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Cost Effectiveness of Gastric Cancer Screening According to Race and Ethnicity

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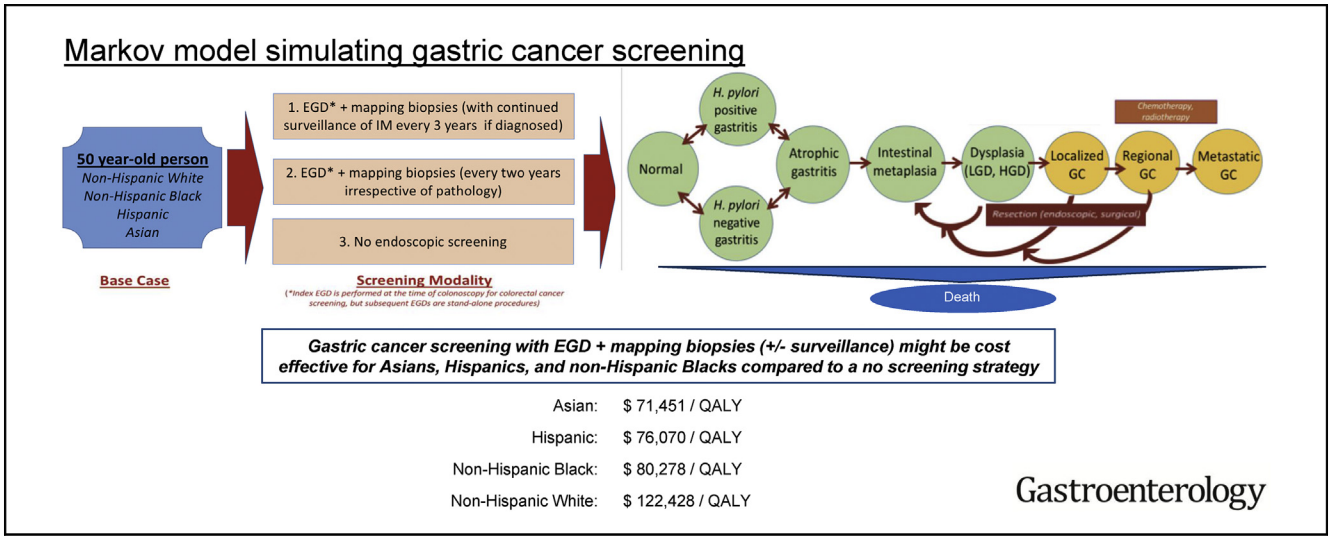

BACKGROUND & AIMS: There are marked racial and ethnic differences in non-cardia gastric cancer prevalence within the United States. Although gastric cancer screening is recommended in some regions of high prevalence, screening is not routinely performed in the United States. Our objective was to determine whether selected non-cardia gastric cancer screening for high-risk races and ethnicities within the United States is cost effective. **METHODS:** We developed a decision analytic Markov model with the base case of a 50-year-old person of non-Hispanic white, non-Hispanic black, Hispanic, or Asian race or ethnicity. The cost effectiveness of a no-screening strategy (current standard) for non-cardia gastric cancer was compared with that of 2 endoscopic screening modalities initiated at the time of screening colonoscopy for colorectal cancer: upper esophagogastroduodenoscopy with biopsy examinations and continued surveillance only if intestinal metaplasia or more severe pathology is identified or esophagogastroduodenoscopy with biopsy examinations continued every 2 years even in the absence of identified pathology. We used prevalence rates, transition probabilities, costs, and quality-adjusted life years (QALYs) from publications and public data sources. Outcome measures were reported in incremental cost-effectiveness ratios, with a willingness-to-pay threshold of $100,000/QALY. **RESULTS:** Compared with biennial and no screening, screening esophagogastroduodenoscopy with continued surveillance only when indicated was cost effective for non-Hispanic blacks ($80,278/QALY), Hispanics ($76,070/QALY), and Asians ($71,451/QALY), but not for non-Hispanic whites ($122,428/QALY). The model was sensitive to intestinal metaplasia prevalence, transition rates from intestinal metaplasia to dysplasia to local and regional cancer, cost of endoscopy, and cost of resection (endoscopic or surgical). **CONCLUSIONS:** Based on a decision analytic Markov model, endoscopic non-cardia gastric cancer screening for high-risk races and ethnicities could be cost effective in the United States.

Keywords: *Helicobacter pylori*; Neoplasm; Precancer; Preneoplasia.

Abbreviations used in this paper: **AG, atrophic gastritis; CRC, colorectal cancer; EGD, esophagogastroduodenoscopy; ESD, endoscopic submucosal dissection; GA, gastric adenocarcinoma; ICER, incremental cost-effectiveness ratio; IM, intestinal metaplasia; NCGA, non-cardia gastric adenocarcinoma; QALY, quality-adjusted life year; SEER, Surveillance; Epidemiology, and End Results.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

There are marked racial and ethnic differences in gastric cancer prevalence within the United States (US). Gastric cancer screening has been associated with improved disease-related outcomes and is a cost-effective intervention in some universally high prevalence countries.

NEW FINDINGS

Based on a decision-analytic Markov model, endoscopic gastric cancer screening initiated at the time of colonoscopy for colon cancer screening might be cost effective for high-risk races and ethnicities.

LIMITATIONS

The true prevalence of gastric preneoplasia in the US according to race and ethnicity is unknown, and data on the rate of progression from preneoplasia to neoplasia according to race and ethnicity are limited.

IMPACT

Selected gastric cancer screening in the US might improve gastric cancer-related morbidity and mortality among high-risk groups.

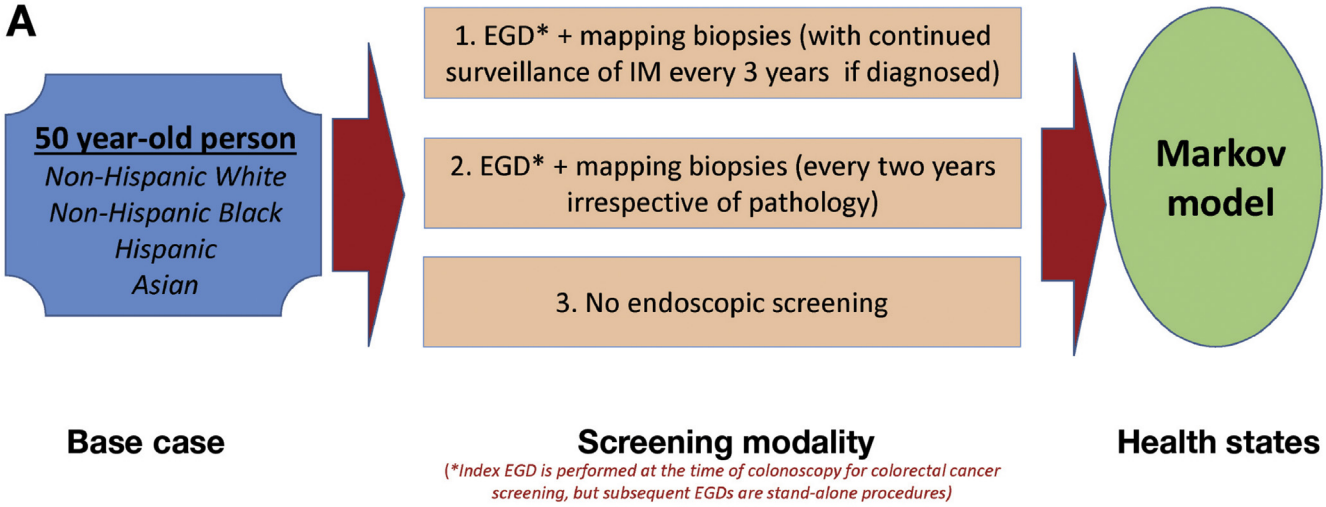
Although decreasing in incidence, gastric adenocarcinoma (GA) remains the third leading cause of cancer death globally, with non-cardia tumors representing more than 80% of all GAs.[1,2] However, when diagnosed at an early and resectable stage, 5-year survival approaches 95%–99% compared with less than 30% when diagnosed in advanced stages.[3–6] For this reason, in countries where non-cardia intestinal-type GA (NCGA) is endemic, such as Japan and Korea, national screening guidelines have been implemented for NCGA that include annual or biennial upper endoscopy in men and women starting at 40–50 years old.[7–9] Screening efforts in these countries are not only associated with significantly lower NCGA-related morbidity and mortality, due at least in part to earlier detection and opportunity for curative resection, but screening is also cost effective.[10–15] By contrast, in the United States (US), 75% of NCGAs are diagnosed in the advanced stage with limited curative options and poor prognosis. Because the US is a relatively low-prevalence country, with gastric cancer ranked the 15th most common cancer overall,[5] population-based NCGA screening is not recommended and has not been proved cost effective.[16,17] However, NCGA screening for high-risk subgroups within otherwise low- to intermediate-prevalence areas has previously been shown to be a cost-effective intervention.[18]

There are high-risk groups in the US who could similarly benefit from targeted screening for NCGA. Race and ethnicity are one way to identify such high-risk groups. Hispanics, non-Hispanic blacks, East Asians, and other immigrant groups from areas where NCGA is endemic have at least 2–3 times the prevalence of NCGA as US-born non-Hispanic whites, if not higher, with a burden of disease even tantamount to colorectal cancer (CRC) in some groups.[1,19–24] Although NCGA has been decreasing overall, these trends are far from uniform in the US; in fact, there has been an increase in gastric cancer incidence in young Hispanic men in the US, particularly advanced-stage NCGA.[25] Intestinal-type GA develops as a stepwise and typically asymptomatic progression from preneoplastic mucosal changes (atrophic gastritis [AG] and intestinal metaplasia [IM]) before malignant transformation, with *Helicobacter pylori* (*H pylori*) believed to be the primary trigger for the cascade.[26] Not surprisingly, the prevalence of *H pylori* and IM in Hispanics, non-Hispanic blacks, and immigrant populations from areas endemic for NCGA is disproportionately higher than in US-born non-Hispanic whites.[20,21,27,28] Because a diagnosis of gastric IM is one of the strongest risk factors for NCGA development, screening offers an opportunity for earlier detection and a higher likelihood of candidacy for endoscopic or surgical curative resection. Although there are no guidelines for NCGA screening in the US, the American Society for Gastrointestinal Endoscopy acknowledges the racial and ethnic differences with respect to NCGA incidence. As such, they recommend *considering* screening for NCGA with upper endoscopy among new US immigrants older than 40 years from high-risk endemic regions (Japan, Korea, China, Russia, and South America), particularly in those with a first-degree relative with a history of NCGA.[29] The society notably offers no recommendations regarding other high-risk races and ethnicities in the US, specifically Hispanics and non-Hispanic blacks. Whether such a targeted model of endoscopic screening for NCGA is cost effective in the US has not been investigated. We hypothesized that targeting NCGA screening for high-risk subgroups in the US according to race and ethnicity would be a cost-effective strategy and could increase the percentage of NCGA cases diagnosed at a curable and resectable stage.

Methods

We developed a state-transition Markov decision process model using TreeAge Pro 2017 release 1.2 (TreeAge, Williamstown, MA), simulating a base case scenario of NCGA screening at 50 years of age for non-Hispanic whites, non-Hispanic blacks, Hispanics, and Asians in the US (Figure 1*A*). This model was used to evaluate the cost effectiveness of implementing 1 of 2 endoscopic modalities for NCGA screening initiated at the time of colonoscopy for CRC screening and compared with a no endoscopic screening strategy: (1) upper endoscopy (esophagogastroduodenoscopy [EGD]) with biopsy examinations (2 sets each from the antrum and body) with continued endoscopic surveillance with biopsy examinations only if IM is identified (or appropriate management if more severe pathology is diagnosed) or (2) EGD with biopsy examination continued every 2 years even if no IM or higher grade pathology is identified (Figure 1*A*).

The Markov model was adapted from a previously published model by Yeh et al.[16,30] A systematic review of the Medline and EMBASE databases for studies published in the English language from 1947 through July 2017 was conducted to identify key variables for the model, including baseline,



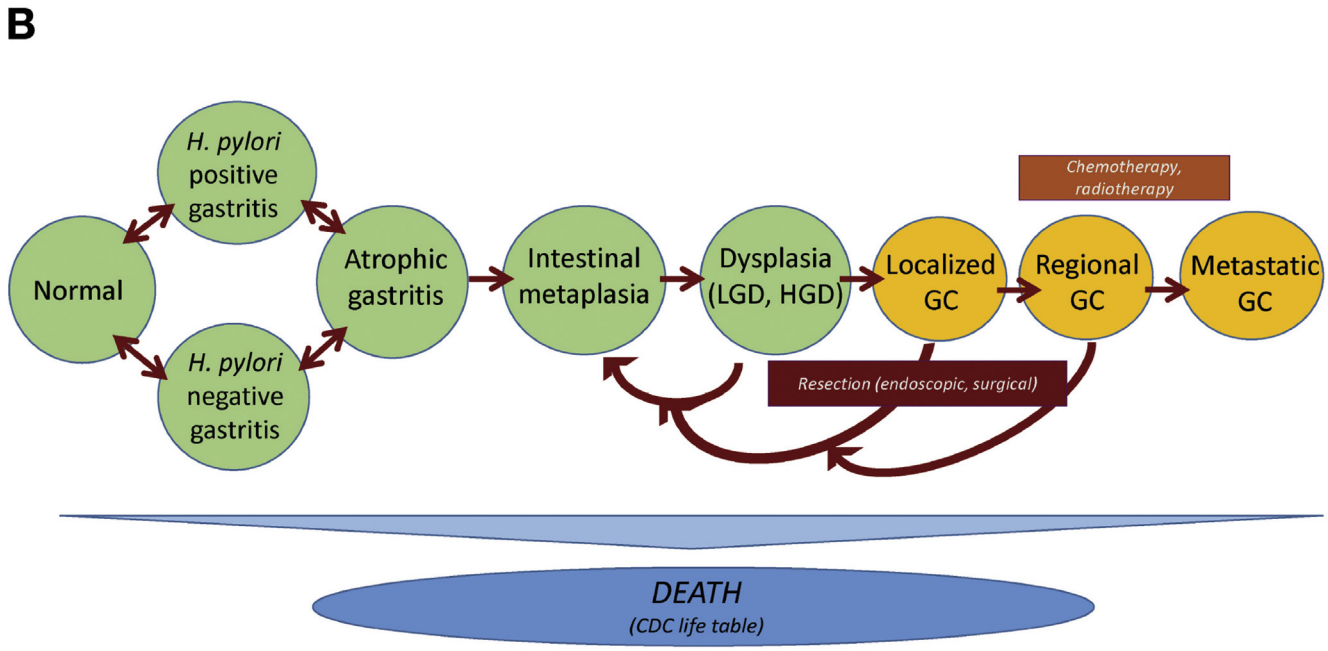


Figure 1. Markov decision process model. CDC, Centers for Disease Control and Prevention; GC, gastric cancer; HGD, upper esophagogastroduodenoscopy; LGD, lower esophagogastroduodenoscopy.

transition, and outcome probabilities for each race and ethnicity with respective parameter ranges (Table 1 and Supplemental Material). Additional details are provided in the Supplemental Material.

All individuals entered the Markov model based on population probabilities for each of the races and ethnicities. Then individuals could transition between health states depending on the assigned probabilities of an event. The different health states included normal gastric mucosa, gastritis (with or without *H pylori*), AG, IM, dysplasia, local (resectable) asymptomatic NCGA, regional asymptomatic NCGA, metastatic asymptomatic NCGA, local (resectable) symptomatic NCGA, regional symptomatic NCGA, metastatic symptomatic NCGA, and death (Figure 1*B*). In the first screening strategy, persons would undergo a bundled screening EGD with biopsy examinations and colonoscopy at 50 years of age and then enter into the appropriate identified health state. If normal mucosa or AG were identified at biopsy examination, then no further screening or surveillance would occur. If IM or neoplasia (defined as dysplasia or carcinoma) of the gastric non-cardia were identified during the initial screening procedure, then individuals would enter into a structured surveillance program as determined by the identified lesion. Individuals with IM as their most severe lesion would undergo surveillance endoscopy with biopsy examinations every 3 years. Individuals found to have dysplasia or localized (resectable) NCGA would undergo resection, followed by a 6-month and then yearly surveillance endoscopy for 3 years. If there was no recurrence of neoplasia

Table 1. Select Model Input Parameters

Inputs: baseline probabilities according to race/ethnicity	Base case	Sensitivity analysis range	Monte Carlo distribution	References
Non-Hispanic whites				
HP gastritis	0.12	0.07–0.35	Beta	21,20,70–72
Non-HP gastritis	0.15	0.07–0.25	Beta	71
AG	0.04	0.01–0.09	Beta	20
IM	0.10	0.06–0.18	Beta	20,71
Dysplasia	0.020	0.006–0.03	Beta	43,73
Local (resectable) NCGA	0.000045	0.00003–0.00010	Beta	5,16
Regional NCGA	0.000015	0.00001–0.00005	Beta	5,16
Distant NCGA	0.000025	0.00001–0.00005	Beta	5,16
Non-Hispanic blacks				
HP gastritis	0.35	0.27–0.65	Beta	27,28,70,72
Non-HP gastritis	0.15	0.07–0.25	Beta	71
AG	0.10	0.08–0.25	Beta	20,71,74
IM	0.22	0.22–0.52	Beta	21,74,75
Dysplasia	0.062	0.008–0.09	Beta	43,73
Local (resectable) NCGA	0.00011	0.00002–0.0003	Beta	5,16
Regional NCGA	0.000035	0.000008–0.00011	Beta	5,16
Distant NCGA	0.00003	0.000001–0.00005	Beta	5,16
Hispanics				
HP gastritis	0.40	0.27–0.65	Beta	28,20,21,72
Non-HP gastritis	0.15	0.07–0.25	Beta	71
AG	0.10	0.06–0.30	Beta	20,76
IM	0.27	0.12–0.40	Beta	21,74,76
Dysplasia	0.062	0.008–0.09	Beta	43,73
Local (resectable) NCGA	0.00011	0.00005–0.0003	Beta	5,16
Regional NCGA	0.00004	0.000008–0.00011	Beta	5,16
Distant NCGA	0.00003	0.000001–0.00009	Beta	5,16
Asians				
HP gastritis	0.22	0.20–0.45	Beta	20,77
Non-HP gastritis	0.12	0.07–0.25	Beta	71
AG	0.26	0.15–0.65	Beta	20,78
IM	0.32	0.25–0.50	Beta	20,69,77,78
Dysplasia	0.07	0.02–0.20	Beta	20,69,77,78
Local (resectable) NCGA	0.00018	0.0001–0.000442	Beta	5,20,69
Regional NCGA	0.00005	0.00001–0.00011	Beta	5,20
Distant NCGA	0.00003	0.00001–0.00015	Beta	5,20

NOTE. For this analysis, base case probabilities were altered when the sum total of all probabilities exceeded 1, for example, in patients with HP gastritis and AG. Thus, each lesion was considered mutually exclusive, with the more severe lesion assigned the higher probability in circumstances of overlap.
HP, *Helicobacter pylori*.

at 3 years, then individuals would be reassigned to the IM health state with surveillance endoscopy extended to every 3 years. In the second screening strategy, persons would undergo bundled screening EGD with biopsy examinations at the time of colonoscopy but would *continue* biennial surveillance endoscopy with biopsy examinations regardless of whether pathology was identified. The third screening strategy was no systematic endoscopic screening for gastric cancer (current standard of care in the US).

Assumptions

As with any cost-effectiveness analysis, certain model assumptions were made a priori. The first assumption was that all individuals were undergoing CRC screening with a colonoscopy at 50 years of age to simulate that the initial screening EGD would be bundled with and performed at the same time as an already scheduled screening colonoscopy without the need for additional anesthesiology support or facility utilization. The second assumption was that individuals found to have IM (and no neoplasia) would be enrolled in subsequent interval surveillance with EGD and gastric mapping biopsies (not bundled with colonoscopy) every 3 years.[29,31,32] All individuals who were identified to have dysplasia were eligible for endoscopic resection (endoscopic submucosal dissection [ESD]) with subsequent surveillance. Only when individuals were identified as having local (resectable) NCGA would they undergo ESD or partial gastrectomy. Because the choice of ESD vs surgical resection for gastric neoplasia in the US is variable and based on the availability and relevant experience of therapeutic endoscopists and the usual factors of lesion size, depth of invasion, surface ulceration, among other factors,[33] we estimated that for NCGA otherwise appropriate for endoscopic resection according to standard criteria, 20% would be resected by ESD

and 80% by partial gastrectomy, based on expert opinion. Furthermore, no economic evaluation has yet been performed in the US for the overall cost of ESD and no Current Procedural Terminology code is available. Therefore, we relied on expert opinion for ESD cost, used the Current Procedural Terminology code for endoscopic mucosal resection, and added an additional 50% to cover the presumed increase in facility and anesthesia use time.

Transition Probabilities

Where possible, transition probabilities, costs, and quality-adjusted life years (QALYs) were identified from published literature and available public data sources (Table 1 and Supplemental Material). The age-specific probability of all-cause mortality was estimated from the 2012 Centers for Disease Control and Prevention US Life Tables adjusted for race or ethnicity as available.[34] For the base case scenario, individuals were assumed to be otherwise healthy, asymptomatic, and undergoing routine age-appropriate CRC screening with colonoscopy. After each 1-year cycle, the individual transitioned to another health state, remained in the same state, or died (Figure 1*B*).

Cost and Utilities

QALYs were used for utilities to describe the health-related quality of life for each state, ranging from 0 (death) to 1 (perfect health). General utility scores were taken from the literature for chronic medical health states (Supplemental Material). Utilities that were unavailable in the published literature were decided by consensus of the authors. Direct procedure cost estimates were based on the 2015 Medicare estimated national average costs publicly available from the Center for Medicare and Medicaid Services[35] (Supplemental Material). The base case point estimates of cost were varied by ±50% for the sensitivity analysis. Estimates for annual direct medical costs associated with each health state and procedure-related complications were determined from the literature. For estimated costs based on expert opinion (eg, ESD), a triangular distribution for cost was used to account for variability. Complications of endoscopy or ESD were defined a priori as gastrointestinal bleeding (early or delayed), perforation, and death. Costs and utilities were discounted at a standard rate of 3% per year.[36]

Analysis

A hypothetical cohort of base case 50-year-old individuals was simulated over a 30-year time horizon with each cycle lasting 1 year. The cost effectiveness of each of the 3 screening algorithms described earlier was reported from a health care perspective. Outcome measures were reported in incremental cost-effectiveness ratios (ICERs; 2015 US dollars per QALY), with a willingness-to-pay threshold of $100,000/QALY.[37,38] One-way sensitivity analyses were performed using a Monte Carlo simulation to evaluate the effect of all defined variables according to each of the 4 races and ethnicities. For the Monte Carlo probabilistic sensitivity analysis, 10,000 iterations were performed using gamma distributions for cost and beta distributions for transition probabilities and utilities.

Results

In the standard base case scenario of a healthy asymptomatic 50-year-old person of non-Hispanic black, Hispanic, or Asian race or ethnicity, endoscopic screening for NCGA at the time of colonoscopy for CRC screening with continued surveillance of IM (or appropriate management of more advanced lesions with surveillance thereafter) was cost effective at the predetermined willingness-to-pay threshold of $100,000/QALY. This was cost effective with an ICER of $71,451/QALY for Asians, $76,070/QALY for Hispanics, and $80,278/QALY for non-Hispanic blacks. However, this strategy was not cost effective for non-Hispanic whites (ICER $122,428/QALY; Table 2). For each race and ethnicity, biennial EGD for screening irrespective of histologic findings (or lack thereof) was not cost effective compared with the other 2 screening strategies.

Model Validation

To ensure the validity of our model, incidence and 5-year mortality rate were validated using the no-screening arm of the model and comparing it with the stomach cancer statistics in the Surveillance, Epidemiology, and End Results (SEER) database.[5] In our model, the incidence of gastric cancer per 100,000 persons was comparable to the reported incidence rates in the SEER database for non-Hispanic whites, non-Hispanic blacks, Hispanics, and Asians. The 5-year relative survival rate according to gastric cancer stage in our model also was comparable to the 5-year survival rates reported by stage in the SEER database (Table 3).

Sensitivity Analyses

One-way sensitivity analyses were performed on all model inputs for each of the Markov decision process models simulating each of the 4 racial and ethnic subgroups (Supplemental Material). In the Asian, Hispanic, and non-Hispanic black subgroups (in which endoscopic screening at 50 years of age with continued surveillance, if indicated, was the most cost-effective strategy), the model was sensitive to the transition probability between the following health states—IM to dysplasia, dysplasia to local NCGA, and local to regional NCGA—and the initial probability of having IM (Table 4 and Supplemental Material). With respect to costs, the model was sensitive to the cost of EGD, ESD, and gastrectomy. Given the a priori assumption regarding the choice of ESD vs partial gastrectomy for lesions meeting standard criteria for endoscopic resection, we performed 1-way sensitivity analyses using a triangular distribution and varied the probability from 0% to 100%. For all 4 racial and ethnic subgroups, varying the probability had no significant impact on the ICER.

The no-screening strategy was the most cost effective approach in the base model only for non-Hispanic whites. Comprehensive sensitivity analyses were performed to determine the threshold at which endoscopic screening would be cost effective. Endoscopic screening (bundled with colonoscopy at 50 years of age) with continued surveillance only if necessary would become a cost-effective strategy if the yearly transition probability from IM to dysplasia

Table 2. Detailed Analysis of ICER of Endoscopic Screening for NCGA Compared With no Endoscopic Screening According to Race and Ethnicity

Race and ethnicity and screening modality[a]	Cumulative cost (USD)	Incremental cost (USD)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (USD/QALY)
Non-Hispanic whites					
No screening	2,314	—	28.05	—	—
EGD (± surveillance)	3,823	1509	28.06	0.01	122,428
EGD every 2 y	24,273	20,451	27.88	−0.19	Dominated[b]
Non-Hispanic blacks					
No screening	3860	—	27.56	—	—
EGD (± surveillance)	6,882	3022	27.60	0.04	80,278
EGD every 2 y	25,939	19,057	27.43	−0.16	Dominated[b]
Hispanics					
No screening	3,944	—	27.49	—	—
EGD (± surveillance)	7,111	3,168	27.53	0.04	76,070
EGD every 2 y	26,031	18,919	27.37	−0.16	Dominated[b]
Asians					
No screening	4,302	—	27.43	—	—
EGD (± surveillance)	7,824	3,523	27.48	0.05	71,451
EGD every 2 y	26,649	18,824	27.32	−0.16	Dominated[b]

NOTE. The ICER is reported in USD per QALY. ICERs might not calculate directly because of rounding.
USD, US dollars.
[a]In the 2 endoscopic screening strategies, the index EGD was bundled with colonoscopy for colorectal cancer screening at 50 years of age. Subsequent EGDs were performed as standalone procedures. Please see text for full descriptions of each strategy.
[b]Dominated describes scenarios in which the strategy is less effective and more costly.

exceeded 4.7%, from dysplasia to local NCGA exceeded 2.9%, or from local to regional NCGA exceeded 20.6%. In addition, this screening strategy would be cost effective if the baseline probability for IM exceeded 15.3%, for dysplasia exceeded 1.1%, or if the cost of EGD was lower than $276.

Probabilistic sensitivity analysis was derived from performing 10,000 Markov model iterations for each race and ethnicity. Cost-effectiveness acceptability curves were generated for each model for each race or ethnicity. In the model for non-Hispanic whites, the no endoscopic screening strategy was the most cost-effective strategy in 56.2% of the iterations. The bundled endoscopic screening strategy at the time of colonoscopy with continued surveillance if indicated was the most cost-effective strategy in 55.2% of iterations for Hispanics, 52.9% for non-Hispanic blacks, and 58.9% for Asians (Figure 2 and Supplemental Material).

Discussion

Using a transition state Markov decision process model, we found that endoscopic screening for intestinal-type NCGA in high-risk racial and ethnic groups, irrespective of additional risk factors, might be a cost-effective intervention. Specifically, endoscopic screening at the time of colonoscopy for CRC screening at 50 years of age with continued endoscopic surveillance every 3 years only if IM was diagnosed or appropriate management if more advanced lesions were diagnosed was cost effective for Asians, Hispanics, and non-Hispanic blacks (ICER $<$ $100,000/QALY), but not for non-Hispanic whites. Routine biennial endoscopic screening was not cost effective for any subgroup.

Although underappreciated, there are clear racial and ethnic differences with respect to incidence in the US. Although gastric cancer ranks 15th among the most common cancers in the US overall, it ranks within the top 7

Table 3. Markov Model Validation

	Model parameter	Markov model output	SEER Cancer Statistics[5] 1992–2014
5-y relative survival	Local NCGA	71.7%	67.2%
	Regional NCGA	33.1%	30.7%
	Distant NCGA	4.6%	5.2%
Incidence per 100,000 persons by race and ethnicity	Non-Hispanic white	5.5	5.8–8.0
	Non-Hispanic black	13.2	10.7–15.0
	Hispanic	13.3	10.7–15.0
	Asian	15.2	10.3–20.7

Table 4. Select Results of Sensitivity Analyses

	Model parameter	Asian	Hispanic	Non-Hispanic black
Transition probability	IM to dysplasia	0.0018	0.024	0.0028
	Dysplasia to NCGA	0.0175	0.0179	0.0184
	Local to regional NCGA	0.087	0.089	0.093
Initial health state probability	IM	0.053	0.081	0.079
Costs (USD)	EGD	$2,024	$1,832	$1,647
	ESD	$16,344	$13,903	$11,541
	Partial gastrectomy	$67,240	$59,366	$51,688

EGD, esophagogastroduodenoscopy; ESD, endoscopic submucosal dissection; IM, intestinal metaplasia; NCGA, non-cardia gastric adenocarcinoma; USD, US dollars.

leading causes of cancer deaths among non-Hispanic blacks, Hispanics, and Asian Americans.[5,39–41] Of concern, there has been an increase in gastric cancer incidence among young Hispanic men in the US, particularly advanced-stage NCGA.[25] The prevalence of gastric preneoplasia mirrors the high-risk groups within the US.[19–21,27] Further, the slow, stepwise progression of gastric precancerous lesions from AG to IM to different degrees of dysplasia, prior to malignant transformation to intestinal-type GA in a very small subset of individuals,[42,43] is analogous to the dysplasia-to-carcinoma sequences for esophageal and colorectal adenocarcinoma. This allows the opportunity for cancer prevention and early detection through screening and surveillance efforts. We found that even within the low-incidence US, targeting endoscopic screening efforts to those subgroups at greatest risk of harboring preneoplastic or even early neoplastic lesions, such as through stratification by race and ethnicity, is a highly cost-effective approach.

Our findings are congruent with a cost-effective analysis performed in Singapore, where, similar to the US, there are identifiable high-risk subgroups for NCGA within the otherwise low- to intermediate-risk background population.[18] In addition, a prospective study from the United Kingdom, another low-incidence area, showed that enrolling individuals with gastric preneoplasia in an endoscopic surveillance program had earlier stage NCGA at diagnosis.[44] When screening high-risk individuals in the asymptomatic stage, there is a higher likelihood of diagnosing early gastric cancer that is amenable to curative resection. Implementation of national screening programs for NCGA in countries such as Japan and South Korea has correlated with a significant mortality benefit. In such countries, the 5-year overall survival is 60%–70% (and 90%–95% for early gastric cancer) compared with 20%–30% in the prescreening era,[12,45,46] which approximates the current 5-year overall survival for NCGA diagnosed in countries such as the US, where routine screening does not occur. Although there are no randomized controlled trials assessing the impact of NCGA screening even in high-incidence countries—and arguably such trials would now be considered unethical—small nonrandomized studies from East Asia suggest that endoscopic screening has decreased mortality by 30%–80%; this is attributed at least in part to earlier detection and opportunity for curative resection.[47–49] Because current gastric cancer screening practices in Japan and South Korea include biennial upper endoscopy,[9,12] we included this as one of the strategies in our model. That this was not a cost-effective strategy even in the Asian subgroup is likely multifactorial. In general, screening endoscopies are associated with a lower cost burden in those countries because they are often performed unsedated and with high throughput in the outpatient setting. Moreover, preneoplasia is often diagnosed by image-enhancing endoscopic techniques, such as magnifying narrow band imaging, thus eliminating the cost of biopsy examinations. In addition to the total cost of endoscopy, our model was most sensitive to the baseline prevalence of gastric preneoplasia and neoplasia. Thus, that biennial endoscopic screening was not cost effective even in Asian Americans also is likely because the prevalence of gastric preneoplasia and neoplasia overall is lower than in the native countries. This follows the "migration effect" on cancer incidence—that is, gastric cancer incidence decreases with successive generations of immigrants depending on the extent of acculturation and other factors.[50]

To our knowledge, there are only 2 cost-effectiveness analyses that have modeled the economic impact of screening for NCGA in the US,[16,17] with the 2 studies concluding that upper endoscopic screening is not cost effective for the US population. However, neither study stratified according to race or ethnicity or accounted for patients diagnosed with gastric IM. Although Yeh et al[16,30] reported that serum pepsinogens might be a cost-effective intervention as a marker of gastric preneoplasia, this biomarker is not commercially available in the US and has been incompletely investigated in non-Asian populations, among several other limitations.[12,51–53] *Helicobacter pylori* testing also is not an ideal screening method because of its poor predictive value for preneoplasia and NCGA. In fact, active *H pylori* infection is often absent in the setting of extensive preneoplasia.[51,54,55] Furthermore, people with IM in the presence of *H pylori* infection remain at increased risk for NCGA despite *H pylori* eradication, because it is generally accepted that IM is an irreversible state.[56] Fluoroscopic imaging also has been offered as a screening modality in high-incidence countries, but the test characteristics for the detection of NCGA in the US are not defined because such

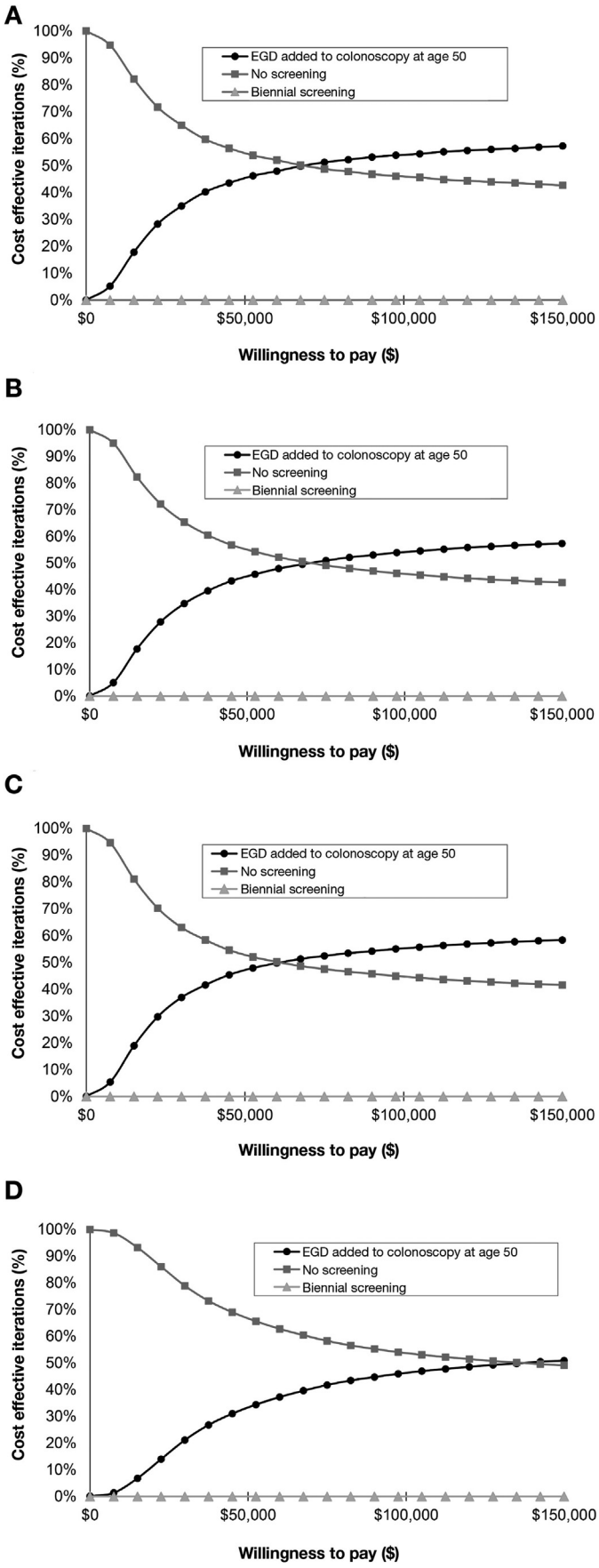


Figure 2. Cost-effectiveness acceptability curves using willingness-to-pay thresholds for each race or ethnicity. CE, cost-effectiveness.

studies are neither routinely available nor interpreted for this purpose; as such, extrapolation of the test performance of upper gastrointestinal radiography for NCGA from endemic countries to the US might not be representative. For these reasons and because there is no recommended screening strategy for NCGA in the West, we designed our model to be practical and clinically relevant for practitioners in the US, where certain image-enhancing technologies are not routinely available and high-definition white light endoscopy with histologic confirmation remains the standard for preneoplasia and neoplasia diagnosis; however, we acknowledge that biopsy examinations add additional costs and are subject to sampling error. We remain hopeful that, in the future, noninvasive biomarkers will reliably identify individuals with preneoplasia in US-based cohorts, because this could prove to be an even more cost-effective approach.

Although cost-effectiveness analyses provide useful model-based simulations and a framework for predicting the cost-to-benefit ratio of different diagnostic and therapeutic modalities for a certain disease state by balancing the cost of the intervention against the risks, they are not without some limitations. As with any decision process model, the incidence and prevalence of the disease states within each group and the estimated rates of progression influence the model outputs. The incidence and prevalence rates according to race and ethnicity for each disease state were determined from a systematic review of the published literature, but this literature has inherent limitations and biases such as variable study design and populations. As an example, because endoscopic screening is not an approved indication for EGD in the US, most studies reporting prevalence and transition rates included individuals with upper gastrointestinal symptoms and thus were not representative of an asymptomatic screening population. Progression rates of preneoplasia and various stages of cancer according to race or ethnicity also are not well described in the literature. Similarly, although the extent and histologic subtype of IM are important when considering NCGA risk, the baseline prevalence and transition probabilities for focal IM of the antrum compared with extensive IM and for complete vs incomplete IM are not well defined, especially in a US population. Histologic subtyping of IM also might not be universally available and is subject to interobserver variability. Accordingly, the IM health state in our model includes any extent and histologic subtype, although we acknowledge that extensive IM and the incomplete histologic subtype are associated with higher NCGA risk.[57] Future studies defining the risk of IM progression with greater granularity will improve risk stratification and might make the present model even more cost effective. We accounted for the heterogeneity in the literature and the uncertainty of natural disease progression by running multiple sensitivity and probabilistic analyses. In addition, because our primary aim was to determine the most cost-effective approach for NCGA screening, we bundled upper endoscopy with colonoscopy for colon cancer screening at 50 years of age to limit the cost of anesthesia and endoscopy facility fees (ie, societal costs) and to maximize participation. Thus, our model assumes that individuals have chosen colonoscopy as their preferred CRC screening modality and assumes screening at 50 years of age. The American College of Gastroenterology and the American Society for Gastrointestinal Endoscopy recommend earlier CRC screening for non-Hispanic blacks at 45 years of age to address the increased incidence and mortality from CRC in this group.[58] Accordingly, we also performed a simulation over 35 years that started at 45 years of age for non-Hispanic blacks. The results were similar and continued EGD surveillance only if IM was diagnosed remained cost effective (Supplemental Material). The model presented in this study is specific to the intestinal histologic subtype of NCGA, the most prevalent type of gastric cancer in the US; therefore, we cannot predict the implications for the diffuse histologic subtype or for that anatomically located in the cardia. Indeed, many of the risk factors for cardia GA, including racial and ethnic demography, are distinct from those for NCGA, and instead encompass established risk factors for adenocarcinoma of the distal esophagus and gastroesophageal junction.[59]

In addition to stratifying by racial and ethnic background, our study has several strengths including a detailed Markov model that considers therapeutic management and continued postresection surveillance over a 30-year time horizon, along with comprehensive probabilistic and sensitivity analyses. Our model accounts for the quality of endoscopy and relies on a careful, systematic visual examination to maximize preneoplasia and early neoplasia detection rate and minimize missed lesions, analogous to colonoscopy quality measures implemented to optimize adenoma detection rate during CRC screening. The possibility of missing lesions at endoscopy can approach 25% in some series, given the often subtle characteristic mucosal abnormalities.[60–63] Importantly, the quality of the screening examination for NCGA can vary in Western vs Eastern societies because of less experience and lack of a defined systematic screening protocol in the West.[9,64] Accordingly, we accounted for the endoscopic miss rate and the risk of recurrence after resection of early gastric cancer in our model. Another difference between Western and Eastern societies is the ability to perform ESD. Currently in the US, ESD is limited to the few academic medical centers that have advanced endoscopists adequately trained in this resection technique. We hope that with further training and experience, ESD outcomes in the US will approach the experience and skill level found in some Asian countries. Although there are, to our knowledge, no published studies of long-term outcomes for ESD in the US, authors of a recent single-center study from Europe published their experience with ESD for early-stage gastric cancer with promising rates of successful resection and rare complications that paralleled the Eastern experience.[65] Because the literature is limited for the Western vs Eastern experience, we performed sensitivity analyses on the ESD-related model variables and found that the likelihood of the lesion being amenable to ESD did not have a significant impact on the overall results. This suggests that the significant measurable benefit of NCGA screening is derived from the early identification and

opportunity for intervention, which ultimately decreases the likelihood of metastatic disease—the health state, which has the highest overall impact on cost and utility. We further acknowledge the risk of lead-time bias, which is an important concern for any screening program. Because endoscopic screening identifies NCGA in an early stage when resection is curative, we believe the risk of lead-time bias is low.

This analysis is a practical study for current clinicians because it models only screening strategies readily available in the US and relies only on racial or ethnic background as the minimum prescreening tool. Although we included only non-Hispanic blacks, Hispanics, and Asian immigrant groups, our sensitivity analyses suggest that the cost effectiveness of endoscopic NCGA screening can likely be extrapolated to other groups immigrating to the US from areas where NCGA rates are endemic.[66] Along similar lines, although our Markov model represents a generalized group of Asian immigrants based on the available published literature including the SEER database, the risk of NCGA varies among different Asian American subpopulations within the US and mirrors their native country of origin. For example, Korean, Japanese, and Vietnamese Americans carry some of the highest risk,[67] whereas Indian, Pakistani, and Bangladeshi Americans have a low incidence of NCGA despite comparable rates of *H pylori* infection in their native countries.[67,68] That said, the high-risk Asian-American populations expectedly constituted the majority of the demographic for the studies from which our model inputs for the Asian subgroup were drawn (eg, the demographic in the study by Abadir et al[69] study was 89% Korean American and that in the study by Choi et al[20] study was nearly 80% Korean or Chinese American). In general, gastric cancer risk decreases with each successive generation and approaches that of the host country after 2–3 generations, thus lending further support to the key role of environmental and other extrinsic determinants in gastric carcinogenesis.[50] This decrease depends on several factors, particularly the level of acculturation. Although the risk of NCGA in Japanese Americans and Chinese Americans has decreased over time, the risk in Korean Americans has remained relatively stable.[24,67] We acknowledge that the cost effectiveness of gastric cancer screening might decrease with successive generations, but this is highly variable and our model is not designed to address this consideration.

In conclusion, we achieved the primary aim of our study by developing a detailed Markov decision process model. We found that targeted endoscopic screening (and surveillance if indicated) for NCGA among high-risk groups according to race and ethnicity might be a cost-effective intervention in the US despite an overall low incidence of disease in the general population. Because of the increasing availability in Western society of endoscopic curative options long practiced in the East for early NCGA, namely ESD, NCGA is now a potentially curable disease when diagnosed in the early stage. We hope that our findings will stimulate efforts to address the racial and ethnic differences with respect to NCGA incidence and mortality in the US through implementation of a multimodal NCGA screening and surveillance protocol for high-risk groups in parallel with continued refinement of therapeutic endoscopic techniques and research focused on prevention efforts.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.05.026.

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Author contributions: MS was involved in the study design, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content; YH and NS were involved in the analysis and interpretation of data and review of the manuscript; MK and RZS reviewed the manuscript for content; and SCS was involved in the study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and guarantor of the article. All authors had full access to the data and take responsibility for the integrity of the data and the accuracy of the analysis.

Conflicts of interest
The authors disclose no relevant conflicts of interest.