ORIGINAL RESEARCH

Impact of patient adherence on the cost-effectiveness of noninvasive tests for the initial diagnosis of *Helicobacter pylori* infection in the United States

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Objective: Previous US-based economic models of noninvasive tests for diagnosis of *Helicobacter pylori* infection did not consider patient adherence or downstream costs of continuing infection. This analysis evaluated the long-term cost-effectiveness of the urea breath test (UBT), fecal antigen test (FAT), and serology for diagnosis of *H. pylori* infection after incorporating information regarding test adherence.

Materials and methods: A decision-analytic model incorporating adherence information evaluated the cost-effectiveness of the UBT, FAT, and serology for diagnosis of *H. pylori* infection. Positive test results led to first-line triple therapy; no further action was taken for nonadherence or negative results. Excess lifetime costs and reduced quality-adjusted life-years (QALYs) were estimated for patients with continuing *H. pylori* infection.

Results: In the base-case scenario with estimated adherence rates of 86%, 48%, and 86% for the UBT, monoclonal FAT, and serology, respectively, corresponding expected total costs were US$424.99, $466.41, and $404.98/patient. Test costs were higher for the UBT, but were fully or partially offset by higher excess lifetime costs for the monoclonal FAT and serology. The QALYs gained/patient with the UBT vs monoclonal FAT and serology were 0.86 and 0.27, respectively. The UBT was dominant vs the monoclonal FAT, leading to lower costs and higher QALYs; the UBT was cost-effective vs serology (incremental cost/QALY gained $74).

Conclusion: Based on a comprehensive modeled analysis that included consideration of patient test adherence and long-term consequences resulting from continuing *H. pylori* infection, the UBT provided the greatest economic value among noninvasive tests for diagnosis of *H. pylori* infection, because of high patient adherence and excellent test performance.

Keywords: *Helicobacter pylori*, urea breath test, fecal antigen test, serology, cost-effectiveness, noninvasive diagnostic testing

Introduction

Helicobacter pylori infection is a common chronic infection that is associated with upper gastrointestinal diseases, including chronic gastritis, peptic ulcers, and gastric cancer (GC).[1] The prevalence of *H. pylori* is estimated at ~30% in the adult US population, based on data from the National Health and Nutrition Examination Survey, with higher rates with increasing age.[2] Individuals infected with *H. pylori* have a 15% (vs 4% among noninfected individuals) risk of developing peptic ulcer disease (PUD), and are at tenfold-higher risk of gastric adenocarcinoma.[3,4] A large majority (70%–90%) of patients with PUD are infected with *H. pylori*, and its eradication is an important component of treatment for preventing ulcer recurrence.[5]

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H. pylori infection in the stomach can be detected using invasive (ie, endoscopic) or noninvasive methods. Noninvasive methods have been developed to detect *H. pylori* antibodies in the blood (serology), *H. pylori* antigen in the feces (fecal antigen test [FAT]), and change in concentration of isotopically labeled carbon dioxide in exhaled breath samples as the result of hydrolysis of isotopically labeled urea by urease-containing *H. pylori* in the stomach (urea breath test [UBT]). The American College of Gastroenterology (ACG) and American Gastroenterological Association recommend noninvasive tests for *H. pylori* in dyspeptic patients aged <55 years who do not have alarm features, such as bleeding, early satiety, unexplained weight loss, progressive dysphagia, and family history of gastrointestinal cancer, and then treatment for those who test positive for the infection.[1,6] Among noninvasive tests, both the ACG and American Gastroenterological Association recommend the UBT and FAT over serology, because both these tests detect active *H. pylori* infection, whereas serology is indicative of both current and previous exposures to *H. pylori*.

Several cost-effectiveness analyses comparing different test methods in the diagnosis of *H. pylori* infection have been published.[7–11] These analyses typically indicated that the UBT and FAT were more cost-effective than serology when used individually to detect *H. pylori* infection (as opposed to when a test was used in tandem with another for confirmatory purposes). Some of these analyses also showed higher cost-effectiveness of the FAT over the UBT, because the FAT generally costs less than the UBT, while displaying high sensitivity, specificity, and positive and negative predictive values in diagnostic testing for *H. pylori*.[8,11,12] These analyses did not, however, include patient preference for type of test or patient compliance with/adherence to testing for *H. pylori* infection in their modeling. Several studies have shown low patient preference for or adherence to collecting stool samples for colorectal cancer screening and *H. pylori* testing.[13–15] Patient-adherence rates in collecting stool samples ranged from 18% in colorectal cancer screening with the fecal occult blood test to 48% in posttreatment testing to confirm eradication of *H. pylori* infection.[13,15]

The objective of the present study was to create a robust US-based cost-effectiveness model that incorporates patient adherence to testing for infection to understand the differences (in terms of both health and economic outcomes) among noninvasive tests (UBT, FAT, and serology) for the diagnosis of *H. pylori* infection.

Materials and methods

A decision-analytic model that incorporated patient adherence was developed from a US third-party payer perspective to evaluate the cost-effectiveness of the UBT, monoclonal and polyclonal FATs, and serology in the initial diagnosis of *H. pylori* infection (Figure 1). The model considered only direct health care costs; indirect costs such as lost
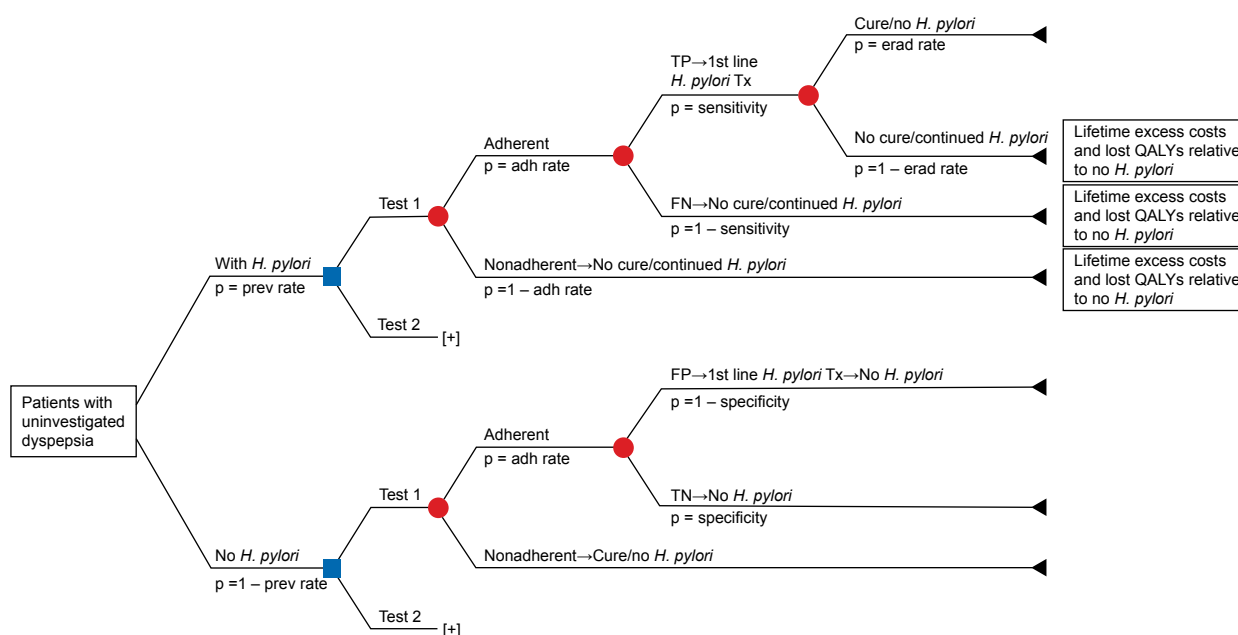

Figure 1 Decision-tree model.
Abbreviations: adh, adherence; erad, eradication; FN, false negative; FP, false positive; p, probability; prev, prevalence; QALYs, quality-adjusted life-years; TN, true negative; TP, true positive; Tx, treatment.

productivity due to treatment and other *H. pylori*-specific impairments were not included. According to US pharmacoeconomic modeling convention, patient copayments were not considered in the cost-effectiveness analysis. The study population consisted of patients aged 18–55 years (average age 35 years) with dyspeptic symptoms, but no gastrointestinal alarm features. In this population, noninvasive *H. pylori*-testing options are preferred to those requiring endoscopy, as recommended in the ACG guidelines.[1]

The decision-analytic model investigated the consequences of choosing between two tests. For each test, the model assumed that patients with positive test results (both true and false positives) received first-line triple therapy for the eradication of *H. pylori* infection. No further action was taken in the model for patients who were nonadherent to testing or who tested negative (both true and false negatives). Excess lifetime costs (LTCs) and reduced quality-adjusted life-years (QALYs) per patient – estimated with respect to patients without *H. pylori* infection – were applied to patients with continuing *H. pylori* infection due to nonadherence, false-negative test results, or treatment failure. The model assumed that true-positive patients respond to first-line treatment, and that no further action was taken for true-negative and false-positive patients without *H. pylori* infection.

Model input parameters included population characteristics, treatment attributes, and data for diseases related to *H. pylori* infection (Table 1). Input parameters for each diagnostic test included its sensitivity, specificity, cost, and rate of adherence to the test (Table 2). The sensitivities and specificities of the UBT, FAT, and serology represent mean values estimated from systematic reviews or meta-analyses evaluating these tests in pretreatment diagnosis of *H. pylori*.[12,16,17] The cost of each test was obtained from the 2014 Resource-Based Relative Value Scale using the Current Procedural Terminology codes indicated in Table 2. The adherence rates of the UBT and FAT (86% and 48%) were determined as the proportion of patients who completed these tests following *H. pylori*-eradication therapy.[13] Due to the lack of published literature on the adherence rate of serology, it was assumed to be the same as that of the UBT, as both require a follow-up visit. Both the monoclonal and polyclonal FATs were considered in the present model. Only information from analyses with the monoclonal FAT are however presented in this manuscript unless specified otherwise, because the monoclonal FAT has higher sensitivity and specificity than the polyclonal FAT (with all other attributes, including cost and adherence, being equal) and can thus be considered to be the better-performing test.

Treatment-related inputs to the model included the cost and eradication rate of first-line triple therapy. The ACG recommends triple therapy with a standard-dose proton-pump inhibitor, amoxicillin 1,000 mg, and clarithromycin 500 mg twice daily for 14 days as first-line treatment of *H. pylori* infection.[1] The cost of this regimen with omeprazole 40 mg/day as the proton-pump inhibitor was determined to be US$205.85 based on average wholesale prices obtained from the Micromedex Red Book (Truven Health Analytics, Ann Arbor, MI, USA). The eradication rate for this 14-day triple-therapy regimen of 81% was obtained from a meta-analysis comparing different durations of therapy.[18]

The *H. pylori* prevalence in the study population was estimated to be 37.4% based on a weighted average of prevalence rates reported for each racial/ethnic group in the 1999–2000 National Health and Nutrition Examination Survey.[19]

Three *H. pylori*-related conditions were considered in the model: GC, PUD, and continuing dyspepsia. Estimates of the excess LTCs for patients with continuing *H. pylori* infection compared with patients without continuing infection were derived from parameters associated with each of these three conditions. For GC, these attributes included lifetime risk of developing GC with or without *H. pylori* infection, median survival with GC, expected LTCs of managing GC, and average time elapsed between diagnosis of *H. pylori* infection and diagnosis of GC. Similar parameters, combined with utility values for each *H. pylori*-related condition, were used to derive the reduced QALYs for patients with continuing *H. pylori* infection relative to patients without continuing infection.

Expected excess LTCs and reduced QALYs due to continuing *H. pylori* infection for each of the three *H. pylori*-related conditions were derived separately and then summed to obtain the total expected excess LTCs and reduced QALYs due to continuing *H. pylori* infection. The following equations describe the derivation of the excess LTCs due to continuing *H. pylori* infection (LTC_{HP}):

$$LTC_{HP} = \sum_{i \in \{GC, PUD, Dysp\}} LTC_i \qquad (1)$$

where Dysp is dyspepsia, and LTC_i is excess LTCs for each *H. pylori*-related disease.

Excess LTCs for each of the three *H. pylori*-related diseases were in turn estimated as cost/patient of managing each disease multiplied by the excess risk associated with developing each disease due to continuing *H. pylori* infection:

Table I Population characteristics, treatment attributes, and data for diseases related to *Helicobacter pylori* infection

Parameter	Value	Variability (range)	Source
Population			
H. pylori prevalence, %	37.4	33.32–41.55	Point estimate based on Cardenas et al;[19] range for SA based on ±20% (assumption)
Expected life-years at age 35 years*	43.6	34.86–52.28	Point estimate from Arias et al;[20] range for SA based on ±20% (assumption)
Treatment attributes			
First-line triple therapy for 14 days			
Efficacy, %	81	77–85	Calvet et al[18]
Cost, US$	205.85	164.68–247.02	Truven Health Analytics[26] for omeprazole, amoxicillin, and clarithromycin for 14 days
Physician visit cost (CPT codes 99214+99244), US$			
PCP visit	107.83	86.26–129.4	Point estimate from OptumInsight;[25] range for SA based on ±20% (assumption)
GI visit	185.92	148.74–223.1	Same as PCP visit
***H. pylori*-related disease parameters**			
Lifetime *H. pylori*-positive outcome probability, %			
Gastric cancer	1	0.5–1.5	Point estimate from Kuipers;[27] range for SA based on ±50% (assumption)
PUD	15	10–20	Point estimate from Peterson et al;[4] range for SA based on ±33.33% (assumption)
Dyspepsia	100	80–100	Clinical expert's input
Lifetime *H. pylori*-negative outcome probability, %			
Gastric cancer	0.1	0.08–0.12	Point estimate based on Kuipers[27] and Kusters et al;[3] range for SA based on ±20% (assumption)
PUD	3.8	3–4.5	Point estimate based on Laine et al[28] and Peterson et al;[4] range for SA based on ±20% (assumption)
Dyspepsia	16.5	6–24	Point estimate based on Kusters et al;[3] range for SA based on range reported in Kusters et al[3]
Median survival, years			
Gastric cancer	2	1.37–2.05	Point estimate based on Davies et al;[29] range for SA based on ±20% (assumption)
Disease duration			
Average time elapsed between diagnosis of *H. pylori* infection and diagnosis of:			
Gastric cancer, years	15	12–18	Estimated based on Asaka et al[30] and Davies et al[29]
Dyspepsia, years	1.55	1.24–1.86	Point estimate based on Chiba et al;[31] range for SA based on ±20% (assumption)
PUD, years	0.5	0.25–0.75	Assumption based on discussion with clinical consultant
Hospitalization due to PUD, days	4.3	3.44–5.16	HCUP with an ICD-9 code of 578.9 (hemorrhage of gastrointestinal tract); range for SA based on ±20% (assumption)
Utility values			
Gastric cancer	0.49	0.17–0.79	Yeh et al;[32] range for SA reported in Yeh et al[32]
PUD	0.92	0.81–0.96	Howard et al;[33] range for SA reported in Howard et al[33]
GI hospitalization due to PUD	0.50	0.4–0.6	Point estimate from Erstad;[34] range for SA based on ±20% (assumption)
Chronic dyspepsia	0.97	0.74–0.98	Point estimate from You et al;[35] range for SA reported in You et al[35]
Associated costs, US$			
Gastric cancer	48,159	44,141–52,086	Estimated based on Yabroff et al[36] and Davies et al;[29] range based on 95% CI reported in Yabroff et al[36]
PUD (managed with medication)	481	385–578	Estimated based on Slawsky et al;[37] range for SA based on ±20% (assumption)
Hospitalization due to PUD	8,896	7,117–10,675	HCUP with an ICD-9 code of 578.9; range for SA based on ±20% (assumption)
Dyspepsia	481	385–578	Estimated based on Slawsky et al;[37] range for SA based on ±20% (assumption)
Reduced QALYs and excess lifetime costs			
Estimated reduced QALYs	6.79	3.82–9.44	Point estimate derived using the *H. pylori*-related disease parameters listed (gastric cancer, PUD and dyspepsia); range for SA estimated from Monte Carlo simulations (generated by sampling from intervals of uncertainty around *H. pylori*-related disease parameters)
Estimated excess LTCs, US$	965	685.51–1,128.21	Same as estimated reduced QALYs

Note: *Life expectancy at age 35 years, which was approximately the midpoint of the age-range of the patient population.
Abbreviations: CI, confidence interval; CPT, Current Procedural Terminology; GI, gastrointestinal; HCUP, Healthcare Cost and Utilization Project; ICD, International Classification of Diseases; LTCs, lifetime costs; PCP, primary care physician; PUD, peptic ulcer disease; QALYs, quality-adjusted life-years; SA, sensitivity analysis.

Table 2 Test characteristics

Parameter	Value	Variability (range)	Source
UBT (CPT codes 83013+83014)			
Sensitivity, %	97.3	77.86–100	Point estimate based on Gisbert and Pajares;[16] range for SA based on ±20% (assumption; upper bound truncated at 100%)
Specificity, %	96.7	77.37–100	Same as UBT sensitivity
Adherence, %	86.2	68.96–100	Point estimate based on Cullen et al;[13] range for SA based on ±20% (assumption; upper bound truncated at 100%)
Cost, US$	102.81	82.25–123.37	Point estimate derived from OptumInsight;[25] range for SA based on ±20% (assumption)
Monoclonal FAT (CPT code 87338)			
Sensitivity, %	96	76.8–100	Point estimate from Gisbert and Pajares;[12] range for SA based on ±20% (assumption; upper bound truncated at 100%)
Specificity, %	97	77.6–100	Same as monoclonal FAT sensitivity
Adherence, %	48.3	38.64–57.96	Point estimate based on Cullen et al;[13] range for SA based on ~±20% (assumption)*
Cost, US$	19.7	15.76–23.64	Point estimate derived from OptumInsight;[25] range for SA based on ±20% (assumption)
Polyclonal FAT (CPT code 87338)			
Sensitivity, %	91	90–91	Point estimate from Gisbert and Pajares;[12] range for SA reported in Gisbert and Pajares[12]
Specificity, %	93	93–94	Same as polyclonal FAT sensitivity
Adherence, %	48.3	38.64–57.96	Point estimate based on Cullen et al;[13] range for SA based on ~±20% (assumption)*
Cost, US$	19.7	15.76–23.64	Point estimate derived from OptumInsight;[25] range for SA based on ±20% (assumption)
Serology (CPT code 86677)			
Sensitivity, %	85	68–100	Point estimate from Loy et al;[17] range for SA based on ±20% (assumption; upper bound truncated at 100%)
Specificity, %	79	63.2–94.8	Same as serology sensitivity
Adherence, %	86.2	68.96–100	Point estimate based on assumption and range for SA based on ~±20% (assumption; upper bound truncated at 100%)
Cost, US$	19.7	15.7–23.64	Point estimate derived from OptumInsight;[25] range for SA based on ±20% (assumption)

Note: *For the purposes of scenario analysis we describe how the incremental cost-effectiveness ratio changes across a monoclonal and polyclonal FAT adherence range of 0.2–0.8 to provide a more complete assessment of the effects of adherence.
Abbreviations: CPT, Current Procedural Terminology; FAT, fecal antigen test; SA, sensitivity analysis; UBT, urea breath test.

$$LTC_i = (p_{i[w]} - p_{i[wo]}) * C_i, \quad \forall i \in \{GC, PUD, Dysp\} \quad (2)$$

where P_i is risk associated with developing each disease, [w] is with *H. pylori* infection, [wo] is without *H. pylori* infection, and C_i is cost for each disease.

The cost/patient of managing PUD was estimated as the sum of the cost of PUD managed by medication (regardless of hospitalization) and the cost of a related hospitalization multiplied by its probability of occurrence:

$$C_{PUD} = \left(t_{PUD} * C_{PUD[med]} + p_{PUD[hosp]} * C_{PUD[hosp]}\right) \quad (3)$$

where C_{PUD} is cost/patient of managing PUD, t_{PUD} is duration of PUD (in years), $C_{PUD[med]}$ is cost/patient of managing PUD by medication (regardless of hospitalization), $C_{PUD[hosp]}$ is cost of related hospitalization, and $p_{PUD[hosp]}$ is its probability of occurrence.

The cost/patient of managing dyspepsia was estimated as the duration of dyspepsia (t_{Dysp}; in units of years) multiplied by the annual cost/patient of managing dyspepsia ($C_{Dysp[ann]}$).

It was assumed that all patients with continuing *H. pylori* infection who do not develop PUD or GC develop dyspepsia:

$$C_{Dysp} = t_{Dysp} * C_{Dysp[ann]} \quad (4)$$

$$p_{Dysp[w]} = 1 - p_{GC[w]} - p_{PUD[w]} \quad (5)$$

where C_{Dysp} is cost/patient of managing dyspepsia, t_{Dysp} is duration of dyspepsia (in years), and p is probability of occurrence.

Estimates of the reduced QALYs associated with continuing *H. pylori* infection were derived in a similar manner. As an illustration of the application of the aforementioned equations, the estimation of excess LTCs associated with PUD is described in a step-by-step manner in Table S1.

One-way and probabilistic sensitivity analyses were conducted to test the robustness of the cost-effectiveness results generated by the model to uncertainty in the input-parameter estimates. Input parameters for the one-way and probabilistic sensitivity analyses (eg, standard errors, ranges) were obtained from literature sources cited previously,

if available, or were estimated based on assumptions of uncertainty around base-case parameter estimates (measures of uncertainty for model-input parameters are summarized in Tables 1 and 2). For probabilistic sensitivity analyses, the beta-distribution was used for the sensitivities, specificities, and adherence rates of the tests, as well as all other probabilities used in the model. Gaussian distribution was used for all costs. Measures of uncertainty for excess LTC and reduced QALY estimates to be used in the one-way and probabilistic sensitivity analyses were estimated using a Monte Carlo simulation. The Monte Carlo simulation generated 3,000 values each for excess LTCs and reduced QALYs associated with continuing *H. pylori* infection, and the means and standard deviations of these parameters were estimated from the resulting simulated data sets. These descriptive statistics were then used to generate lower and upper bounds for the one-way sensitivity analyses. For the probabilistic sensitivity analyses, appropriate distributions were selected based on the resulting simulated data sets. Excess LTCs and reduced QALYs were estimated for patients aged 35 years, which was representative of the study population and is near the midpoint of the age range (18–55 years) considered in the study. The expected life years remaining for these representative patients were obtained from life tables (1999–2001) for the total US population when life expectancy at birth was 77 years.[20] The estimate of expected life years remaining was allowed to vary in the Monte Carlo simulations.

Results

In the base-case scenario, wherein the estimated patient-adherence rates were 86%, 48%, and 86% for the UBT,

monoclonal FAT, and serology, respectively, the corresponding expected total costs/patient were estimated to be $424.99, $466.41, and $404.98 (Table 3). The polyclonal FAT was also evaluated in the model, showing a total cost of $483.25/patient, which was similar to that for the monoclonal FAT. (Hereafter, results for the FAT refer to those obtained with the monoclonal FAT.) Despite the higher testing costs of the UBT vs the FAT, the total cost associated with the UBT was less than that with the FAT, reflecting the substantially higher excess LTCs (associated with the FAT) of managing continuing dyspepsia, PUD, and GC in patients with continuing *H. pylori* infection. Moreover, the cost per accurately diagnosed case of *H. pylori* infection was approximately twice as high for the FAT vs the UBT. The estimated QALYs gained/patient with the UBT vs the FAT and serology were 0.86 and 0.27, respectively. The reduced QALYs due to continuing *H. pylori* infection were estimated to be 0.78, 1.63, and 1.05 for the UBT, FAT, and serology, respectively.

The UBT was cost-effective when compared with the FAT and serology as a diagnostic test for the detection of *H. pylori* infection. Furthermore, the UBT achieved a decrease in total costs, as well as an increase in QALYs, compared with the FAT (Table 3). The estimated incremental cost/QALY gained (ie, incremental cost-effectiveness ratio [ICER]) was negative for the UBT vs FAT comparison, indicating that the UBT was dominant (cost-saving while also improving health outcomes). In comparison with serology, there was a modest increase of ~5% in total cost and a ~26% increase in QALYs for the UBT. The ICER for the UBT vs serology comparison was $74.20/QALY gained. Further, the UBT had the lowest

Table 3 Base-case economic and health outcomes

Outcome	UBT	Monoclonal FAT	Serology
Economic outcomes/patient, US$			
Total costs	424.99	466.41	404.98
Tests	88.62	9.52	16.98
Physician visits	146.88	146.88	146.88
First-line eradication therapy	79.25	77.85	92.55
Excess lifetime costs	110.24	232.17	148.57
Incremental outcomes			
Costs/accurately diagnosed case, US$	508.58	999.38	578.25
ICER, US$/QALY gained, UBT vs test*	–	UBT dominant	74.20
UBT cost-effective in comparison with test?	–	Yes	Yes
Health outcomes/patient			
Cases accurately diagnosed as positive (n)	0.31	0.17	0.27
Cases accurately diagnosed as negative (n)	0.52	0.29	0.43
Reduced QALYs due to continued *H. pylori* infection	0.78	1.63	1.05

Notes: *In cases where the UBT was both less costly and more effective than another test (ie, FAT), the UBT was considered "dominant"; in cases where the UBT was more costly and more effective than another test (ie, serology), the ICER was below the commonly cited threshold for willingness to pay US$50,000/QALY gained.
Abbreviations: FAT, fecal antigen test; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; UBT, urea breath test.
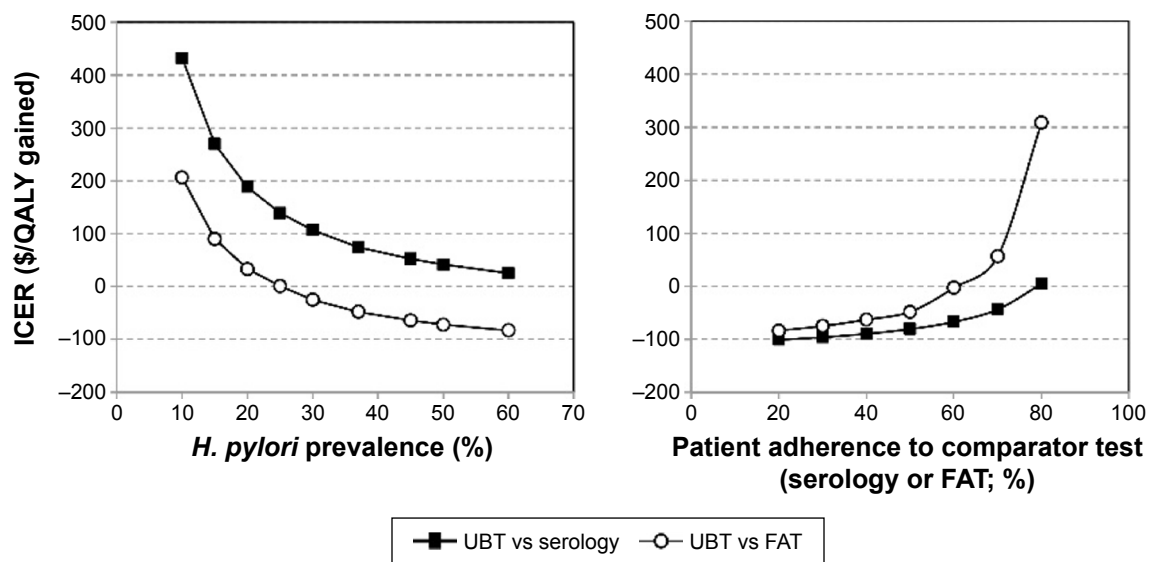
Figure 2 Effect of adherence and prevalence.
Abbreviations: FAT, fecal antigen test; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; UBT, urea breath test.

cost per correct diagnosis among the three noninvasive tests evaluated. The primary driver of the cost-effectiveness of the UBT was its higher adherence rate vs the FAT, and its higher sensitivity and specificity vs serology.

The effects of patient-adherence rates and *H. pylori* prevalence on the cost-effectiveness of the UBT vs FAT and serology were assessed in one-way sensitivity analyses (Figure 2). The UBT was cost-saving vs the FAT across patient-adherence rates with the FAT of 20%–62%; the UBT remained cost-effective vs the FAT when the adherence rate with the FAT was between 63% and 87%. The FAT became more cost-effective than the UBT when the patient-adherence rate with the FAT exceeded ~87.4%. The UBT remained cost-effective even with *H. pylori* prevalence <25%. The UBT was cost-saving vs serology at patient-adherence

rates with serology of 20%–70% and cost-effective across *H. pylori* prevalence rates of 10%–60%.

Probabilistic sensitivity analyses indicated that under uncertainty in the input parameters, the probabilities of the UBT being cost-effective compared with the FAT and serology were 1.00 and 0.58, respectively, at a willingness-to-pay threshold of $50,000/QALY gained (Figure 3). Therefore, the cost-effectiveness outcomes of the UBT vs FAT did not change under uncertainty in the model parameters, whereas the cost-effectiveness outcomes of the UBT vs serology was able to change.

Discussion

The present study is the first cost-effectiveness analysis of noninvasive testing of *H. pylori* infection to incorporate
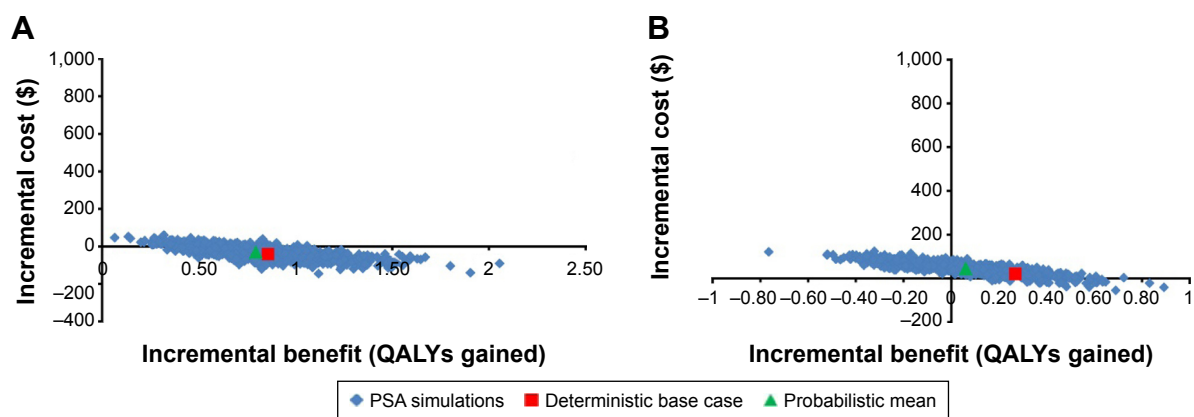

Figure 3 Cost-effectiveness scatterplots for comparisons of urea breath test with (**A**) monoclonal fecal antigen test and (**B**) serology.
Abbreviations: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life-years.

patient-adherence information, as well as downstream costs and health outcomes (as measured by reduced QALYs) of continuing *H. pylori* infection, from a US perspective. Downstream costs and health outcomes were included in this analysis based on two reasons: first, the cost of testing and treating *H. pylori* infection (in the vicinity of hundreds of dollars) is substantially less than that of managing potential *H. pylori*-related long-term complications, such as peptic ulcers and GC (both of which could incur substantial management costs, including hospitalization); and second, the cost of testing and treating *H. pylori* infection may not be incurred again for a majority of patients, because recurrence of *H. pylori* in the US is <2.5%/year after successful eradication therapy.[21]

The incorporation of patient adherence into the model is clinically important. Patients with continuing *H. pylori* infection due to nonadherence to the test-and-treat order by the physician will be at an increased risk of developing more severe and costly complications, such as peptic ulcers and GC. Previous studies have described patient preference for or adherence to tests based on different sample matrices. For example, it is established that the fecal occult blood test is an effective screening method for early detection of colorectal cancer.[22] Low patient adherence to completing the stool-sample collection, however, is also well recognized.[23] In an Israeli study of 2,000 men and women, only 18% of the participants sent stool samples to the testing laboratory.[15] Two published studies specific to *H. pylori* testing were identified. In a posteradication study of 29 patients with *H. pylori* infection, 25 (86%) returned for the UBT, but only 14 (48%) returned with a stool sample for the FAT.[13] Moreover, in a survey of attitudes toward *H. pylori* testing when serology was not available for initial diagnosis, 58% of patients preferred the UBT compared with 34% opting for the FAT.[14] These studies suggest that the difference in patient preference/adherence between noninvasive tests is not insignificant in routine clinical practice. Such information should thus be incorporated into pharmacoeconomic analyses involving different tests.

Decision-tree and Markov models have been used in some studies to evaluate the cost-effectiveness of *H. pylori* testing.[7–11] Those studies considered similar populations (patients aged <50 or <55 years who presented with symptoms of dyspepsia, but no alarm features), and used sensitivity and specificity data, together with testing costs, as input parameters to the economic models. These studies differed, however, in whether the analyses were restricted to *H. pylori* testing alone[8,10,11] or whether test and treat also was considered in the model.[7,9] Holmes et al[9] concluded that

the available endoscopic tests had similar costs and levels of effectiveness, whereas Elwyn et al[8] determined that the FAT was associated with the lowest cost and yielded a slightly higher number of true-positive test results than did the UBT. Masucci et al[10] evaluated the UBT as a diagnostic test and confirmatory test in a two-step strategy for positive serologic findings. The two-step strategy was costlier, but resulted in fewer false positives than did serology alone; however, it was less costly and more effective than the UBT alone. All these models used such outcomes as cost per misdiagnosis (eg, false positive and false negative), cost per correct diagnosis, appropriateness of eradication therapy given a patient's active infection status, and cost per symptom-free year; however, none of these models incorporated long-term outcomes, such as excess LTCs and reduced QALYs associated with continuing *H. pylori* infection. Patient adherence was not incorporated in the models either.

The present analysis addressed the aforementioned limitations of previous studies, and demonstrated that the UBT provided the greatest economic value among the tests considered for diagnosis of *H. pylori* infection after adjusting for patient-adherence rates. The UBT was dominant over the FAT, increasing QALYs and reducing total costs. Moreover, the UBT substantially increased QALYs at a modest increase in cost compared with serology, and was found to be cost-effective when compared against an ICER threshold of $50,000/QALY gained. This threshold value was recently suggested to be a conservative estimate for the cost-effectiveness threshold.[24]

Patient adherence and test performance were important determinants of the cost-effectiveness of detection and management of *H. pylori* infection. One-way sensitivity analysis showed that the UBT was cost-effective compared with the FAT, except when adherence to the FAT was greater than to the UBT; the UBT was cost-saving compared with serology when adherence to the UBT was the same or higher than to serology.

The prevalence of *H. pylori* affects the cost-effectiveness of noninvasive *H. pylori* tests. In the decision model by Vakil et al,[11] the most cost-effective strategies were as follows: at low *H. pylori* prevalence (30%), the FAT, followed by confirmatory testing with the UBT of positives; at intermediate prevalence (60%), the UBT, followed by the rapid urease test for negatives; and at high prevalence (90%), the UBT, followed by the rapid urease test for negatives and further confirmation with histology. In the present model, which incorporated patient adherence and used a long-term outcome, *H. pylori* prevalence affected ICER magnitude, but did not change the overall conclusions regarding cost-effectiveness (Figure 2).

These results should be interpreted with caution, due to the assumptions in the model structure, patient populations, and input parameters used to populate the model. The primary limitation of the model results from the assumptions in parameters for which data were not available from the literature or for which only limited data were available. Although the assumptions regarding parameter estimates were confirmed as realistic by an expert clinician, it would be appropriate to update parameter estimates as additional information in the literature becomes available. The adherence rate with serology is unknown, but is of particular interest, since adherence is a significant driver of the cost-effectiveness of the UBT compared with both serology and the FATs.

Conclusion

The economic analysis conducted with this model (from the perspective of a US third-party payer) suggests that the UBT is a cost-effective alternative to other noninvasive tests, including the polyclonal and monoclonal FATs and serology. The principal drivers of the cost-effectiveness of the UBT were its higher adherence rate vs the FAT and its better performance (ie, increased sensitivity and specificity) vs serology. Notably, the higher cost of the UBT within the range of current reimbursement schemes was not a factor in the outcome of this cost-effectiveness analysis. Therefore, the UBT provided the greatest economic value among these noninvasive tests for diagnosis of *H. pylori* infection.

Acknowledgments

Disclosure

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Supplementary material

Table S1 Estimation of excess lifetime costs associated with peptic ulcer disease

Calculation step	Equation	Estimate
Excess lifetime costs associated with PUD due to continuing *H. pylori* infection, US$	$\left(LTC_{PUD} = (p)_{PUD[w]} - P_{PUD[wo]}\right) * C_{PUD}$	28.09
Expected cost/patient with PUD	$C_{PUD} = C_{med} + C_{hosp}$	249.65
Expected cost/patient of PUD-related hospitalization	$C_{hosp} = P_{PUD[hosp]} * C_{PUD[hosp]}$	8.9
Cost of GI hospitalization event due to PUD	$C_{PUD[hosp]}$	8,896
Probability of GI hospitalization event due to PUD, %	$P_{PUD[hosp]}$	0.1
Expected cost/patient of PUD regardless of hospitalization (managed by medication), US$	$C_{med} = t_{PUD[med]} * C_{PUD[med]}$	240.75
Duration of PUD, years	$t_{PUD[med]}$	0.5
Cost/year of managing PUD with medication, US$	$C_{PUD[med]}$	481.5
Excess lifetime risk of PUD due to continuing *H. pylori* infection, %	$P_{PUD[w]} - P_{PUD[wo]}$	11.25
Lifetime risk of developing PUD with continuing *H. pylori* infection	$P_{PUD[w]}$	15
Lifetime risk of developing PUD without continuing *H. pylori* infection	$P_{PUD[wo]}$	3.75

Abbreviations: C, cost; GI, gastrointestinal; hosp, hospitalization; LTC, lifetime cost; med, medication; P, patient; PUD, peptic ulcer disease; t, duration; w, with *H. pylori*; wo, without *H. pylori*.