ORIGINAL RESEARCH—CLINICAL

Cost-Effectiveness of Serum Pepsinogen as a Gastric Cancer Targeted Screening Strategy in the United States

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BACKGROUND AND AIMS: Current gastric cancer (GC) screening modalities are invasive and expensive. Noninvasive screening for GC precursors with serum pepsinogen (PG) may improve early detection and prevention. Test characteristics of PG based on US prospective data was recently reported and used to study the cost-effectiveness of PG screening vs no screening in the US. **METHODS:** A patient-level state transition microsimulation of gastric adenocarcinoma analyzed noninvasive screening vs no screening in a hypothetical cohort of average risk US individuals. Primary outcomes included life expectancy, quality-adjusted life years, total costs, and incremental cost-effectiveness ratios. Secondary outcomes included total GC incidence and mortality. Base-case PG sensitivity and specificity were 34.1% and 94.7%, respectively, with a wide range of PG performance characteristics also examined. **RESULTS:** One-time serum PG screening at age 40 was cost-effective compared to no screening with an incremental cost-effectiveness ratio of $4913.29 per quality-adjusted life year. PG screening resulted in 10.9% relative reduction in lifetime GC incidence and 10.8% relative decrease in cumulative GC mortality. Localized stage at diagnosis increased from 30.5% to 33.6% and metastatic stage decreased from 40.8% to 37.4%. Sensitivity analysis showed PG screening was most sensitive to endoscopy costs, chronic atrophic gastritis quality of life, and PG prevalence. PG screening remained cost-effective across a wide range of test values. **CONCLUSION:** PG screening is a cost-effective strategy to improve GC mortality; however, mortality benefit will depend on the test characteristics of the biomarker. Future blood-based screening tests that have better performance characteristics could further improve GC prevention.

Keywords: Gastric Cancer; Serum Pepsinogen; Cancer Screening; Cancer Prevention; Cost-Effectiveness Analysis

Introduction

Gastric cancer (GC) remains a major global health concern, ranking fourth in cancer deaths worldwide.[1] Although incidence of GC is steadily decreasing in the United States (US), a low 5-year survival rate of 36% reflects the frequency with which it is diagnosed at late stage.[2] GC disproportionately affects racial and ethnic minorities in the US. The American Association for Cancer Research State of Cancer Health Disparities in 2022 report highlight that GC has the highest cancer-specific disparity in Hispanics, and second highest in Blacks and Asian/Pacific Islanders with a doubling of risk for cancer specific death in these groups compared to Whites (rate ratio 1.9–2.0).[3]

In countries with high GC incidence, screening efforts have focused on early detection of gastric lesions where curative treatment is more effective in order to reduce mortality.[4] Although esophagogastroduodenoscopy (EGD) is the gold standard for screening,[5] its high cost and invasive nature hinder population-wide screening in countries with low GC incidence like the US.[6] Targeted screening, which identifies persons at higher risk of developing GC to undergo further evaluation, may reduce the burden of this disease in low incidence regions. Once precancerous lesions are identified, recent guidelines including American Gastroenterological Association, European Society of Gastrointestinal Endoscopy and British Society of Gastroenterology guidelines suggest aggressive surveillance and treatment, including endoscopic surveillance every 3 years for intestinal metaplasia (IM), and annual surveillance for gastric dysplasia and early cancers, particularly for high-risk individuals.[7,8]

Unlike the existence of robust guidelines on the management of precancerous lesions, there remains a great void in strategies to seek and identify precancerous lesions for GC control. Using known risk factors for GC, it has been suggested that racial/ethnic groups, recent immigrants from high-risk countries and individuals with family history of GC should be considered for EGD screening.[9] However, the US Preventative Services Taskforce have been silent on this issue resulting in EGDs being unable to get insurance coverage as a screening test. Use of a noninvasive blood-

Abbreviations used in this paper: **CAG, chronic atrophic gastritis; EGD, esophagogastroduodenoscopy; GC, gastric cancer; ICER, incremental cost-effectiveness ratio; IM, intestinal metaplasia; PG, pepsinogen; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness-to-pay.**

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based test that can be performed readily in primary care offices to identify patients at risk of precancerous lesions and GC to be referred for EGD would greatly aid the adoption of GC early detection and screening efforts.

Biomarker-based pepsinogen (PG) screening has potential to be markedly cheaper and a less invasive option to identify individuals at risk of GC who might be harboring pre-cancerous lesions. PG test is performed using fasting blood. The majority of gastric adenocarcinoma develops following a linear carcinogenesis pathway termed the Correa Cascade, starting with chronic atrophic gastritis (CAG), followed by IM, dysplasia, and ultimately, gastric adenocarcinoma.[10] The gastric mucosa produces 2 biochemically distinct classes of PG, PG-I and PG-II,[11] which can reflect its functional status. When chief cells are replaced by pyloric glands in response to chronic inflammation, the overall ratio of PG-I to PG-II decreases.[11] Accordingly, PG-I and PG I/II ratio are considered markers of atrophic gastritis. PG is reflective of the functional and morphological status of the stomach's condition and can serve as an indicator of increased cancer risk.[11] In this study, we aimed to study the cost-effectiveness of a one-time PG screening strategy and its potential impact on reducing GC mortality in the US.

Methods

Decision Model

A patient-level state transition microsimulation model (Our analysis was done using a microsimulation model, which is similar to a Markov model. Both are considered state-transition models; however, a Markov model is considered "memoryless" and generally a simpler model where the transition probabilities between states do not depend on history while a microsimulation is not subject to this limitation. We incorporated a microsimulation as there are many permutations of health state transitions which require a track of patient's history [eg PG status + no cancer vs precancer vs cancer status].) was constructed using TreeAge Pro (TreeAge LLC, 2021, Williamstown, MA). The hypothetical patient was defined as a 40-year-old individual at average risk of GC. A 40-year-old individual was chosen as the target population of our model due to the sharp increase in GC incidence after 40 years of age.[12] In addition, in Korea where a screening program exists, the recommended start age is also 40 year old.[13] The base-case analysis was run with 100,000 samples. The model had a cycle length of one month and followed patients for 60 years or until death.

The model compared a one-time serum PG screening strategy with no screening or natural history of GC. In the simulation for screening, patients underwent a serum PG test at the start of the model. All individuals with positive PG test (both true and false positive) for atrophy subsequently underwent EGD. If patients were found to have dysplasia or early GC on EGD, they underwent endoscopic resection and had annual surveillance until age 80.[8] For patients diagnosed with later stages of cancer, they were assumed to be treated according to National Comprehensive Cancer Network guideline recommendations for GC which uses a combination of chemotherapy, radiation therapy and surgical resection.[14] Patients who were found to have IM on EGD had surveillance every 3 years until age 80.[7] Patients who were found to have CAG or normal gastric mucosa on EGD received no further intervention and would follow the natural history progression. The natural history model mimics the Correa cascade and patients could progress and regress in a stepwise manner between the various precursor lesions of GC. Once patients develop cancer, they could only remain in their current stage or progress to later stages (Figure 1). Patients could move from any health state to death due to all-cause mortality, surgical mortality, or GC.

Outcomes

The primary outcomes of interest included life expectancy, quality-adjusted life years (QALYs), total cost, and incremental cost-effectiveness ratios (ICERs). The ICER between strategies demonstrates the costs per additional QALY gained and is compared to a willingness-to-pay (WTP) threshold of $100,000/QALY to determine cost-effectiveness. Secondary clinical outcomes of interest included total lifetime GC incidence, stage at diagnosis and mortality.

Parameter Estimates and Model Assumptions

Model parameters were based on estimates from the literature. Base-case values and ranges used for the sensitivity analyses are summarized (Table 1). The natural history strategy was calibrated to reflect published SEER lifetime GC risk and cancer stage distributions at time of diagnosis.[2] PG sensitivity and specificity data were obtained from a study by In et al,[16] which is the only US study that used prospectively collected samples to examine test characteristic of PG. Due to concerns that data from Asian studies would not appropriately reflect the distribution of gastric lesions found on EGD after positive PG testing in the US, European data from Sjomina et al were used to inform the model.[18]

Costs

The present study was performed from a third-party payer perspective. The model included direct medical costs of serum PG testing, EGD, endoscopic resection, and surgery. Endoscopic procedure costs reflect the national averages of Medicare reimbursement rates published by the Centers for Medicare and Medicaid Services (CMS).[30] GC treatment costs were informed by the work of Mariotto et al which looked at SEER registry data linked with CMS data to estimate health care cancer-attributable costs.[31] Published cost estimates from prior years were converted to 2021 dollars using the Consumer Price Index (US Bureau of Labor Statistics), and all costs were discounted at an annual rate of 3%.

Utilities

Utility values are measures of the quality of life associated with a given health state. Utility values can vary from 0 for death to 1 for perfect health. Quality of life utility values related to perfect health, precancerous gastric lesions, and GC were incorporated into the model (Table 1). QALYs were discounted at an annual rate of 3%.

Sensitivity Analyses

One-way deterministic sensitivity analysis was performed by altering individual variables across a range of values to

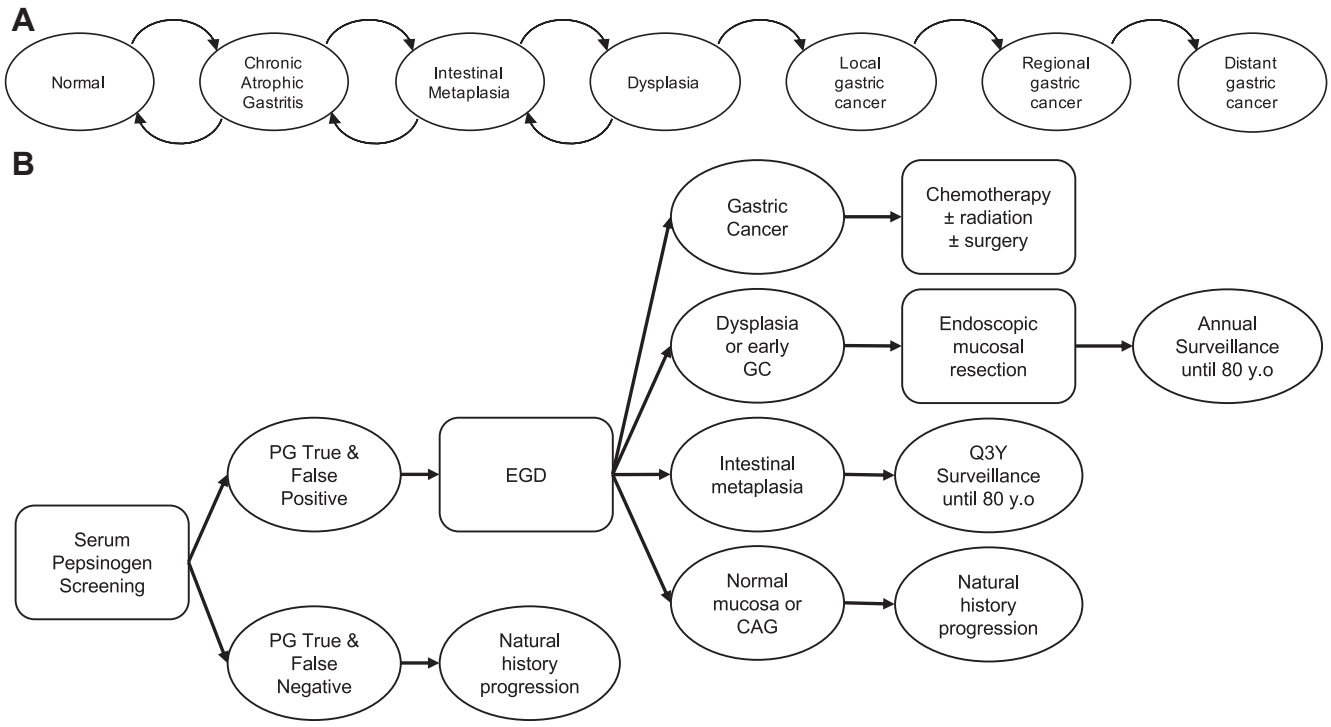

Figure 1. A. Model schematic for No Screening Strategy. This figure depicts the natural history progression of to the Correa cascade, from normal mucosa to gastric cancer. Patients can move from any health state to death, either due to all-cause mortality or to gastric cancer related mortality. B. Model schematic for Pepsinogen Screening Strategy. In this model, patients are offered pepsinogen screening age 40 to detect those at high risk of gastric cancer precursor lesions and offer surveillance for earlier detection of gastric cancer. Patients can move from any health state to death.

investigate the key parameters that most impacted the outcomes of the model. A probabilistic sensitivity analysis (PSA) was also performed by allowing every variable to simultaneously sample a value from an assigned distribution in order to address model uncertainty and quantify confidence in the results of our model. β distributions were fitted for transition probabilities and utilities, while γ distributions were fitted for cost parameters. The PSA was performed with 1000 reruns of the model each with cohorts of 10,000 patients, for a total of 10,000,000 iterations of the model.

Cost-Effectiveness and Mortality Benefit of Alternative Sensitivity and Specificity Combinations

The potential impact of varying PG screening biomarker performance characteristics were assessed by applying alternative sensitivities (ranging from 30% to 80%) and specificities (ranging from 50% to 99% were) as model inputs.

Results

Model Calibration

Calibration targets for the natural history strategy in our model used SEER estimates of lifetime risk of GC (0.84%) and local (30.35%), regional (28.88%), and distant (40.77%) stage distributions for 40-64-year olds.[2] Our model closely approximated this estimated lifetime risk of GC of 0.85% (vs 0.84% SEER), and stage distribution (local 30.53 vs 30.35%; regional 28.72 vs 28.88%; distant 40.75 vs 40.77%) which we deemed a sufficient model fit.

Base-Case Analysis

The base case analysis (Table 2) demonstrated that serum PG screening was the cost-effective strategy over no screening with an ICER of $4913.29 per QALY gained. The PG testing strategy, though costlier, resulted in 0.08 greater life years (~1 month) and 0.03 greater QALYs (~0.36 months) compared to the no screening strategy. In our model comprising of 100,000 patients, the PG testing strategy resulted in 35,730 additional endoscopies, while reducing the number of new cancer cases to 587 compared to 609 in the no screening arm.

The cumulative cancer incidence was 0.757% in the PG screening strategy compared to 0.850% in the no-screening strategy, a 10.9% relative risk reduction. The local, regional, and distant stage distributions were 30.5%, 28.7%, and 40.8%, respectively, in the no screening strategy and 39.1%, 26.5%, and 34.4%, in the PG screening strategy. This resulted in a 7.6% and 15.5% relative reduction in regional and distant staged cancers, respectively, and a 27.9% relative increase in local staged cancers for the PG screening strategy. The cumulative mortality risk fell to 0.528% with screening vs 0.592% for the natural history strategy, resulting in a 10.8% relative decrease.

Table 1. Model Inputs: Base-Case Values and Ranges Used for Sensitivity Analyses

Parameters	Base-case estimate	Range used in sensitivity analysis	PSA distribution	Sources
Age	40			
Probabilities				
All-cause mortality	Lifetable			
Surgical mortality	0.005	0.0002–0.015	β	15
Local GC mortality	0.0060	0.00453–0.00755	β	2
Regional GC mortality	0.01881	0.01410–0.02351	β	2
Distant GC mortality	0.04719	0.03539–0.05898	β	2
PG test sensitivity	0.314	0.227–0.412	β	16
PG test specificity	0.947	0.908–0.973	β	16
PG positive prevalence	0.175	0.1–0.33	β	17
PG positive w/CAG	0.083	0.06225–0.10375	β	18
PG positive w/IM	0.015	0.01125–0.01875	β	18
PG positive w/dysplasia	0.128	0.096–0.16	β	18
PG positive w/local GC	0.015	0.01125–0.01875	β	18
Proportion of local GC eligible for EMR	0.65	0.55–0.7	β	19
Proportion of complete resections	0.94	0.91–0.97	β	20
Incomplete resections requiring surgery	0.36	0.31–0.42	β	21,22
Normal to CAG	0.00581	0.00499–0.00673	β	23
CAG to IM	0.00482	0.00358–0.00640	β	23
IM to dysplasia	0.00175	0.00092–0.00291	β	23
Dysplasia to local GC	5.0092E-4	0.00019–0.00064	β	23
Local to regional GC	0.08956	0.06717–0.11195	β	24,25
Regional to distant GC	0.15980	0.04081–0.31960	β	24,25
CAG to normal	0.00142	7.470E-05–0.00241	β	23
IM to CAG	0.00449	0.00316–0.00615	β	23
Dysplasia to IM	0.01312	0.00656–0.05817	β	23,26,27
Utilities				
Healthy	1		β	
CAG	0.98	0.735–1	β	28
IM	0.98	0.735–1	β	28
Dysplasia	0.98	0.735–1	β	28
Local GC	0.773	0.580–0.966	β	29
Regional GC	0.590	0.442–0.737	β	29
Distant GC	0.404	0.303–0.505	β	29
Costs				
Serum PG test	48.19	24–98	γ	19
EMR	1838.72	919.36–3677.44	γ	30
Endoscopy	949.87	474.94–1899.74	γ	30
Surgery	27,744.56	13,872.28–55489.12	γ	19
First year local GC costs	70,086.41	35,043.21–140172.82	γ	31
Last year local GC costs	108,882.36	54,441.18–217764.72	γ	31
First year regional GC costs	111,419.43	55,709.72–222838.86	γ	31
Last year regional GC costs	128,861.75	64,430.87–257723.50	γ	31
First year distant GC costs	108,142.39	54,071.19–216284.78	γ	31
Last year distant GC costs	142,498.47	71,249.24–284996.94	γ	31
GC continuing care costs	9936.84	4968.42–19873.68	γ	31

CAG, chronic atrophic gastritis; PSA, probabilistic sensitivity analysis.

Sensitivity Analyses

The results of the one-way sensitivity analysis showed that serum PG screening was most sensitive to the cost of EGD, progression rate of normal mucosa to CAG, and the health state utility of CAG (Figure 2). However, even within the prescribed ranges of the one-way sensitivity analysis, PG screening remained the cost-effective strategy.

The results of the PSA showed the model was robust to model uncertainty with the PG screening strategy remaining cost-effective 89.7% of iterations at a WTP of $50%,00% and 91.4% of iterations when the WTP increased to $100,000 (Figure 3).

Alternative Sensitivity and Specificity Combinations

The effects of varying performance characteristics of a screening biomarker are shown in Table 3. Higher sensitivity results in greater mortality benefit; cancer incidence and proportion of cancers found at metastatic stages decreased, while proportion of localized cancers increase. To illustrate, a test sensitivity of 30% results in mortality

Table 2. Base-Case Results

	Total cost	Life years	QALYs	ICER	Local GC	Regional GC	Distant GC	# Of additional endoscopies	# Of new cancers
No screening	209.40	40.09	22.38	–	30.53%	28.72%	40.75%		609
Serum pepsinogen screening	489.95	40.17	22.41	7494.96	39.05%	26.52%	34.43%	35,730	587

QALYs, quality-adjusted life years.

benefit of 10% while improved sensitivity of 80% results in a 30.71% mortality benefit. Cost-effectiveness is influenced more by specificity (high specificity is more cost-effective) and less by sensitivity; the least cost-effective combination was a sensitivity/specificity combination of 30% and 50% resulting in ICER of $17,159.99 per QALY and the most cost-effective combination was our base-case (sensitivity of 31.4%, specificity 94.7% resulting in ICER of $7494.96 per QALY). Compared to our base case, a hypothetical biomarker with sensitivity of 80% with corresponding specificity 50% would result in substantial increase in mortality benefit to 30.9% (compared to 10.9%) while remaining cost-effective at ICER of $13,501.95 per QALY gained.

Discussion

Our study found a one-time serum PG testing at age 40 to be a cost-effective screening strategy for GC in the US, a low-incidence country. In addition, we found that with PG screening, there is a 10.9% relative reduction in GC incidence and notably, diagnoses were downstaged to when GC is more treatable, with localized stage incidence increasing from 30.5% to 39.1% and the metastatic stage decreasing from 40.8% to 34.4%. Our model also showed there was a 10.8% relative decrease in the lifetime cumulative risk of GC mortality. These findings held true 89.7% and 91.4% of the time, using WTP of $50,000 and $100,000, respectively.

Numerous studies, mostly in Asia but some in Europe and Central America, have explored the possibility of using PG as a screening tool for GC, with pooled sensitivities of 70% and specificity of 79% of PG for GC detection.[32] In the first nested case-control study of a large prospective US cohort, PG test was found to have sensitivity of 31.4% and specificity of 94.7%.[16] These test performance characteristics as well as variations of test performance have not previously been explored on its effect on cost-effectiveness and mortality benefit. In addition, prior cost-effectiveness analysis did not incorporate recent guidelines suggesting active management and surveillance of pre-cancerous lesions.

At present, there is no population-wide screening program for GC in the US despite the relatively low costs of prevention compared to treatment for cancer. Over one-third of US patients are diagnosed with GC after it has metastasized, with a median survival of 6 months, and a dismal 5-year survival at 31%.[33] Early identification of GC provides an opportunity for treatment and even cure, given the pronounced differences in 5-year survival by stage at diagnosis, ranging from 90% to 96% for Tis and T1a lesions to 67% for local, 29% for regional and 4% for metastatic disease.[34,35] There is an urgent need to develop a screening strategy for GC in the US.

National screening programs for GC have been in effect in Japan and Korea since 1960 and 1999, respectively, and have been found to reduce GC mortality by 21%–60%.[36] EGD is the preferred modality in Japan and Korea.[36]

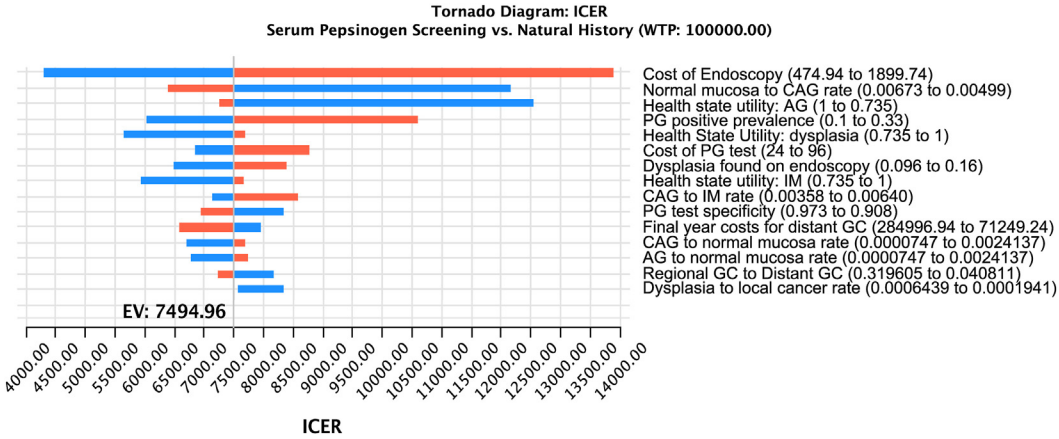

Figure 2. The one-way sensitivity analysis revealed that serum PG screening is most sensitive to the cost of EGD, the health state utility of CAG, and PG positive prevalence. All variables were tested but only the most sensitive variables were displayed.

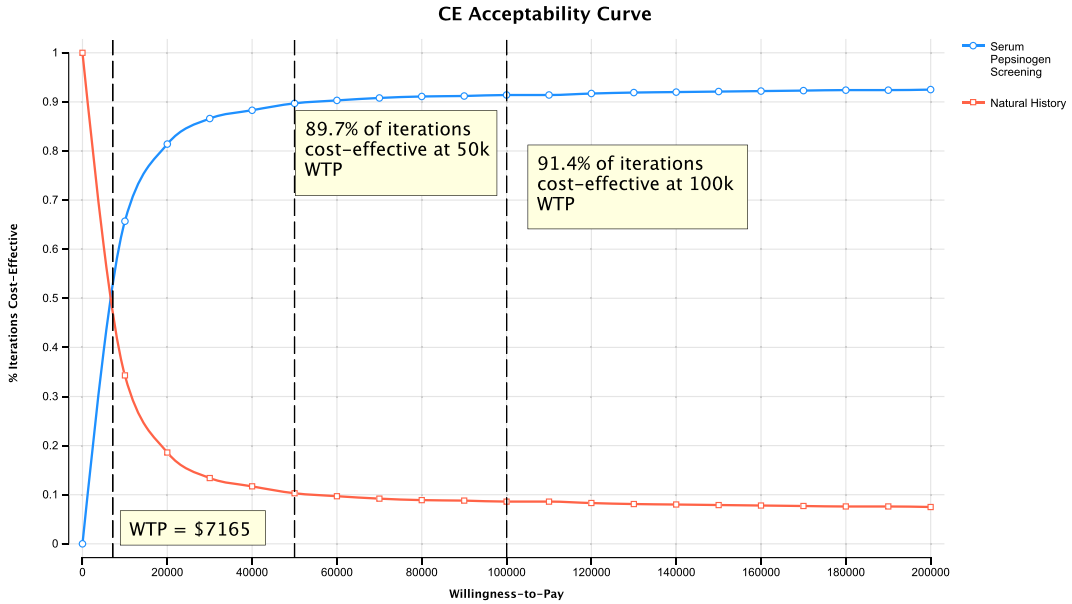

Figure 3. Willingness-to-pay (WTP) vs percent iterations cost-effective.

While effective, EGD for screening is practical only in high-incidence countries, due to its resource intense nature and higher costs. A study comparing cost-effectiveness of EGD screening for multiple countries found that it was only a cost-effective screening strategy for Japan, while it was the least cost-effective for the US due to high costs of EGD.[37] For low-incidence countries like the US, targeted screening strategies through screening of high risk subsets of the population have been suggested. The American Society for Gastrointestinal Endoscopy (ASGE) highlight the significantly higher risk of GC precursor lesions (ie IM) and GC in subsets of the population, and recommend EGD screening for GC in first-generation US immigrants from high-risk regions around the world.[38] Yet large knowledge gaps among primary care physicians and gastroenterologist with respect to GC risk factors and treatments exist, resulting in lack of standardized and effective GC screening programs for these high-risk individuals.[39] An inexpensive and noninvasive test that can identify individuals at high-risk to be referred for further testing may promote the adoption of GC screening.

A stepwise strategy starting with serological PG testing followed by EGD could differentiate between low and high-risk patients, identifying those who would benefit from further screening and surveillance.[40] PG testing has been evaluated in Asia as well as other parts of the world for its potential as a biomarker for the identification of GC and its precursors. Long term population-based studies largely from Japan and a few from China, Korea and Portugal report sensitivities ranging from 35% to 88% and specificities from 34% to 96%.[41] Despite support from several studies reporting on the potential value of PG testing, studies on its use are limited.[42–45] Furthermore, the ability of PG to detect GC in US populations is largely understudied except for a few retrospective studies.[46,47]

Recently, in a nested case control study of Prostate, Lung, Colon and Ovarian (PLCO) Screening Study, our group found that after a median follow-up of 6.7 years for patients who developed GC and 13.1 years for controls, a positive serum PG test at time of study entry was associated with an 8.5-fold increased risk for future development of GC.[16] The test characteristics of PG + using cut-offs commonly used in other studies (PG-I levels $\leq$ 70 mg/L and PG-1:PG-2 $\leq$ 3.0)[42] yielded low sensitivity of 31.4% but high specificity of 94.7% for future development of GC. The current model utilized the test characteristic data from this study to better describe US subjects.

The test performance for PG reported in the PLCO study and used in this analysis has much room for improvement. These test characteristics were based on serum PG threshold values developed in other countries, whereas alternative thresholds resulting in greater sensitivity albeit lower specificity may be more suitable for the US population. Yet, even with this subpar test performance, we demonstrated that PG was highly cost-effective and led to improved GC mortality rates. An exploratory analysis of alternative sensitivity and specificity combinations revealed a greater mortality benefit and decrease in cancer incidence when sensitivity was increased, and higher ICER with decreased specificity, although still well below a WTP threshold of $100,000 (Table 3). Alternative threshold values for PG continue to be explored.[48]

To this date, there have been several CEA of GC screening and prevention strategies.[49] In contrast to our study, previous studies on screening for premalignant gastric lesions via EGD or PG levels were generally not found to be cost-effective.[49] The greatest difference with prior CEA of PG and our model is in the use of more recent guidelines that suggest continued management and

Table 3. Alternative Biomarker Sensitivity and Specificity Combinations and Its Effect on Incidence, Stage, and Mortality

Biomarker sensitivity	Biomarker specificity	ICER per QALY	Relative reduction in cancer incidence (total GC incidence %)	Relative reduction in cancer incidence (total GC incidence %)	% Found at localized cancer stage (relative change %)	% Found at metastatic cancer stage (relative change %)	Cancer mortality – PG screening (compared to natural history model 0.592%)
31.4%	94.7%	7494.96	10.9% (0.757%)	10.9% (0.8%)	39.1% (+27.9%)	34.4% (−15.5%)	0.528%
30%	50%	17,159.99	10.0% (.765%)	10.0% (0.8%)	38.8% (+27.0%)	34.8% (−14.7%)	0.533%
40%	50%	14,373.91	13.6% (0.734%)	13.6% (0.7%)	40.5% (+32.5%)	33.1% (−18.8%)	0.51%
50%	50%	15,076.73	17.6% (0.700%)	17.7% (0.7%)	42.4% (+39.0%)	32.2% (−21.0%)	0.483%
60%	50%	14,463.52	22.5% (0.659%)	22.5% (0.7%)	44.6% (+46.2%)	31.8% (−21.9%)	0.454%
70%	50%	14,451.54	26.6% (0.624%)	26.6% (0.6%)	47.24% (+54.8%)	30.7% (−24.6%)	0.433%
80%	50%	13,501.95	30.7% (0.589%)	30.7% (0.6%)	48.9% (+60.1%)	29.7% (−27.1%)	0.409%
30%	60%	15,012.72	10.0% (0.765%)	10.0% (0.8%)	38.8% (+27.0%)	34.8% (−14.7%)	0.533%
40%	60%	12,745.32	13.6% (0.734%)	13.6% (0.7%)	40.5% (+32.5%)	33.1% (−18.8%)	0.51%
50%	60%	13,510.41	17.7% (0.700%)	17.7% (0.7%)	42.4% (+39.0%)	32.2% (−21.0%)	0.483%
60%	60%	13,081.26	22.5% (0.659%)	22.5% (0.7%)	44.6% (+46.2%)	31.8% (−21.9%)	0.454%
70%	60%	13,173.28	26.6% (0.624%)	26.6% (0.6%)	47.24% (+54.8%)	30.7% (−24.6%)	0.433%
80%	60%	12,397.21	30.7% (0.589%)	30.7% (0.6%)	48.9% (+60.1%)	29.7% (−27.1%)	0.409%
30%	70%	12,899.69	10.0% (0.765%)	10.0% (0.8%)	38.8% (+27.0%)	34.8% (−14.7%)	0.533%
40%	70%	11,142.71	13.6% (0.734%)	13.6% (0.7%)	40.5% (+32.5%)	33.1% (−18.8%)	0.51%
50%	70%	11,969.07	17.7% (0.700%)	17.7% (0.7%)	42.4% (+39.0%)	32.2% (−21.0%)	0.483%
60%	70%	11,721.05	22.5% (0.659%)	22.5% (0.7%)	44.6% (+46.2%)	31.8% (−21.9%)	0.454%
70%	70%	11,915.40	26.6% (0.624%)	26.6% (0.6%)	47.24% (+54.8%)	30.7% (−24.6%)	0.433%
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40%	80%	9509.56	13.6% (0.734%)	13.6% (0.7%)	40.5% (+32.5%)	33.1% (−18.8%)	0.51%
50%	80%	10,398.36	17.7% (0.700%)	17.7% (0.7%)	42.4% (+39.0%)	32.2% (−21.0%)	0.483%
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70%	80%	10,633.55	26.6% (0.624%)	26.6% (0.6%)	47.24% (+54.8%)	30.7% (−24.6%)	0.433%
80%	80%	10,202.23	30.7% (0.589%)	30.7% (0.6%)	48.9% (+60.1%)	29.7% (−27.1%)	0.409%
30%	90%	8549.71	10.0% (0.765%)	10.0% (0.8%)	38.8% (+27.0%)	34.8% (−14.7%)	0.533%
40%	90%	7843.50	13.6% (0.734%)	13.6% (0.7%)	40.5% (+32.5%)	33.1% (−18.8%)	0.51%
50%	90%	8796.00	17.7% (0.700%)	17.7% (0.7%)	42.4% (+39.0%)	32.2% (−21.0%)	0.483%
60%	90%	8920.86	22.5% (0.659%)	22.5% (0.7%)	44.6% (+46.2%)	31.8% (−21.9%)	0.454%
70%	90%	9325.88	26.6% (0.624%)	26.6% (0.6%)	47.24% (+54.8%)	30.7% (−24.6%)	0.433%
80%	90%	9072.06	30.7% (0.589%)	30.7% (0.6%)	48.9% (+60.1%)	29.7% (−27.1%)	0.409%
30%	99%	6597.72	10.0% (0.765%)	10.0% (0.8%)	38.8% (+27.0%)	34.8% (−14.7%)	0.533%
40%	99%	6363.02	13.6% (0.734%)	13.6% (0.7%)	40.5% (+32.5%)	33.1% (−18.8%)	0.510%
50%	99%	7372.12	17.7% (0.700%)	17.7% (0.7%)	42.4% (+39.0%)	32.2% (−21.0%)	0.483%
60%	99%	7664.30	22.5% (0.659%)	22.5% (0.7%)	44.6% (+46.2%)	31.8% (−21.9%)	0.454%
70%	99%	8163.86	26.6% (0.624%)	26.6% (0.6%)	47.24% (+54.8%)	30.7% (−24.6%)	0.433%
80%	99%	8067.78	30.7% (0.589%)	30.7% (0.6%)	48.9% (+60.1%)	29.7% (−27.1%)	0.409%

QALYs, quality-adjusted life years.

surveillance of pre-cancerous lesions, including IM, dysplasia and early cancer. To further elaborate, Yeh et al (2016) evaluated the cost-effectiveness of once-only PG testing in men aged 50 years and found PG screening to increase QALYs but at an ICER of $105,000.[19] Despite being marginally not cost-effective, the PG strategy estimated a 26.4% reduction in the risk for noncardia GC in patients over 50 year old.[19] Some possible reasons for this discrepancy are as follows; the study by Yeh et al incorporated a one-time post treatment EGD after high risk lesions were endoscopically removed, whereas our model incorporates annual surveillance after endoscopic resection for gastric dysplasia and early cancers[8] as well as surveillance every 3 years for patients with IM.[7] Surveillance strategy after endoscopic resection of premalignant lesions is well justified. The majority of recurrences after curative attempt occur in the first 2 years, emphasizing the need for more diligent surveillance after endoscopic resection.[50] Although

endoscopic resection aims to be curative, metachronous neoplasms can occur in 12.1%–14.6% of patients with gastric dysplasia during intermediate follow-up.[51] In addition, the lifetime risk in our natural history strategy was higher at 0.85% compared to 0.236% used by Yeh et al (2016) due to our use of data on the prevalence of precancerous lesions of people based on PG positivity in contrast to age-based prevalence without stratification by PG status in Yeh et al[19] The clinical benefit of these additional endoscopies resulted in our study reporting a larger incremental QALYs of +0.03 vs +0.0013 reported by Yeh et al, resulting in much larger benefit in ICER calculation seen in our study. Second, Third, our total cost estimates were much lower than those by Yeh et al largely due differing PG test characteristics used to our study (Yeh et al used sensitivity of 71% and specificity of 98%). This resulted in lower percentage of patients with positive PG (due to lower sensitivity) in our model, resulting in fewer people undergoing EGD. However, the high specificity used in our model and by Yeh et al resulted in nearly all people who got EGD to have findings necessitating treatment or follow-up, benefiting these patients greatly.

Limitations

A limitation of the present study is that cost-effectiveness analyses are simplifications of complex clinical paradigms. Further, due to the paucity of US data, the sensitivity and specificity data applied to the creation of the model was drawn from only one US-based study, and prevalence of premalignant lesions from one European study. While this lacks the robustness of the Asian data, extensive sensitivity analysis showed stability of the results, and variations of test characteristics remained robustly cost-effective. Our analysis modeled the benefit of one-time PG testing at age 40. In reality, PG testing could be conducted over time and may provide further benefit. Another limitation of our study is that our model did not stratify by race or ethnicity which can influence factors such as *H.pylori* prevalence, diet, smoking, access to healthcare, and screening compliance potentially exaggerating the clinical benefit for certain groups and minimizing the clinical benefit for others. In addition, American Gastroenterological Association suggests that patients with CAG with advanced features should be considered for surveillance endoscopy every 3 years.[52] Given paucity of data on prevalence of advanced features, surveillance for CAG was not included in our model, but may have resulted in greater clinical benefit in the screening arm. Finally, our model is limited to costs to third party payers and does not include indirect costs, such as lost time from work, caregiving expenses, and transportation. These costs are beyond the scope of this study.

Conclusion

One-time serum PG testing at age 40 is associated with reduction in GC incidence and mortality. PG screening is a cost-effective screening strategy to improve GC mortality and should be considered in developing early detection and prevention strategies for GC. Furthermore, mortality benefit will depend on the test characteristics of the biomarker. Continued efforts to identify blood-based screening tests that have better performance characteristics could further improve GC prevention.

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Haejin In conceived the study, obtained research funding, data interpretation, provision of study materials, model design/conception, manuscript writing and editing. Aaron Oh contributed to the data conception, analysis and interpretation, provision of study materials, model design/conception and manuscript writing and editing. Sheila D. Rustgi and Chin Hur contributed to the data conception and interpretation, model design/conception and manuscript revisions. Haejin In takes responsibility for the paper as a whole.

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This author discloses the following: Chin Hur has consulted for Roche Diagnostics. The remaining authors disclose no conflicts.

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