Original Article

Cost-effectiveness of screening with polymerase chain reaction for *Helicobacter pylori* to prevent gastric cancer and peptic ulcers

Aaron Oh[1]^, Han Truong[2], Judith Kim[3], Sheila D. Rustgi[4], Julian A. Abrams[4,5], Chin Hur[4,5]

[1]Albert Einstein College of Medicine, Bronx, NY, USA; [2]Harvard University, Cambridge, MA, USA; [3]Department of Medicine, New York University Grossman School of Medicine, New York, NY, USA; [4]Department of Medicine, New York Presbyterian, Columbia University Medical Center, New York, NY, USA; [5]Herbert Irving Columbia Cancer Center, New York, NY, USA

Contributions: (I) Conception and design: A Oh, H Truong, J Kim, JA Abrams, C Hur; (II) Administrative support: C Hur; (III) Provision of study materials or patients: A Oh, H Truong, J Kim, SD Rustgi; (IV) Collection and assembly of data: A Oh, H Truong, J Kim, SD Rustgi; (V) Data analysis and interpretation: A Oh, H Truong, C Hur; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Chin Hur. New York Presbyterian Columbia University Irving Medical Center, 622 West 168th Street, New York, NY 10032, USA. Email: ch447@cumc.columbia.edu.

Background: *Helicobacter pylori* (*H. pylori*) is a major risk factor for gastric cancer. Screening and treatment of *H. pylori* may reduce the risk of gastric cancer and peptic ulcer disease (PUD). Polymerase chain reaction (PCR) of gastric biopsies provides superior sensitivity and specificity for the detection of *H. pylori*. This study explores whether population-based *H. pylori* screening with PCR is cost-effective in the US.

Methods: A Markov cohort state-transition model was developed to compare three strategies: no screening with opportunistic eradication, ^{13}C-UBT population screening and treating of *H. pylori*, and PCR population screening and treating of *H. pylori*. Estimates of risks and costs were obtained from published literature. Since the efficacy of *H. pylori* therapy in gastric cancer prevention is not certain, we broadly varied the benefit 30–100% in sensitivity analysis.

Results: PCR screening was cost-effective and had an incremental-cost effectiveness ratio per quality adjusted life-year (QALY) of $38,591.89 when compared to ^{13}C-UBT strategy with an ICER of $2,373.43 per QALY. When compared to no screening, PCR population screening reduced cumulative gastric cancer incidence from 0.84% to 0.74% and reduced PUD risk from 14.8% to 6.0%. The cost-effectiveness of PCR screening was robust to most parameters in the model.

Conclusions: Our modeling study finds PCR screening and treating of *H. pylori* to be cost-effective in the prevention of gastric cancer and PUD. However, the potential negative consequences of *H. pylori* eradication such as antibiotic resistance could change the balance of benefits of population screening.

Keywords: *Helicobacter pylori* (*H. pylori*); gastric cancer; peptic ulcer disease (PUD); polymerase chain reaction (PCR)

Submitted Dec 24, 2021. Accepted for publication Jun 16, 2022.
doi: 10.21037/jgo-21-911
View this article at: https://dx.doi.org/10.21037/jgo-21-911

Introduction

Helicobacter pylori (*H. pylori*) is a known risk factor for gastric cancer, which is the third leading cause of cancer death worldwide (1). Though more than half of the global population is infected with *H. pylori*, rates of colonization vary greatly, with higher rates in lower income nations generally related to socioeconomic status and hygiene levels (2). While most people infected with *H. pylori*

^ ORCID: 0000-0001-9951-5087.

are asymptomatic, approximately 10% develop peptic ulcer disease (PUD) and 1% to 3% develop gastric adenocarcinoma (3). *H. pylori* promotes gastric carcinogenesis through chronic gastric inflammation which progresses through the stages of atrophic gastritis, intestinal metaplasia, dysplasia, to gastric adenocarcinoma (4). Eradication of *H. pylori* infection has been shown to reduce gastric cancer incidence (5). With more than 60% of gastric cancers attributable to *H. pylori*, early detection and eradication of infection is important in reducing the risk of cancer (6).

H. pylori infection fulfills many of the criteria for population screening (7). It can be detected through both noninvasive and invasive methods, each with its own advantages and limitations (8). There are a variety of diagnostic tests available yet no single gold standard has been established in clinical practice. However, diagnostic tests with sensitivity and specificity exceeding 90% are necessary for accurate diagnosis of *H. pylori* infection. American College of Gastroenterology guidelines recommend noninvasive ^{13}C-UBT in populations with low probability of *H. pylori* infection due to its inexpensive costs and quick results (9). Compared to this, polymerase chain reaction (PCR) of gastric biopsies has superior sensitivity and specificity for the detection of *H. pylori* (10). However, use of PCR testing of gastric biopsies is limited by accessibility, its inherent invasive nature, and expertise level of laboratories. Though screening and treating the population for *H. pylori* infection may reduce gastric cancer morbidity and mortality, such screening programs can be costly and difficult to implement. In this study, we aimed to evaluate the cost-effectiveness of ^{13}C-UBT and PCR population screening strategies of *H. Pylori* for the prevention of PUD and gastric cancer in the United States. We present the following article in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-911/rc).

Methods

Model design

A Markov state-transition cohort model was constructed in TreeAge Pro (TreeAge 2020, Williamstown, Massachusetts, USA). The model compared three strategies: (I) no screening with opportunistic eradication, (II) single population screening for *H. pylori* using ^{13}C-UBT and treating those who tested positive with eradication therapy, and (III) single population screening for *H. pylori* with upper endoscopy and PCR of gastric biopsies and treating those who tested positive with eradication therapy. The hypothetical patient for this analysis is a 40-year-old individual from the U.S. general population. A 40-year-old individual was chosen as the target population of our model due to the sharp increase in gastric cancer incidence after 40 years of age (11). Additionally, in countries such as Japan and Korea where screening programs exist, the recommended start age is also 40 years old (12). The model has a cycle length of one year and follows patients for 60 years or until death in order to estimate life time risks of cancer.

Management strategies

The management strategies in our analysis consisted of no screening, population based ^{13}C-UBT with eradication therapy, and population-based *H. pylori* PCR screening with eradication therapy. The health states in our model included *H. pylori* positive, *H. pylori* negative, gastric cancer, and death (*Figure 1*). In addition, both *H. pylori* positive and negative individuals had ongoing risks of PUD throughout the model. Patients could move from any health state to death due to all-cause mortality, bleeding from peptic ulcers, or gastric cancer.

In the no screening strategy, the distribution of the cohort at the beginning of the simulation (i.e., cycle 0) was based on U.S. *H. pylori* prevalence rates. Though none of the patients initially received screening, those who developed PUD were tested with UBT and given eradication therapy.

For the screening strategies, the entire cohort began with screening and eradication therapy was given to those who tested positive (i.e., true- and false-positive). Both first-line triple therapy [proton pump inhibitors (PPI), clarithromycin, and amoxicillin] and second-line quadruple therapy (PPI, bismuth, tetracyline, and metronidazole) were modeled. Individuals who failed both lines of eradication therapy were considered permanently *H. pylori* positive in the model. Risk of reinfection was restricted to the first five years after successful eradication.

Outcomes

The primary outcomes of interest were total cost, life expectancy, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERS). QALYs are a composite measure of the value of health outcomes that

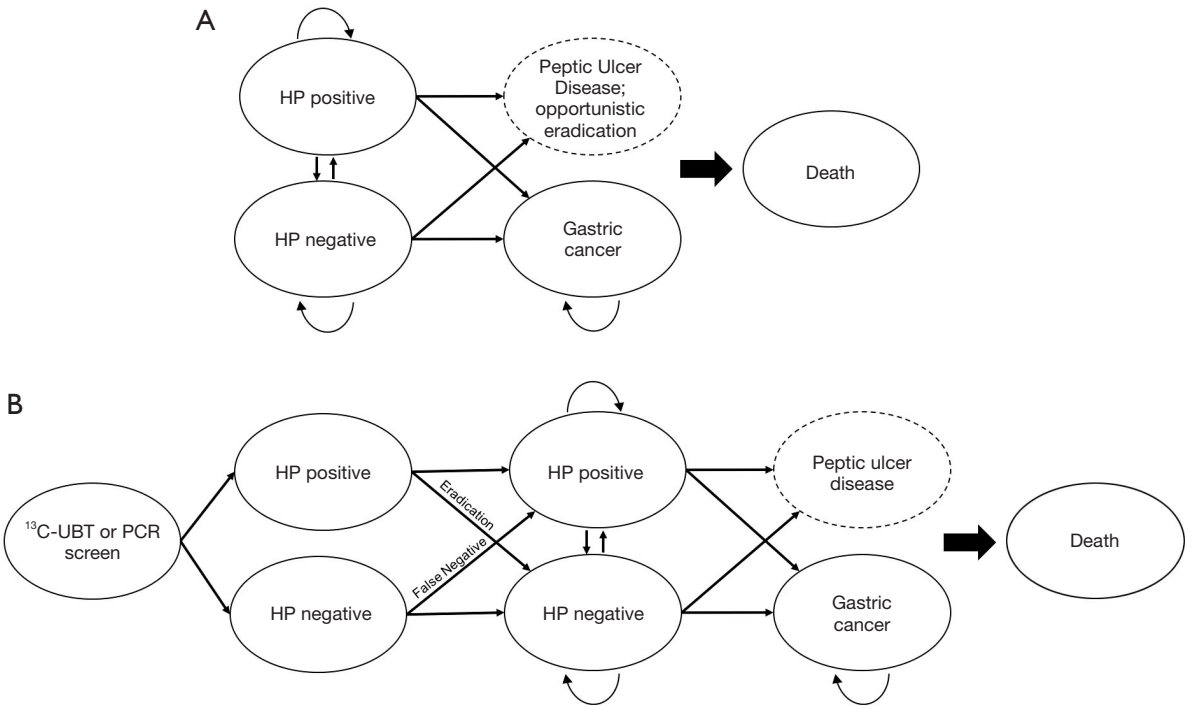

Figure 1 (A) Model schematic for no screening strategy. Patients can move from any health state to death. (B) Model Schematic for Screening Strategies. Patients can move from any health state to death. HP, *Helicobacter pylori*; PCR, polymerase chain reaction.

can be used to compare medical interventions where a value of 0 represents death and a value of 1.0 represents a year of perfect health. To calculate a QALY for a patient, we multiplied the utility value associated with a given health state multiplied by the cycle length of 1 year. Life expectancy was calculated as the total number of years the hypothetical patient was alive throughout the model duration without applying the health state utility values that reflected disease morbidity. A willingness to pay (WTP) threshold of $100,000/QALY was used to determine cost-effectiveness. Secondary clinical outcomes of interest included total lifetime gastric cancer incidence. In the model, total lifetime gastric cancer incidence was determined by aggregating the proportion of patients who were in the gastric cancer health state with those who died of gastric cancer by the end of the simulation duration.

Parameter estimates and model assumptions

Model parameters were based on estimates from the literature (2,11,13-27). Base-case values and ranges used in sensitivity analyses are summarized in *Table 1*. *H. pylori* prevalence in the U.S. was obtained from a meta-analysis by Hooi *et al.* (2). The cumulative gastric cancer incidence in the no-screening strategy was 0.84% and was calibrated to reflect published SEER life gastric cancer risks for an average 40-year-old in the US (11).

Risks of PUD and gastric cancer varied based on *H. pylori* status. The incidence of PUD in *H. pylori* positive individuals was 6- to 10-fold higher than for uninfected individuals (23,34). For patients who were *H. pylori* negative, they had a 0.66 relative risk of gastric cancer compared to those who were *H. pylori* positive (15). Due to scarce data regarding gastric cancer risk for individuals who were never infected compared to those were successfully eradicated of *H. pylori*, the 0.66 relative risk was applied for both groups. Though the risk of gastric cancer in individuals successfully treated of *H. pylori* could still be higher than the risk for those never infected due to developed gastric atrophy, we assumed the two risks were the same in the principal analysis.

Costs

The present study was performed from a third-party payer perspective. The model included direct medical costs of

Table 1 Model inputs

Parameter	Base-case estimate	Range used in sensitivity analysis	Distribution for PSA	Sources
Start age	40			
Probabilities				
All-cause mortality - general	Life table			(13)
UBT sensitivity	0.96	(0.92–1.00)	β	(14)
UBT specificity	0.93	(0.86–1.00)	β	(14)
PCR sensitivity	1	(0.96–1.00)	β	(22)
PCR specificity	0.98	(0.96–1.00)	β	(22)
HP prevalence	0.356	(0.267–0.445)	β	(2)
HP recrudescence rate	0.0267	(0.0200–0.0334)	β	(21)
HP reinfection rate	0.0145	(0.0108–0.0181)	β	(21)
1st line eradication success rate	0.80	(0.60–1.00)	β	(17,18)
2nd line eradication success Rate	0.81	(0.61–1.00)	β	(16)
Risk of PUD – HP negative	0.00125	(0.000938–0.00156)	β	(25)
Risk of PUD – HP positive	0.01	(0.0075–0.0125)	β	(23)
PUD mortality	0.031	(0.023–0.039)	β	(19,27)
Risk of gastric cancer – HP negative	0.000183	(0.000137–0.000229)	β	(11,15,20,24)
Risk of gastric cancer – HP positive	0.000277	(0.000208–0.000346)	β	(11,26)
Excess gastric cancer risk reduction attributable to HP eradication	100%	(30.00–100.00)	β	
GC 5-year mortality ages <45	0.66	(0.495–0.825)	β	(11)
GC 5-year mortality ages 45–54	0.646	(0.485–0.808)	β	(11)
GC 5-year mortality ages 55–64	0.653	(0.490–0.816)	β	(11)
GC 5-year mortality ages 65–74	0.655	(0.491–0.819)	β	(11)
GC 5-year mortality ages 75+	0.761	(0.561–0.951)	β	(11)
Utilities				
Healthy	1			(28)
HP infection	0.90	(0.80–1.00)	β	(29)
Gastric cancer	0.68	(0.58–1.00)	β	(29)
Disutility of upper endoscopy	–0.0012	(–0.0015 to –0.0009)	β	(28)
Disutility of PUD	–0.11	(–0.1375 to –0.0825)	β	(30)

Table 1 *(continued)*

Table 1 *(continued)*

Parameter	Base-case estimate	Range used in sensitivity analysis	Distribution for PSA	Sources
Costs				
Cost of UBT	75.56	(37.78–151.12)	γ	CMS, HCPCS 83013
Cost of PCR	603.66	(301.83–1,207.32)	γ	CMS, HCPCS 0008U
Cost of upper endoscopy with biopsy	614.80	(307.40–1,229.60)	γ	(31)
Cost of 1st line eradication therapy	425.61	(212.81–851.22)	γ	(31)
Cost of 2nd line eradication therapy	118.64	(59.32–237.28)	γ	(32)
Cost of PPI	48.00	(24.00–96.00)	γ	(31)
First year gastric cancer costs, <65 years old	106,199.47	(53,099.74–212,398.94)	γ	(33)
First year gastric cancer costs, ≥65 years old	88,499.46	(44,249.73–176,998.92)	γ	(33)
Final year gastric cancer costs, <65 years old	187,222.03	(93,611.02–374,444.06)	γ	(33)
Final year gastric cancer treatment, ≥65 years old	12,4815.08	(62,407.54–249,630.16)	γ	(33)
Continuing gastric cancer care	4,888.13	(2,444.07–9,776.26)	γ	(33)

PSA, probabilistic sensitivity analysis; CMS, Centers for Medicare & Medicaid services; GC, gastric cancer; HP, *Helicobacter pylori*; PCR, polymerase chain reaction; PPI, proton pump inhibitor, PUD, peptic ulcer disease; UBT, urea breath test.

^{13}C-UBT, upper endoscopy and PCR of gastric biopsies, and eradication therapies (31,32). Gastric cancer treatment costs varied with age and were divided into first year, continuing care, and final year of death (33). Costs were accrued from time of screening until death. Published cost estimates from prior years were converted to 2020 dollars using the Consumer Price Index (U.S. Bureau of Labor Statistics), and all costs were discounted an annual rate of 3% (35).

Utilities

Quality of life utility values relating to healthy, *H. pylori* positive, and gastric cancer states were incorporated in our model (28-30). Utility decrements due to upper endoscopy and PUD were also applied. Quality adjusted life years were discounted at an annual rate of 3% (35).

Sensitivity analyses

We performed one-way deterministic sensitivity analyses by altering individual variables across a range of values to investigate the key parameters that most impacted the outcomes of the model. Due to uncertainty in the true clinical efficacy of *H. pylori* therapy for reducing excess gastric cancer risk, we varied efficacy rates with sensitivity analysis from 30–100%. In addition, a probabilistic sensitivity analysis (PSA) was performed to address parameter uncertainty. β distributions were fitted for transition probabilities and utilities, while γ distributions were fitted for cost parameters. The PSA was performed using Monte Carlo simulations with 100,000 reiterations.

Results

Our base case analysis demonstrated that both ^{13}C-UBT and PCR were cost-effective treatment strategies (*Table 2*). The no-screening strategy yielded the lowest costs at $1,146.55 and the lowest QALY with 21.99. The ^{13}C-UBT strategy had a total cost of $1,201.19 and resulted in 22.45 QALY. The PCR strategy was the most expensive strategy at $2,329.69 and yielded 22.48 QALY. Compared to the ^{13}C-UBT strategy, in the context of an efficiency frontier, the ICER for the PCR strategy was $38,591.89 per QALY. Compared with the no-screening strategy, the ICER was $2,373.43 per QALY for the PCR strategy and $116.46 per QALY for the ^{13}C-UBT strategy.

The cumulative gastric cancer incidence in the no-screening strategy was 0.84% and was calibrated to reflect published SEER life gastric cancer risks for an average 40-year-old in the US (11). The lifetime gastric cancer incidence for the PCR strategy and ^{13}C-UBT strategy was 0.74% and 0.75% respectively. In the no-screening strategy,

Table 2 Model outputs

Strategy	Total cost	QALYs	ICER		GC incidence	PUD incidence
			vs. no-screening	*vs.* ^{13}C-UBT		
No screening	$1,146.55	21.99	Reference		0.84%	14.8%
^{13}C-UBT	$1,201.19	22.45	$116.46	Reference	0.75%	6.4%
PCR + Biopsy	$2,329.69	22.48	$2,373.43	$38,591.89	0.74%	6.0%

QALYs, quality adjusted life years; ICER, incremental cost-effectiveness ratio; GC, gastric cancer; PUD, peptic ulcer disease; PCR, polymerase chain reaction.

there was a 14.8% lifetime risk of PUD. In the PCR and UBT strategies, the lifetime risk of PUD dropped to 6.0% and 6.4%, respectively.

When each *H. pylori* eradication strategy was compared to the no-screening strategy, the results of the one-way sensitivity analysis showed that the ^{13}C-UBT and PCR strategies were most sensitive to the risk of gastric cancer if *H. pylori* positive, the risk of gastric cancer after *H. pylori* eradication, *H. pylori* prevalence, and costs of screening (*Figure 2*). However, even within the prescribed ranges of the one-way sensitivity analysis, the ^{13}C-UBT and PCR strategies remained more cost effective than the no-screening strategy. When varying the efficacy of *H. pylori* eradication from 30–100%, PCR remained the most cost-effective strategy at a WTP of $100,000 per QALY (*Figure 3*).

Cost-effectiveness acceptability curves were used to present the results of the PSA and determine the probability of any strategy being the cost effective at a given WTP (*Figure 4*). When the WTP was <$5,000 per QALY, the no screening strategy was the most cost-effective strategy majority of the time. As the WTP exceeded $60,000 per QALY, PCR became the cost-effective the majority of times.

Discussion

In this study, we compared the lifetime cost-effectiveness of different population-based *H. pylori* screening strategies for the prevention of gastric cancer for average 40-year-old Americans. To our knowledge, our study is the first to determine the cost-effectiveness of PCR as a potential screening strategy. Based on our results, the PCR strategy was the most cost-effective at the prescribed WTP threshold of $100,000 per QALY as it resulted in the lowest lifetime risks of gastric cancer at 0.74% and PUD at 6.0%.

Our study findings are similar to the conclusions of prior cost-effectiveness analyses that suggest population-based screening and eradication treatment can be a viable option for the reduction of gastric cancer (36,37). While previous cost-effectiveness studies focused mostly on gastric cancer reduction, we also considered the additional benefits of *H. pylori* screening and eradication on PUD. Relative to gastric cancer, the incidence of PUD is much higher and can confer significant physical and financial burden in patients due to hospitalization costs, bothersome symptoms, and chronic PPI use. Our model determined that screening and eradicating *H. pylori* decreased the lifetime incidence of PUD from 14.8% to 6%. The inclusion of PUD allowed us to incorporate opportunistic eradication within the no screening strategy and provide a more clinically accurate representation within our model to mitigate any bias towards the intervention strategies.

Due to its superior sensitivity and specificity, PCR screening and treatment of *H. pylori* can achieve significant benefits towards long term gastric cancer reduction. However, implementation of population PCR screening is challenged by unequal availability of necessary diagnostic facilities. Furthermore, PCR of gastric biopsies requires endoscopy, an invasive procedure that comes with risk of complications such as perforation, although rates may be as low as 0.009–0.02% (38). As determined by our model, compared to no screening, ^{13}C-UBT is a cost-effective and noninvasive alternative that also reduces gastric cancer and PUD. While the results of our model showed only marginal benefits towards gastric cancer reduction with PCR compared to ^{13}C-UBT, there can be cases where the most accurate measures are required. High risk patients for gastric cancer, such as in the context of hereditary diffuse gastric cancer or Lynch syndrome, often have earlier onset and worst prognoses (39). In these higher risk populations, PCR screening and treating of *H. pylori* could be recommended due to its superior sensitivity and specify to reduce as much excess risk of gastric cancer as possible. With PCR's superior performance characteristics, the small incremental benefits could lead to cancer and overall outcome benefits even when accounting for potential net

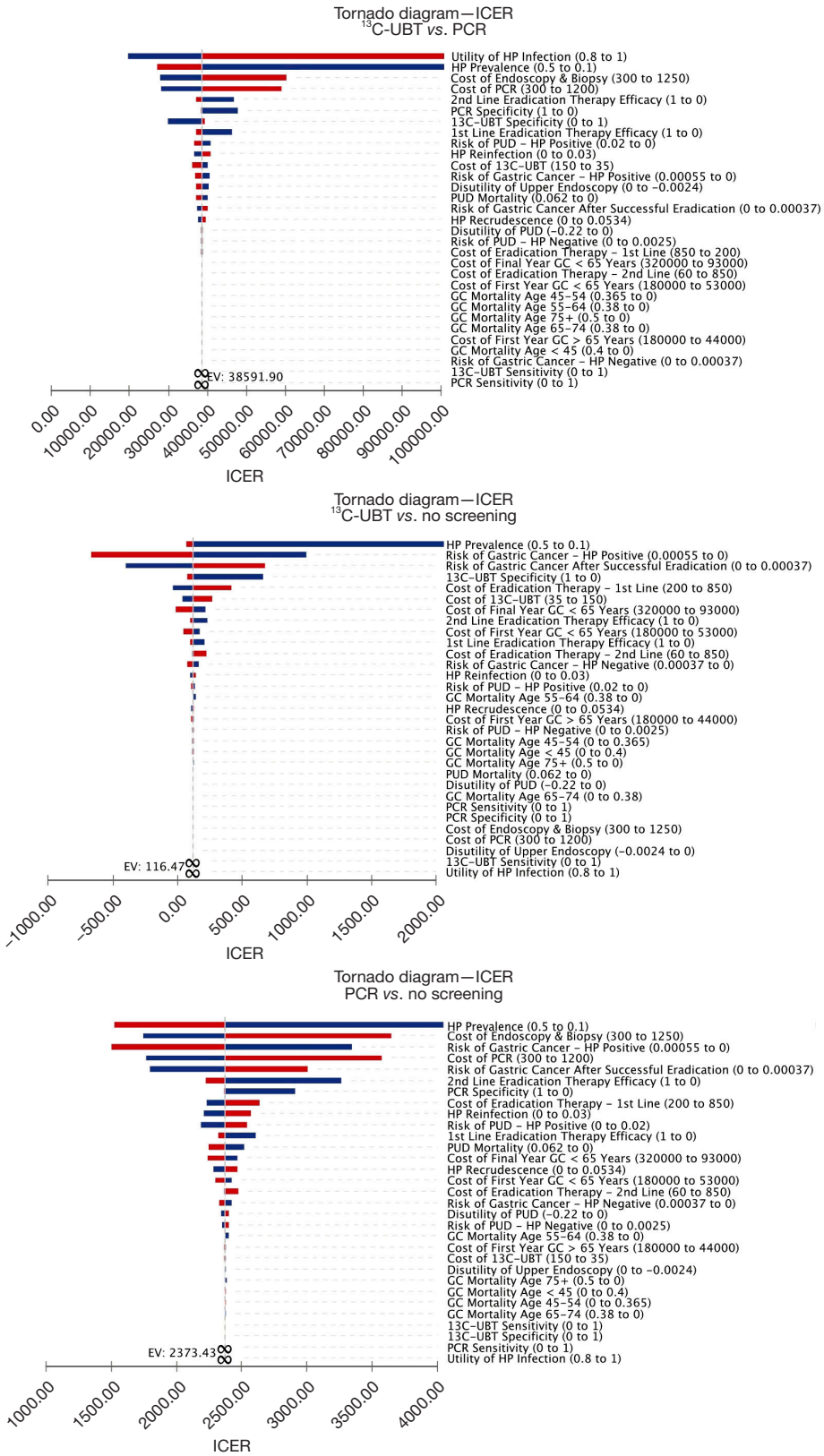

Figure 2 Tornado diagrams. ICER, incremental cost-effectiveness ratio; HP, *Helicobacter pylori*; PCR, polymerase chain reaction.

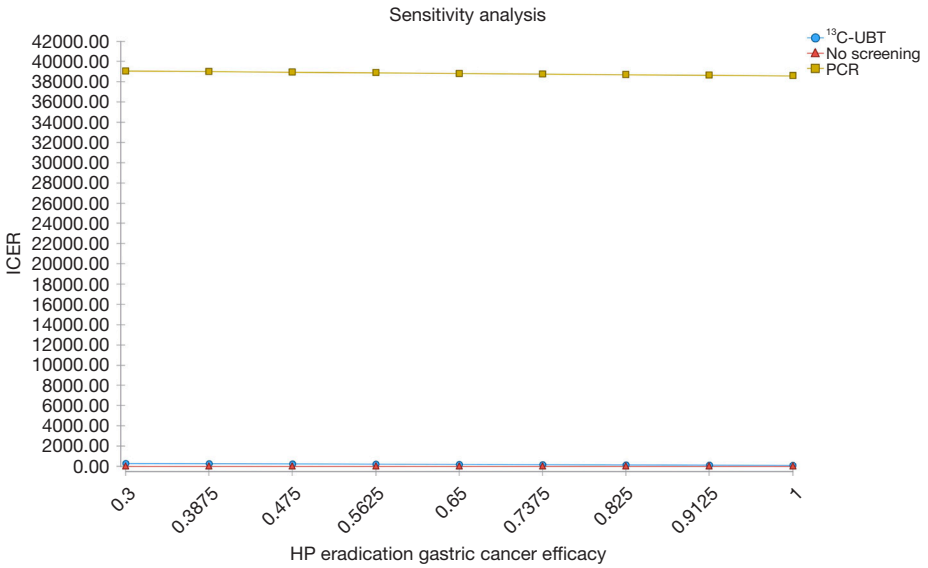

Figure 3 Sensitivity analysis of HP eradication gastric cancer efficacy. ICER, incremental cost-effectiveness ratio; HP, *Helicobacter pylori*; PCR, polymerase chain reaction.

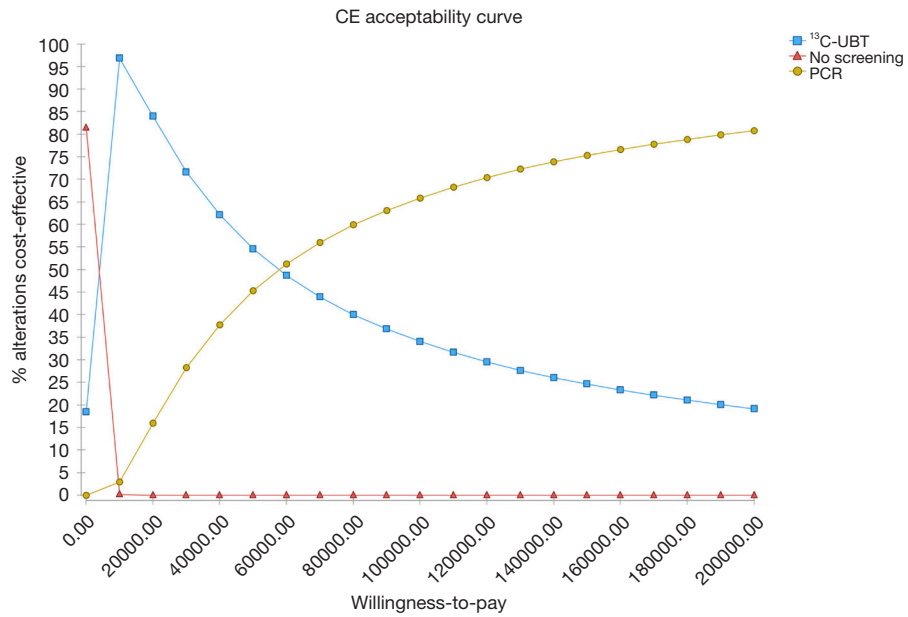

Figure 4 PSA cost-effectiveness acceptability curve. PSA, probabilistic sensitivity analysis; PCR, polymerase chain reaction; CE, cost-effectiveness.

negative consequences such as perforations.

Our study does have several limitations. Data were combined from multiple sources and some values for variables were imprecise. The relative risk of gastric cancer for *H. pylori* positive patients in our model was more conservative than what other studies had published (26,40). However, this conservative measure would bias the results of our model against screening and treatment. Adherence to eradication therapy is critical to the effectiveness of screening programs, and within our model we assumed 100% adherence. Compliance to a treatment program is a multifactorial process which can include factors such as

complexity of treatment, trust in doctor-patient relations, and side effects of treatment. Incorporating such factors into the model was not possible and therefore a limitation in our study. While 100% adherence is not feasible in a real-world context, we assumed a perfect scenario for model simplicity and function. The exact efficacy of *H. pylori* therapy toward gastric cancer reduction is unknown. We assumed 100% efficacy in our principal analysis but varied the efficacy from 30–100% within the sensitivity analysis to account for this limitation. While development of resistance to existing eradication therapies is an important consideration, and significant concern to public health, it is difficult to quantify the specific clinical harm it would confer to an individual patient and therefore was not included in our model. Risk of antibiotic resistance is a significant concern to public health and a considerable counterargument to a population wide test and treat strategy. Though implementation of population screening can be challenged by risks of antibiotic resistance, PCR screening can confer an additional advantage by determining which strains of *H. pylori* could be carrying genes for antibiotic resistance. Beyond even clarithromycin resistance, rates of multi-drug resistance in *H. pylori* are increasing worldwide (41,42). The efficacy of a 'one-size-fits-all' standardized therapy approach will continue to decline as strains with different permutations of drug resistance flourish. Therefore, tailored therapy based on PCR results of antimicrobial susceptibility testing, is an alternative method of treatment that can significantly improve eradication rates and decrease costs by reducing the need for re-tests and later line treatments. PCR could also provide similar benefits when testing strains for cytotoxin-associated gene A (CagA) status. As CagA positive strains are associated with higher risk of gastric cancer development, patients that are determined CagA negative by PCR could potentially withhold or delay eradication treatment for surveillance. While our study focused on the attributable risk of gastric cancer due to *H. pylori* infection, we do not account for inherited predispositions to gastric cancers. Though inherited gastric cancers make up only small fraction of all gastric cancers, the subset of the population with these heightened risk factors can benefit from a PCR screening strategy as cancer onset often occurs at younger ages for them. Furthermore, we did not consider the potential adverse effects of curing *H. pylori*, such as the development of reflux esophagitis, esophageal cancer, and autoimmune diseases (43,44). Rubenstein *et al.* have observed infection with *H. pylori* was inversely associated with esophagitis and Barrett's esophagus, while Lin *et al.* have noted increased risk of developing inflammatory bowel disease after receiving *H. pylori* treatment (44,45).

Model uncertainty is an inevitable challenge faced in cost-effectiveness analyses. While the true efficacy of *H. pylori* eradication toward gastric cancer reduction is controversial, our model remained robust despite varying efficacy rates. Although our study considers the benefits of screening specifically within the United States, other countries with higher prevalence of *H. pylori* and gastric cancer, screening and treating could be even more cost-effective, or possibly cost-saving. In the US context, there is a wide ethnic and racial disparity in *H. pylori* and gastric cancer prevalence and incidence. While our model does not take into account specific racial and ethnic differences in gastric cancer risk, cost-effectiveness studies targeted for immigrants and people from higher risk regions and people groups could show increased effectiveness of screening programs.

Conclusions

In summary, our modeling analysis finds that *H. pylori* testing with upper endoscopy and PCR testing of gastric biopsies is a cost-effective option to prevent gastric cancer and PUD in the US population. Additional clinical studies to affirm some of our model assumptions, especially those regarding the differences in risk of gastric cancer between individuals cured of *H. pylori* and those were never infected with *H. pylori*, are needed. A preprint has previously been published (46).

Acknowledgments

Funding: This work was supported by the National Institutes of Health [grant number CA0136969 to CH].

Footnote

Reporting Checklist: The authors have completed the CHEERS reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-911/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-911/coif). CH reports grant U01CA265729 and consulting fees from Roche Diagnostics. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Oh A, Truong H, Kim J, Rustgi SD, Abrams JA, Hur C. Cost-effectiveness of screening with polymerase chain reaction for *Helicobacter pylori* to prevent gastric cancer and peptic ulcers. J Gastrointest Oncol 2022;13(5):2186-2196. doi: 10.21037/jgo-21-911

