)	Comparable Measurements	Appropriate Analysis of Outcomes	OVERALL QUALITY LEVEL
Furuta et al. 2007	YES	NO Higher dropout rate in control group (12/150, 8.0%) compared with experimental group (3/150, 2.0%)	NO Numerous variations in protocol within experimental group creating difficulties in assessing comparability of interventions	YES	YES	FAIR Study does not meet all quality criteria but does not contain any "fatal flaws"

on the basis of CYP2C19 status from the effect of other differences in treatment protocol.

A total of 293 out of 300 patients completed the study. Seven patients (6 in standard treatment group, 1 in pharmacogenomics group) did not complete the initial treatment protocol due to poor compliance (i.e., less than 80% of prescribed medications taken) or loss to follow-up. An additional 7 patients (6 in the standard treatment group, 1 in the pharmacogenomics group) who were initial treatment failures did not complete retreatment.

Results are summarized in Tables 8 and 9. Overall *H. pylori* eradication rates at 1 month were 96% (95% CI: 91.5–98.2%) in the pharmacogenomics-based treatment group versus 70% (95% CI: 62.2–77.2%) in the standard-therapy group (Table 8). The difference in eradication rates was significant at the $p < 0.001$ level. When analyzed according to genetic status, the improvement in eradication rates in the pharmacogenomics group was greater for EM patients (100% vs. 58%) and IM patients (95% vs. 72%), compared to PM patients (91% vs. 91%) (Table 9). 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%; Table 9).

Patients who failed eradication following first-line treatment were retreated, and eradication rates following retreatment were compared among groups (Table 8). By intent-to-treat analysis, eradication rates following retreatment were 97.8% for the pharmacogenomics group (95% CI: 94.3–99.6%) compared to 88% for the standard-regimen group (95% CI: 81.7–92.7%). However, there were more patients lost to follow-up in the standard-treatment group (12 versus 2) and all patients lost to follow-up were counted as treatment failures. This approach to analysis favored the pharmacogenomics group. Accordingly, when the retreatment data were analyzed as per-protocol, the eradication rates were 99.3% for the pharmacogenomics group (95% CI: 96.3–100%) compared to 95.7% for the standard-treatment group (95% CI: 90.8–98.4%), and this difference between treatment groups was not statistically significant.

Discussion

This study is an example of how pharmacogenomics can be used to individualize medication regimens with the goal of optimizing benefit and minimizing risk, and how a clinical trial can be constructed to evaluate the impact of a pharmacogenomics-based treatment approach. This study is also notable in that it addresses a common, real-life clinical problem, and uses commercially available technology for pharmacogenomics-based clinical decision-making.

For this clinical problem, i.e., the eradication of *H. pylori*, there is a relatively strong rationale for use of a pharmacogenomics-based treatment approach. Genetic research has confirmed that common polymorphisms exist in the CYP2C19 gene that impact metabolism of PPI drugs and the extent of gastric acid suppression. Basic science research has, in turn, elucidated pathophysiologic mechanisms by which variable gastric acid suppression and variable gastric pH might impact efficacy of *H. pylori* eradication. Observational research has confirmed that individuals who are extensive metabolizers of PPIs have *H. pylori* eradication rates that are lower compared to individuals who are poor metabolizers of PPIs.

While this study reports a significantly increased rate of *H. pylori* eradication in the pharmacogenomics strategy compared with a standard approach, the data do not provide definitive evidence that use of a pharmacogenomics-based treatment regimen improves health outcomes. The main limitation to internal validity in this study is the inability to isolate the specific factor(s) that resulted in superior eradication rates for the pharmacogenomics group, due to numerous variations in the treatment protocol within the pharmacogenomics group.

In the pharmacogenomics group, the treatment regimen varied both as a function of the patients' genetic status (CYP2C19 status) and as a function of sensitivity of the *H. pylori* bacterium to clarithromycin. This resulted in six distinct treatment regimens in the pharmacogenomics group, which varied on a number of factors including PPI dose, antibiotics used and antibiotic dose, and length of treatment. The researchers also introduced other minor variations in the treatment regimen for unclear reasons, possibly convenience. For example, among patients in the pharmacogenomics

Table 8. Randomized, Controlled Trial Evaluating Pharmacogenomics-based Treatment Regimen – Study Outcomes

Study/Year	Follow-up	Treatment Groups	Initial Treatment		Retreatment	
			ITT	PP	ITT	PP
Furuta et al. 2007	1 month	Pharmacogenomics	96% (144/150)	97% (144/149)	99% (147/150)	99% (147/148)
		Standard	70% (105/150)	73% (105/144)	88% (132/150)	96% (132/138)
			p<0.001	p<0.001	p<0.001	p=NS

Abbreviations

ITT intent-to-treat analysis
 PP per-protocol analysis

Table 9. *H. pylori* Eradication Rates by Antibiotic Resistance/Sensitivity and CYP2C19 Status

Study/Year	Treatment Group	All Patients			Clarithromycin-sensitive			Clarithromycin-resistant		
		EM	IM	PM	EM	IM	PM	EM	IM	PM
Furuta et al. 2007	Pharmacogenomics	100% (54/54)	95% (69/73)	91% (21/23)	100% (37/37)	94% (50/53)	93% (14/15)	100% (17/17)	95% (19/20)	88% (7/8)
	Standard	58% (30/52)	72% (53/74)	91% (22/24)	73% (30/41)	82% (42/51)	100% (14/14)	0% (0/11)	48% (11/23)	80% (8/10)

group, the PPI doses in the EM and IM groups were different for patients with and without clarithromycin resistance (30 mg three times daily vs. 30 mg four times daily; and 15 mg three times daily vs. 15 mg four times daily, respectively).

The numerous variations in treatment regimen for the experimental group make it difficult to isolate the specific aspects of the treatment regimen that may have led to benefit. While it is possible that the changes in PPI dose according to CYP2C19 status were responsible for the improvement in eradication rates, it is not possible to exclude the impact of other factors unrelated to CYP2C19 status. In particular, the influence of clarithromycin resistance on outcomes and a possible interaction between clarithromycin resistance and CYP2C19 status is of concern.

Subgroup analysis examining eradication rates by specific treatment group are shown in Table 9. The greatest improvements in eradication rates for the pharmacogenomics group are seen in the subgroup of patients with clarithromycin-resistance. Particularly striking are the low eradication rates of less than 50% seen in the standard-treatment group for EM patients and IM patients with clarithromycin resistance, much lower than the eradication rates for EM and IM patients with clarithromycin sensitivity. This raises the possibility of an interaction between clarithromycin resistance and CYP2C19 genetic status that is not completely examined in this study.

Furthermore, patients with clarithromycin resistance received 2 weeks of a single antibiotic (amoxicillin) versus one week of dual antibiotic treatment (amoxicillin/clarithromycin) for patients with clarithromycin sensitivity. It is possible that the increased length of treatment was the more important factor in the improved eradication rates for this group, as opposed to the changes made in the PPI regimen based on genetic status.

In addition to limitations of internal validity, there are other factors that limit confidence in the clinical relevance of this study. The treatment approach used was relatively intensive, including genetic testing for CYP2C19, EGD with biopsy for all patients, and testing of *H. pylori* isolates for clarithromycin resistance. This is a much more intensive treatment approach than that generally used in the U.S.

In the U.S., the diagnosis of *H. pylori* is usually made by noninvasive methods and initial empiric treatment instituted without isolating *H. pylori* or testing for resistance.

Also, the study primarily focused on eradication rates after first-line treatment of *H. pylori*. In the U.S., the most common approach to patients who fail first-line treatment is empiric retreatment with a different antibiotic regimen targeting *H. pylori* organisms with clarithromycin resistance. If a patient fails two empiric regimens, then further invasive testing with EGD and testing of *H. pylori* sensitivity is recommended. Therefore, a more relevant clinical comparison would be eradication rates following retreatment of first-line failures for standard regimens versus pharmacogenomics-based regimens.

This comparison was reported as a secondary outcome by Furuta et al., with diminished benefit for the pharmacogenomics group. The eradication rates were higher for the pharmacogenomics group when the data was analyzed by intent-to-treat, but not when analyzed per-protocol. The intent-to-treat analysis favored the pharmacogenomics group since there were a larger number of patients lost to follow-up in the standard-treatment group, and all patients who were lost to follow-up were counted as treatment failures.

The authors did not consider the utilization of a higher dose of PPI in all patients as an alternative strategy. Given that the adverse effect profile of PPIs is relatively benign, and the highest doses used in this study are within the recommended range of PPI dosing, the administration of higher doses to all patients is a defensible strategy that may have little additional risk. This is particularly true for non-Asian populations, for whom the vast majority of patients will be EMs.

Another alternative strategy not addressed by this study is the use of a PPI that is less dependent on CYP2C19 status for efficacy. It has been demonstrated that rabeprazole metabolism is less dependent on the CYP2C19 enzyme than omeprazole and lansoprazole. Therefore, incorporation of rabeprazole into standardized treatment guidelines for eradication of *H. pylori* could eliminate the problem of variable gastric acid suppression seen with other PPIs. However, rabeprazole is a newer agent with limited use to date in the U.S., and it may be premature to replace proven drugs with this agent.

Finally, this study was performed in Japan and therefore has reduced generalizability for patients elsewhere, including the U.S. The prevalence of CYP2C19 polymorphisms is substantially lower in Western populations as compared to Asians. Therefore, the potential utility of testing prior to treatment is less for non-Asian populations. Proportionally fewer patients will be in the PM and IM groups for non-Asian populations, and there will be less inherent variability in PPI response as a result.

Summary of Application of the Technology Evaluation Criteria

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether the use of a pharmacogenomics-based treatment regimen for *H. pylori* meets the Blue Cross and Blue Shield Association's Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

At least one commercially available genetic test, the Roche AmpliChip® CYP450 test, has been cleared for diagnostic use by the U.S. Food and Drug Administration (FDA). This test examines polymorphisms in CYP2D6 and CYP2C19 isoenzymes of the cytochrome P450 enzyme system. Clearance for this device was originally granted in December 2004 as an aid in determining treatment choice and individualizing treatment dose for therapeutics that are metabolized primarily by the CYP2D6 enzyme. Subsequent clearance for CYP2C19 testing was granted in January 2005.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

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 was 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.

3. The technology must improve the net health outcome; and

4. The technology must be as beneficial as any established alternatives.

It cannot be determined whether pharmacogenomics-based treatment of *H. pylori* improves the net health outcome, nor whether pharmacogenomics-based treatment of *H. pylori* is as beneficial as any established alternatives, since the evidence is not sufficient to permit conclusions on its effect on health outcomes.

5. The improvement must be attainable outside the investigational settings.

It cannot be determined whether improvement is attainable outside the investigational setting since the evidence is not sufficient to permit conclusions on the effect of pharmacogenomics-based treatment for *H. pylori* on health outcomes.

For the above reasons, the use of a pharmacogenomics-based treatment regimen for *H. pylori* does not meet the TEC criteria.

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