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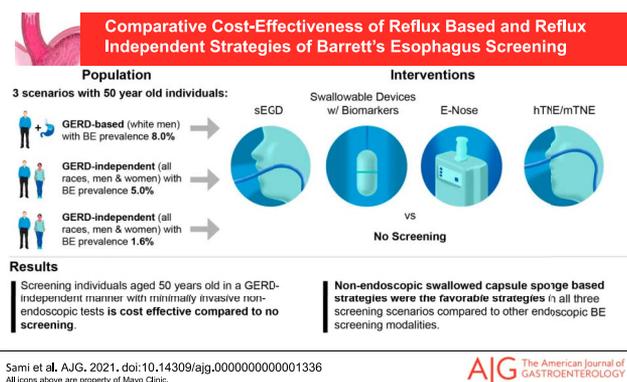
Comparative Cost Effectiveness of Reflux-Based and Reflux-Independent Strategies for Barrett's Esophagus Screening

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INTRODUCTION: Minimally invasive tests for Barrett's esophagus (BE) detection have raised the prospect of broader nonreflux-based testing. Cost-effectiveness studies have largely studied men aged 50 years with chronic gastroesophageal reflux disease (GERD) symptoms. We evaluated the comparative cost effectiveness of BE screening tests in GERD-based and GERD-independent testing scenarios.

METHODS: Markov modeling was performed in 3 scenarios in 50 years old individuals: (i) White men with chronic GERD (GERD-based); (ii) GERD-independent (all races, men and women), BE prevalence 1.6%; and (iii) GERD-independent, BE prevalence 5%. The simulation compared multiple screening strategies with no screening: sedated endoscopy (sEGD), transnasal endoscopy, swallowable esophageal cell collection devices with biomarkers, and exhaled volatile organic compounds. A hypothetical cohort of 500,000 individuals followed for 40 years using a willingness to pay threshold of \$100,000 per quality-adjusted life year (QALY) was simulated. Incremental cost-effectiveness ratios (ICERs) comparing each strategy with no screening and comparing screening strategies with each other were calculated.

RESULTS: In both GERD-independent scenarios, most non-sEGD BE screening tests were cost effective. Swallowable esophageal cell collection devices with biomarkers were cost effective (<\$35,000/QALY) and were the optimal screening tests in all scenarios. Exhaled volatile organic compounds had the highest ICERs in all scenarios. ICERs were low (<\$25,000/QALY) for all tests in the GERD-based scenario, and all non-sEGD tests dominated no screening. ICERs were sensitive to BE prevalence and test costs.



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DISCUSSION: **Minimally invasive nonendoscopic tests may make GERD-independent BE screening cost effective. Participation rates for these strategies need to be studied.**

SUPPLEMENTARY MATERIAL accompanies this paper at <http://links.lww.com/AJG/C53>, <http://links.lww.com/AJG/C54>, <http://links.lww.com/AJG/C55>

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INTRODUCTION

The incidence of esophageal adenocarcinoma (EAC) has increased approximately 6-fold over the last 3 and a half decade in Europe and North America (1). Diagnosis after symptom onset is associated with incurable disease in up to 50% of patients (2). The 5-year survival rate remains less than 20% in patients diagnosed after the onset of symptoms (3). Conversely, the 5-year survival rate of early asymptomatic cancers (SCs) is substantially higher (>80%) (3). Barrett's esophagus (BE) is the only known precursor for EAC, but two-thirds of cases remain undiagnosed in the community (4). BE screening is currently endorsed by sedated endoscopy (sEGD) or unsedated transnasal endoscopy (TNE). Although TNE in the hospital (hTNE) or in a mobile unit (mTNE) (5) has been shown to have comparable effectiveness as sEGD, its utilization for BE screening remains limited. Given the low rates of progression in nondysplastic BE, prospective studies to assess the impact of screening on EAC-related outcomes are challenging to perform. As a result, several modeling studies have attempted to evaluate whether BE screening followed by surveillance and endotherapy for early neoplasia can reduce the incidence and mortality from this lethal cancer (6–8).

Gastroesophageal reflux disease (GERD) symptoms are a strong predictor of BE and EAC (9). Current BE screening recommendations are GERD symptom based (10), but up to 40% of patients with BE and EAC deny previous chronic GERD symptoms (9,11). Substantial BE prevalence has been reported in patients who do not report chronic GERD symptoms (12,13). In addition, unlike long-segment BE, short-segment BE does not seem to be associated with GERD symptoms (14). Despite this, all previous cost-effectiveness studies for minimally invasive BE screening have only focused on individuals with chronic GERD symptoms (6–8,15–18). Relying on GERD symptoms as an essential screening criterion will lead to missing a substantial proportion of patients with BE and EAC, substantially reducing the effectiveness of this strategy (19).

Given the limitations of sEGD and uTNE, minimally invasive nonendoscopic tests have been developed to increase access and participation, showing promising accuracy, tolerability, and safety (20,21). These include (1) swallowable esophageal cell collection devices combined with biomarkers: Cytosponge + trefoil factor 3 (TFF3) as a biomarker (22–24), EsophaCap + methylated DNA markers (MDMs) (25) referred to subsequently as the sponge on a string (SoS) test, and EsoCheck + MDMs (26), and (2) exhaled volatile organic compounds (eVOCs) testing (27).

Cost-effectiveness studies have only evaluated the Cytosponge + TFF3 test and TNE (6–8) for BE screening in men with chronic GERD symptoms. Given their minimally invasive nature and lower costs, it is possible that these tests could be used to detect BE in a broader population (including those without chronic GERD symptoms but with other risk factors) to improve the effectiveness of an EAC prevention strategy. However, the cost effectiveness of this expanded strategy with minimally invasive tests

has not been studied. In addition, most published studies assume participation in screening tests to be 100%, which is also unlikely to be accurate (5).

We aimed to evaluate the comparative cost effectiveness of newer minimally invasive BE screening tests in GERD-based and GERD-independent strategies using recently published data on prevalence, accuracy, test participation, and costs (direct and indirect). Specifically, the primary aim was to compare the cost effectiveness of screening tests compared with no screening. Our secondary aim was to determine the optimal screening test to choose from (by comparing the screening approaches to each other) to implement BE screening in clinical practice.

METHODS

Study population

Two patient populations were considered in the analysis. The first population of interest was white men aged 50 years with chronic GERD symptoms (GERD-based). The BE prevalence in this population was assumed to be 8% (28). The second population corresponded to the general US population aged 50 years with or without GERD symptoms (GERD-independent). In this population, the BE prevalence was assumed to be either 1.6% as reported in one Swedish population-based study (29) or 5.0%, which was reported in US population-based studies (5,30). The model simulated hypothetical cohorts of 500,000 individuals. The specific health states considered in the simulation included no BE, nondysplastic BE, low-grade dysplasia, high-grade dysplasia (HGD), intramucosal cancer (IMC), and SC. Patients could die from any of the health states.

Study design

This analysis used a Markov model to simulate disease development and progression. The simulation was designed to compare 6 screening tests: sEGD, hTNE, mTNE, Cytosponge + TFF3, SoS, and eVOCs to no screening. sEGD was considered the gold standard test. As such, it was assumed that a positive finding on all other screening tests was confirmed by sEGD. Screening was performed only once. Once a patient was diagnosed with BE, it was assumed that all subsequent surveillance to track disease progression or therapy was performed using sEGD.

The overall model design is shown in Figure 1. The model used time intervals (cycles) of 1 month in length to simulate advancement of time toward possible disease progression, treatment, or death. With such a short time duration between model cycles, it was assumed that individuals could only move between adjacent health states during a single cycle. The overall time horizon of the simulation was 40 years (i.e., 480 monthly cycles). We assumed that the initial prevalence of IMC and SC of the screening populations were both zero (5,22,29). This meant an individual could only progress to those health states. It was also assumed that individuals could not improve from either of those health states without treatment (Figure 1).

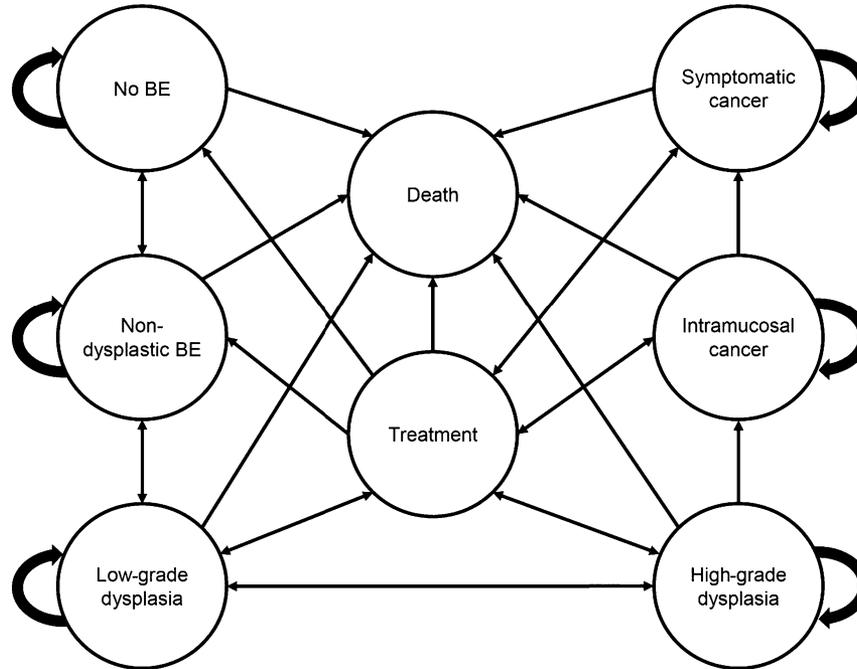


Figure 1. Model structure. BE, Barrett's esophagus.

Screening participation

Participation in diagnostic testing was incorporated in the model. Individual patient participation was assumed to be fixed in that patient's decision on whether to undergo any diagnostic test was constant. In other words, patients' willing to undergo initial screening (with whichever test) would continue to be willing to undergo subsequent confirmation with sEGD as they progress through the model. Conversely, those unwilling to undergo initial screening would continue to be unwilling to undergo subsequent confirmation.

Model probabilities

Model probabilities and sources are referenced in Table 1. All transition probabilities (i.e. probabilities moving from one health state to another) are reported as annual probabilities but were converted to monthly probabilities in the simulation because of the 1-month cycle length. Age-specific mortality probabilities used in the model came from the National Vital Statistics Report (31). In the case of the GERD population, these mortality probabilities were based on year-specific values for US white men (31). All estimates were drawn from the published literature or sources referenced in previous cost-effectiveness analyses. We used the most up-to-date evidence including systematic reviews and meta-analyses where available. Some studies reported ranges which were then used to inform those used in the sensitivity analysis, whereas other ranges were based on authors' estimates within clinical feasibility. If multiple studies were available, the highest quality level was selected for assumptions based on the authors critical appraisal of the literature and consensus opinion.

Costs and utilities

Analysis was performed from a third-party payer perspective based on Medicare reimbursement rates estimates for direct costs (32). Costs included in the analysis were restricted to the costs of diagnostic procedures (sEGD) and treatment costs of the dysplasia and cancer

health states. The cost of endoscopy included only procedure costs. Sedation costs were not included, given the differences in endoscopy sedation across institutions and practices. Costs of moderate sedation (for first 22 minutes, current procedure terminology G0500, average national Centers for Medicare and Medicaid Services reimbursement \$5.77) and monitored anesthesia (for first 22 minutes, current procedure terminology code 00731, average national Centers for Medicare and Medicaid Services reimbursement \$143.57) were factored into sensitivity analysis. Patients diagnosed with low-grade dysplasia, HGD, or IMC were treated with endotherapy, whereas those diagnosed with SC had surgery with esophagectomy and/or chemotherapy. Endotherapy was in the form of an initial session of circumferential radiofrequency ablation, followed by another 3 sessions of focal ablations in the first year. Patients with HGD/IMC would receive a session of endoscopic mucosal resection before radiofrequency ablation. Subsequent endoscopic surveillance was then performed at 3, 6, and 12 months and then annually thereafter (33,34). It was assumed that patients in these 3 health states would only have a single instance of treatment regimens for a given health state. For example, a patient diagnosed with HGD and improving after treatment would not undergo subsequent endotherapy treatment should that patient recur with HGD later on in the simulation. Utilities (Table 1) were based on previously published values. All costs and utilities were discounted at a 3% annual discount rate.

Study outcomes

The mean costs and quality-adjusted life years (QALYs) were calculated for each screening approach. These values were used to calculate incremental cost-effectiveness ratios (ICER).

The primary outcome was to compare the ICER values (cost effectiveness) of the 6 screening tests with no screening to identify whether BE screening could be cost effective. The secondary outcome was to compare the ICER values of the 6 screening tests with each other to identify the optimal screening strategy defined as the one providing the most QALYs at a cost less than the willingness to

Table 1. Model inputs and assumptions

Parameter	Base case	Range	Ref.
Prevalence estimates			
BE in general population	0.016 (29) or 0.05 (5,30)	0.00–0.05	(5,29,30)
BE in GERD centric population	0.08 (28)	0.05–0.15	(5,22,28–30,40)
Subtype distribution			
Proportion of NDBE	0.855 (5)		(2,5)
Proportion of LGD	0.09 (5)		(2,5)
Proportion of HGD	0.055 (5)		(2,5)
Proportion of IMC/SC	0.00 (5)		(2,5)
Health state transition rates (annual)			
No Barrett's to NDBE	0.0050		(6,16,17)
NDBE to no Barrett's	0.0243		(2)
NDBE to LGD	0.0289		(2)
LGD to NDBE	0.1291		(2)
LGD to HGD	0.0345		(2)
HGD to LGD	0.0476		(2)
HGD to IMC	0.1187		(2)
IMC to SC	0.1430		(2)
Test sensitivities and specificities			
Cytosponge + TFF3 sensitivity	0.733	0.449–0.922	(22)
Cytosponge + TFF3 specificity	0.938	0.913–0.958	(22)
EsophaCap + MDM (SoS) sensitivity	0.930	0.590–0.980	(41)
EsophaCap + MDM (SoS) specificity	0.980	0.700–0.990	(41)
eVOC sensitivity	0.810	0.500–0.900	(27,42)
eVOC specificity	0.510	0.250–0.900	(27,42)
TNE sensitivity	0.910	0.840–0.960	(43,44)
TNE specificity	0.960	0.940–0.980	(43,44)
Test costs \$			
sEGD	889.6	400.0–2000.0	(45)
Cytosponge + TFF3	182.0	50.0–1,000.0	(7)
EsophaCap + MDM (SoS)	200.0	50.0–1,000.0	Authors
eVOC	200.0	50.0–1,000.0	Authors
hTNE	406.0	100.0–1,000.0	(46)
mTNE	188.0	100.0–1,000.0	(46)
Participation rate			
sEGD	0.450	0.25–0.65	(5)
Cytosponge + TFF3	0.600	0.40–0.80	Authors
EsophaCap + MDM (SoS)	0.600	0.40–0.80	Authors
eVOC	0.800	0.60–1.00	Authors
hTNE	0.450	0.25–0.65	(5)
mTNE	0.450	0.25–0.65	(5)
sEGD after positive screening	1.00		(6)
Health state utilities			
No BE	1.00		(47)
NDBE	0.910	0.850–1.000	

Table 1. (continued)

Parameter	Base case	Range	Ref.
LGD	0.850	0.770–0.910	
HGD/IMC	0.770	0.675–0.850	
SC	0.675	0.575–0.770	
Treatment			
Efficacy of endotherapy			(48,49)
HGD/IMC to no BE	0.89		
HGD/IMC to NDBE	0.04		
HGD/IMC to LGD	0.03		
LGD to no BE	0.90		
LGD to NDBE	0.07		
LGD to HGD	0.015		
LGD to IMC	0.015		
Mortality from endotherapy for HGD/IMC	0.001		(50)
Proportion of SC suitable for surgery	0.50		(2,47)
Mortality from surgery for SC	0.045		(6,16,17)
5-yr survival after surgery for SC ^a	0.150		(51)
Annual mortality from inoperable disease	0.78		(47)
Mortality from any cause	Age dependent		^d
Cost of endotherapy (LGD or HGD or IMC) ^b	\$8,000		(52)
Cost of surgery for cancer or HGD/IMC ^c	\$25,882		(52)

^apT2 disease.

^bComposite cost for the first year which would include the initial endoscopic mucosal resection, circumferential RFA, and subsequent focal treatments and endoscopies including anesthesia costs.

^cCost of esophagectomy including investigations and hospital stay.

^dNational Vital Statistics Report.

BE, Barrett's Esophagus; EAC, esophageal adenocarcinoma; eVOC, exhaled volatile organic compounds; GERD, gastroesophageal reflux disease; HGD, high-grade dysplasia; hTNE, hospital unsedated transnasal endoscopy; IMC, intramucosal cancer; LGD, low-grade dysplasia; mTNE, mobile van unsedated transnasal endoscopy; NDBE, nondysplastic Barrett's esophagus; SC, symptomatic cancer; sEGD, sedated endoscopy; SoS, sponge on a string.

pay (WTP) threshold of \$100,000 per QALY. This principle of extended dominance would address the question of which test should be chosen if one were to implement BE screening in clinical practice. In addition, the incidence of symptomatic EAC, reduction in incidence of symptomatic EAC, and reduction in deaths (EAC-related and overall) for each of the screening tests in the 3 prevalence scenarios were also calculated and reported.

Statistical analysis

Base case results of the 3 cohorts (GERD-based population, GERD-independent population with BE prevalence of 1.6%, and 5.0%) report the mean costs, mean QALYs, QALYs gained, and ICER values (using the no screening strategy as a reference). One-way sensitivity analyses were performed (for both primary and secondary outcomes) on all parameters across the ranges displayed in Table 1. We also performed an additional analysis assuming equal 100% participation across all strategies to demonstrate the relative maximal effectiveness of each strategy. Probabilistic sensitivity analysis used through Monte Carlo simulations was not performed because of concerns regarding limited data availability for certain model parameters.

RESULTS

Base case model analyses

Primary outcome (screening vs no screening). The results are presented in Table 2. In the GERD-independent scenario, using a 1.6% BE prevalence, all screening strategies were more expensive but produced higher QALYs compared with the no screening strategy. Although eVOC analysis was the most expensive and effective strategy (cost = \$549 and QALYs generated = 19.1398, respectively), it also had the second highest ICER after sEGD. Both the capsule sponge + biomarker strategies (Cytosponge + TFF3 and SoS tests) were cost effective with ICERs < \$30,000/QALY. Sedated EGD had the highest ICER at \$92,381/QALY gained.

In the GERD-independent scenario with a higher (5%) BE prevalence, the results were overall similar. However, unlike the 1.6% BE prevalence scenario, ICERs for all screening strategies were less than \$30,000/QALY. Both capsule sponge + biomarker strategies (Cytosponge + TFF3 and SoS tests) had ICERs < \$10,000/QALY.

In the GERD-based screening strategy (8% BE prevalence), all screening strategies were cost effective compared with no screening, with each having an ICER well below \$100,000/QALY. The

Table 2. Base-case results

Strategy	Cost (\$)	QALY	QALY gain ^a	ICER – compared with reference arm	ICER – using extended dominance
Population: GERD-independent (50 year olds) with BE prevalence 1.6%					
No screening	28	19.1318	Reference	Reference	Reference
mTNE	121	19.136	0.0042	22,143	22,143 ^b
SoS	162	19.1362	0.0044	30,455	Extendedly dominated
Cytosponge	167	19.1368	0.005	27,800	57,500 ^b
hTNE	219	19.136	0.0042	45,476 (dominated)	Purely dominated
sEGD	416	19.136	0.0042	92,381 (dominated)	Purely dominated
eVOC	549	19.1398	0.008	65,125	127,333
Population: GERD-independent (50 year olds) with BE prevalence 5.0%					
No screening	53	19.0535	Reference	Reference	Reference
mTNE	161	19.0709	0.0174	6,207	6,207 ^b
Cytosponge	217	19.0712	0.0177	9,265	Extendedly dominated
SoS	226	19.0753	0.0218	7,936	14,773 ^b
hTNE	259	19.0709	0.0174	11,839 (dominated)	Purely dominated
sEGD	448	19.0738	0.0203	19,458 (dominated)	Purely dominated
eVOC	634	19.0758	0.0223	26,054	816,000
Population: GERD-based (white men 50 year old) with BE prevalence 8.0%					
No screening	86	18.3575	Reference	Reference	Reference
mTNE	223	18.3768	0.0193	7,112	Extendedly dominated
SoS	285	18.4203	0.0628	3,174	3,169 ^b
Cytosponge	294	18.3805	0.023	9,048 (dominated)	Purely dominated
hTNE	321	18.3768	0.0193	12,194 (dominated)	Purely dominated
sEGD	497	18.3768	0.0193	21,312 (dominated)	Purely dominated
eVOC	759	18.396	0.0385	17,484 (dominated)	Purely dominated

^aCompared with no screening.

^bSignifies optimal options using extended dominance principles.

eVOC, exhaled volatile organic compounds; hTNE, hospital unsedated transnasal endoscopy; ICER, incremental cost-effectiveness ratio; mTNE, mobile van unsedated transnasal endoscopy; QALY, quality-adjusted life year; sEGD, sedated endoscopy; SoS, sponge on a string test (EsophaCap1MDM).

strategy with the lowest ICER was the SoS test at \$3,174/QALY, and it generated the highest number of QALYs (18.4203).

All 3 model simulation scenarios resulted in sEGD and hTNE having greater costs and worse outcomes (dominated) compared with at least one other screening strategy. The Cytosponge + TFF3 and eVOC tests were both more costly and less effective (dominated) compared with the SoS test in the GERD-based population (Table 2). Base case model results assuming 100% participation rate for all 6 strategies are presented in Supplementary Table 1 (<http://links.lww.com/AJG/C55>).

After screening strategies that were costlier and less effective than another strategy were removed, extended dominance principles were followed to identify the optimal BE screening strategy in each scenario. In the GERD-independent 1.6% BE prevalence scenario, the optimal strategy was the Cytosponge + TFF3 test (ICER = \$57,500/QALY). In the GERD-independent 5% BE prevalence, the SoS test was optimal (ICER = \$14,773/QALY). Similarly, in the chronic GERD-based scenario (8% BE prevalence), the SoS test was the optimal strategy (ICER = \$3,169/QALY). Detailed steps for the extended dominance process for the 3 scenarios are provided in supplementary appendix 1 (<http://links.lww.com/AJG/C53>).

Sensitivity analyses

Primary outcome (screening vs no screening). The results of the one-way sensitivity analyses for the GERD-independent 1.6% BE prevalence scenario are shown in a tornado diagram in Figure 2. This figure shows how much the ICER varies when a given parameter changes between the ranges of high and low values for individual variables. Only parameters resulting in a change of the ICER exceeding the WTP threshold (\$100,000/QALY) are shown in the figure. The ICER for sEGD, SoS, hTNE, eVOC, and mTNE crossed the WTP threshold at BE prevalence values below 1.4%, 0.4%, 0.6%, 0.7%, and 0.2%, respectively (Figure 2). Model results were also sensitive to the cost of the test in each strategy. For example, when the cost of sEGD procedure exceeds \$959, the sEGD screening strategy becomes not cost effective because the ICER exceeds the WTP threshold of \$100,000/QALY. Adding in costs of sedation or Monitored Anesthesia Care, we can infer that sEGD with moderate sedation (total cost \$896) remains cost effective for screening, but sEGD with Monitored Anesthesia Care (total cost \$1,037) is not cost effective for screening in the 1.6% BE prevalence GERD-independent population. Similarly, the costs of the SoS, hTNE, mTNE, and eVOC tests were each sensitive parameter for

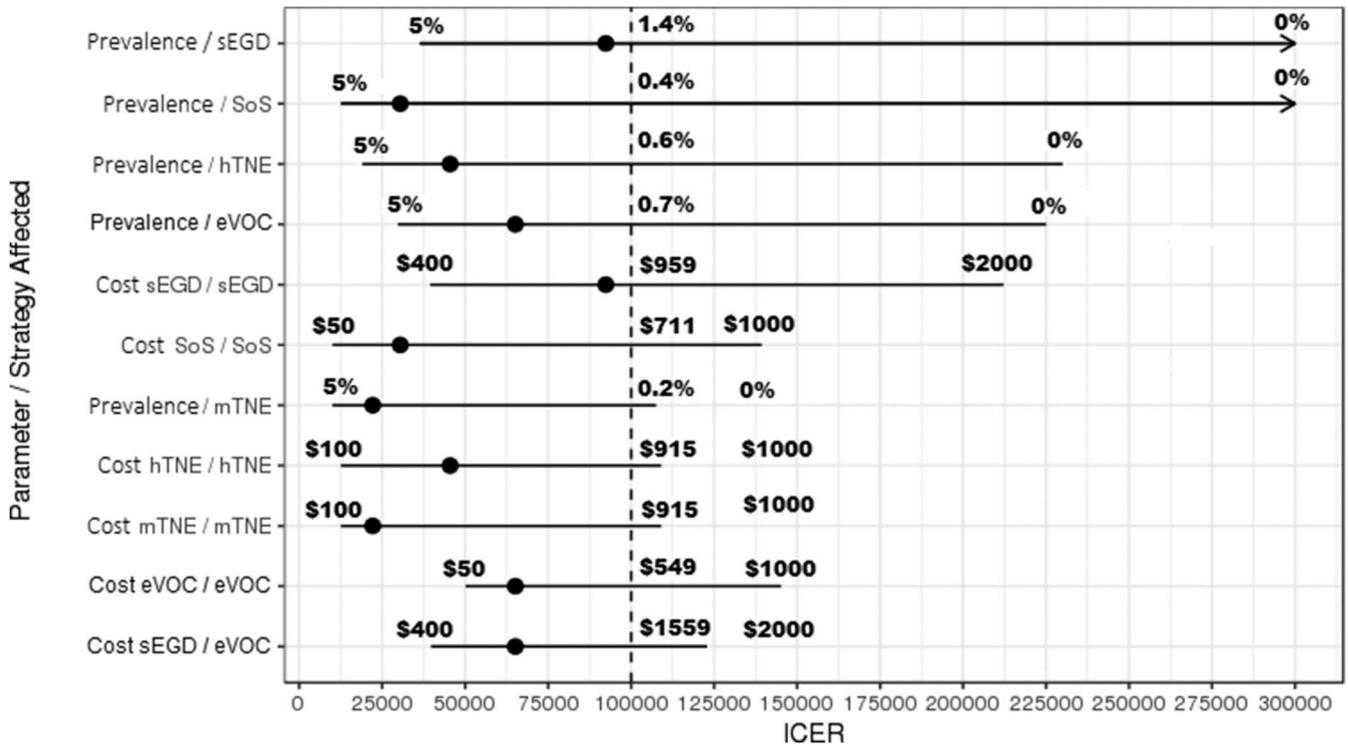


Figure 2. Tornado diagram of parameters model is sensitive (GERD-independent 1.6% prevalence). y axis signifies the sensitive parameter and which strategy is affected compared with no screening; arrows on ICER lines indicate that the line extends beyond the limit on the x axis. Dots represent ICER for base case assumption. Values on each end of a tornado bar represent the ranges for sensitivity analysis. The dotted line is the cost-effectiveness threshold. Figures to the right of the dotted line are the values at which the sensitive parameter results in an ICER equal to the threshold value of \$100,000/QALY. eVOC, exhaled volatile organic compounds; GERD, gastroesophageal reflux disease; hTNE, hospital transnasal endoscopy; ICER, incremental cost-effectiveness ratio; MDM, methylated DNA marker; mTNE, mobile transnasal endoscopy; sEGD, sedated endoscopy; SoS, sponge on a string test (Esophacap + MDMs).

their own respective screening strategies at cutoffs of \$711, \$915, \$915, and \$549, respectively.

All sensitivity analyses (within the ranges of variables modeled; see parameter ranges in Table 1) for the GERD-independent 5% BE prevalence and GERD-based scenarios resulted in all ICER values remaining below the WTP threshold. Therefore, there is no analogous tornado diagram for these 2 scenarios.

Secondary outcome (optimal screening strategy)

Two of the 3 analysis scenarios were found to have parameters that changed the optimal strategy within the sensitivity range. Those 2 were the GERD-independent BE prevalence 5% population (Figure 3) and the GERD-independent BE prevalence 1.6% population (Figure 4). For example, in Figure 3, where the SoS test is the optimal strategy, eVOC becomes the preferred strategy at an SoS uptake of <0.526, SoS sensitivity of <0.82, or SoS cost of >\$438. Similarly, in Figure 4, where the Cytosponge + TFF3 test is the optimal strategy, SoS becomes the optimal strategy at a SoS cost of <\$80. If the Cytosponge + TFF3 test uptake is <0.56, then mTNE becomes the preferred strategy. The eVOC test becomes the optimal strategy at an eVOC cost <\$97.50.

Incidence of and mortality from EAC

Estimates of incidence rates of EAC without screening from the study model are shown in supplementary Figure 1 (<http://links.lww.com/AJG/C54>) for the 3 populations. Of note, these are comparable with those reported in previous studies that validated

their incidence estimates with those of population-based registries (35,36). The impact of screening on incidence and mortality from EAC and all-cause mortality are shown in Table 3. Screening resulted in reduction in the incidence of SC in all populations across all strategies at base case assumptions. There was a direct relationship between the effect size and BE prevalence with the highest reduction seen in the GERD-based population compared with GERD-independent populations. Moreover, the reduction in incidence was highest when the assumption of 100% participation across all strategies was applied (see Supplementary Table 2, <http://links.lww.com/AJG/C55>).

Screening also resulted in lower EAC mortality with similar patterns to incidence (higher reductions in higher BE prevalence populations). The reduction in all-cause mortality was very small in all strategies and scenarios at base case assumptions.

DISCUSSION

Principal findings

Findings from this health economic modeling study suggest that screening for BE in a GERD-independent manner (in 50-year-old men and women regardless of race or the presence of GERD symptoms) may be cost effective compared with no screening, particularly when using newer nonendoscopic tests. In the GERD-independent setting, mTNE, Cytosponge + TFF3, and SoS tests were all less costly and more effective than other screening tests. The Cytosponge + TFF3 test was the optimal choice at the lowest prevalence (1.6%), whereas the

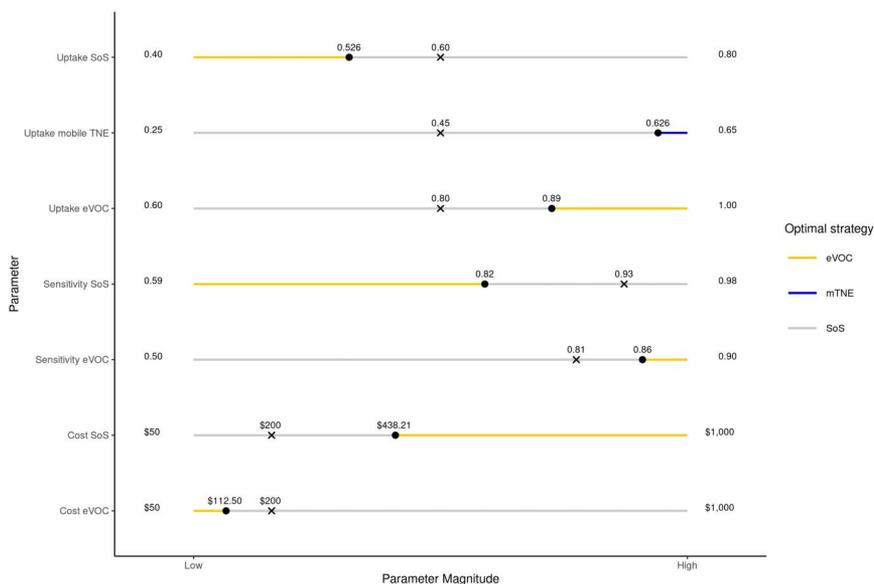


Figure 3. “Pseudo”tornado diagram of parameters: the optimal strategy model is sensitive to in the GERD-independent 5% prevalence population, where the SoS test is optimal. The color of the line represents which strategy is optimal at that level of the parameter magnitude. There are 10 parameters (y axis) which had crossover points in this analysis. The X sign on the line marks the base case value (and result), whereas the dot marks the crossover point at which the optimal strategy changes. This change is demonstrated by the lines on either side being different colors. eVOC, exhaled volatile organic compounds; GERD, gastroesophageal reflux disease; hTNE, hospital transnasal endoscopy; MDM, methylated DNA marker; mTNE, mobile van transnasal endoscopy; sEGD, sedated endoscopy; SoS, sponge on a string test (Esophacap + MDMs).

SoS test was the optimal test in both higher prevalence settings (5%, GERD-independent and 8% GERD-based). Variation in test cost and BE prevalence estimates had a significant impact on the cost effectiveness of screening in the GERD-independent low (1.6%) prevalence scenario, but not in the other 2 scenarios (Figure 2).

Screening resulted in a reduction in the incidence of symptomatic EAC, which was more pronounced in high-prevalence compared with low-prevalence GERD-independent scenarios. Reduction in symptomatic EAC incidence was highest in the GERD-based scenario and varied depending on the strategy used. There was also a similar pattern for reduction in EAC-related

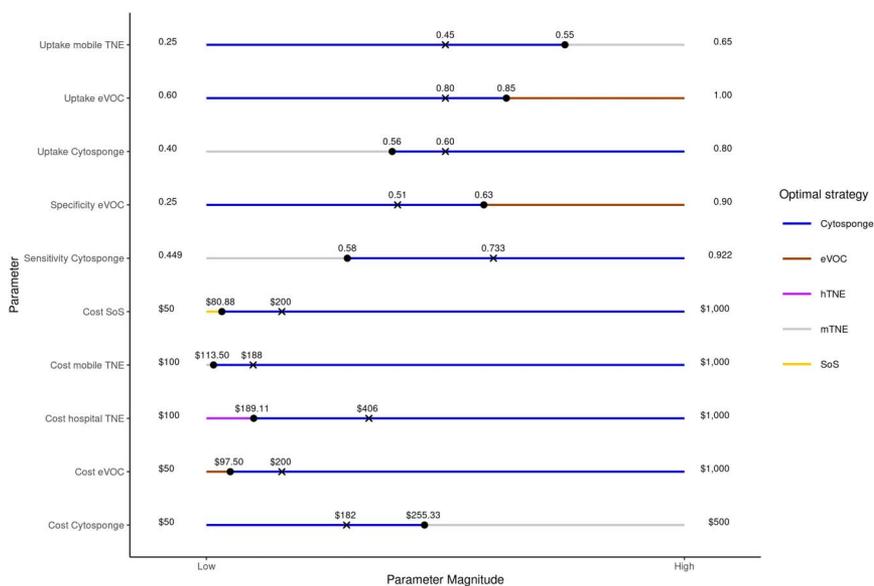


Figure 4. “Pseudo”tornado diagram of parameters the optimal strategy model is sensitive to in the GERD-independent 1.6% prevalence population, where the Cytosponge + TFF3 test is optimal. The color of the line represents which strategy is optimal at that level of the parameter magnitude. There are 10 parameters (y axis) which had crossover points in this analysis. The X sign on the line marks the base case value (and result), whereas the dot marks the crossover point at which the optimal strategy changes. This change is demonstrated by the lines on either side being different colors. eVOC, exhaled volatile organic compounds; GERD, gastroesophageal reflux disease; hTNE, hospital transnasal endoscopy; mTNE, mobile van transnasal endoscopy; sEGD, sedated endoscopy; SoS, sponge on a string test (Esophacap + MDMs); TFF3, trefoil factor 3.

Table 3. The impact of BE screening on the reduction in the incidence of symptomatic esophageal adenocarcinoma cases, esophageal adenocarcinoma related, and all-cause mortality compared with no screening

Outcome: Reduction in incidence of symptomatic EAC			
Strategy	GERD-independent (BE prevalence = 1.6%)	GERD-independent (BE prevalence = 5%)	GERD-based (BE prevalence = 8%)
sEGD	7.1%	12.8%	15.8%
Cytosponge	7.0%	13.2%	16.1%
SoS	9.2%	16.4%	19.7%
hTNE	7.2%	11.5%	15.0%
mTNE	7.2%	11.5%	15.0%
eVOC	8.6%	19.5%	24.1%
Outcome: Reduction in EAC-related mortality			
Strategy	GERD-independent (BE prevalence = 1.6%)	GERD-independent (BE prevalence = 5%)	GERD-based (BE prevalence = 8%)
sEGD	11.5%	15.8%	16.4%
Cytosponge	11.4%	15.8%	16.4%
SoS	13.8%	19.4%	20.2%
hTNE	11.6%	14.6%	15.8%
mTNE	11.6%	14.6%	15.8%
eVOC	13.6%	23.0%	25.1%
Outcome: Reduction in all-cause mortality			
Strategy	GERD-independent (BE prevalence = 1.6%)	GERD-independent (BE prevalence = 5%)	GERD-based (BE prevalence = 8%)
sEGD	0.14%	0.15%	0.12%
Cytosponge	0.12%	0.14%	0.11%
SoS	0.12%	0.15%	0.12%
hTNE	0.12%	0.12%	0.10%
mTNE	0.12%	0.12%	0.10%
eVOC	0.13%	0.17%	0.13%

The total number of patients screened in all 3 scenarios is the same (n = 500,000).

BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; eVOC, exhaled volatile organic compounds; GERD, gastroesophageal reflux disease; hTNE, hospital unsedated transnasal endoscopy; mTNE, mobile van unsedated transnasal endoscopy; sEGD, sedated endoscopy; SoS, sponge on a string.

mortality (Table 3). Reductions in EAC incidence and mortality are not directly comparable across the 3 scenarios because the denominator in the GERD-based population (only those with GERD) is different from the denominator in the GERD-independent population (all comers). In addition, the total number of individuals being modeled in the 3 scenarios is fixed at 500,000. Therefore, if resources were limited to screening only a specific number of patients (500,000 individuals in our study), then targeting those with GERD will have the highest impact for EAC incidence and mortality reduction. However, that approach will lead to a higher incidence and higher mortality in the non-GERD populations that could otherwise be prevented by a GERD-independent screening strategy (Table 3) in a cost-effective manner (Table 2). Our results also demonstrate that the reduction in EAC incidence is also driven by test adherence. At 100% participation rate, the reduction in EAC incidence was higher than base case results across all 3 populations (see Supplementary Table 2, <http://links.lww.com/AJG/C55>).

Several BE risk prediction models have been developed for use as prescreening risk assessment tools. Their aim is to improve the selection of the target population for screening and maximize BE yield (20). Their accuracy (area under the receiver operating

characteristic) ranges from 0.72 (37) to 0.85 with the addition of serum biomarkers (38). However, because all these prediction models have incorporated GERD in their scoring criteria, hence they may be susceptible to missing BE (and potentially EAC) that may otherwise be detected in a GERD-independent screening strategy.

This is the first study evaluating the cost effectiveness of minimally invasive screening for BE in a GERD-independent scenario. Previous studies with these techniques have only focused on male GERD-based populations (6–8,17). Moreover, they only evaluated a single technique in one model. One of these studies evaluating the Cytosponge + TFF3 used a prevalence of 1.6% in a supplementary analysis and reported an ICER of \$39,400/QALY (6) (compared with \$27,800/QALY in our study). However, mortality data used in that model were those of a chronic GERD population rather than in a broader population and therefore may lack external validity in this setting.

ICERs in the 2 studies evaluating the Cytosponge + TFF3 in chronic GERD male populations were \$15,700/QALY (6) and \$26,358 to \$33,307/QALY (7) compared with no screening, respectively. A third study evaluated hTNE and mTNE with

corresponding values of \$29,446/QALY and \$26,218/QALY, respectively. We performed similar modelling in GERD-centric population in our study with lower ICERs for all 3 strategies. The reasons for the lower estimates in our study are likely to be related to the difference in model design and input values for several parameters such as screening participation. Nonetheless, our results are in line with previous studies demonstrating that screening can be cost-effective and ICER values remain below the commonly used WTP thresholds of \$50,000–\$100,000 per QALY. The reduction in symptomatic EAC incidence in our study was also in line with previous studies (6).

Our study is also the first to compare several screening strategies. Cost-effectiveness studies vary in their model design and assumptions, and therefore, it may not be possible to make direct comparisons between tests from different models. Our approach of including several tests in one model allowed direct comparisons between different tests, both compared with no screening and also to each other, using the principles of extended dominance.

Study strengths and limitations

Our model design is reflective of the current best knowledge of the natural history of BE and modern minimally invasive therapies for BE with early neoplasia. We used data from recently published randomized trials and systematic reviews to enhance the validity of our methodology and findings. Our model estimates for the incidence of EAC in the 3 populations evaluated were in line with estimates from studies using population-based EAC registries, adding validity to our results (35). Previous modeling studies had limitations about assumptions on disease prevalence, participation rates, and costs of screening in the community because data were not available at the time. For instance, participation rates of 95% has been used in some studies for TNE (39), but recent data suggest that these are much lower (45.7%) (5). Other studies used estimates for participation in sEGD of 23% (6), which is lower than that used in this study (45%) (5). The latter may account for differences in ICER estimates between studies and reinforces the importance of comparing different strategies in one study rather than across multiple studies.

We performed one-way sensitivity analyses in this study. This approach assesses changes in only 1 parameter at a time rather than varying multiple parameters, which may be a limitation of this study. Moreover, although it is possible that a reduction in quality of life could occur from invasive testing, and even a false positive from a minimally invasive test, these aspects were not taken into consideration for this analysis. However, these reductions in quality of life would have been over periods of time shorter than a single cycle of the simulation (1 month). Our sensitivity analyses of the health states were over the entire model period and showed no change in results. Finally, our base case assumptions for accuracy of both eVOC and SoS tests were superseded by published studies reporting modestly different accuracy values (25,27). However, we accounted for these values in our sensitivity analyses and found no impact on both primary and secondary outcomes of the study. In addition, most studies reporting performance characteristics of these tests were of case control design in enriched secondary care populations (27) and included longer BE segment lengths (25). Hence, test accuracy may have been overestimated. These tests need to be evaluated in screening populations. However, the sensitivity analyses

presented in this article may account for some of these anticipated issues. Lastly pending published data on the performance of the EsoCheck + MDM test in additional studies, the inclusion of the SoS test in the analyses addresses the concept of esophageal cytology collection combined with MDMs for BE screening.

CONCLUSIONS AND IMPLICATIONS FOR CLINICAL PRACTICE

Screening for BE with newer nonendoscopic tests even in a GERD-independent strategy appears to be cost effective. Capsule sponge + biomarker tests were the most cost effective and optimal screening strategies in all 3 BE prevalence scenarios incorporating GERD-based and GERD-independent testing approaches. Capsule sponge + biomarker tests are less operator-dependent and potentially suitable for widespread application. Future research is needed to evaluate uptake, acceptability, and accuracy in screening populations using these minimally invasive strategies.

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CONFLICTS OF INTEREST

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Study Highlights

WHAT IS KNOWN

- ✓ Minimally invasive nonendoscopic methods for Barrett's esophagus (BE) screening have promising performance characteristics compared with sedated endoscopy.
- ✓ BE screening is cost effective in white 50-year-old men with chronic gastroesophageal reflux disease (GERD).

WHAT IS NEW HERE

- ✓ Multiple endoscopic and nonendoscopic minimally invasive BE screening strategies were compared in 1 model with no screening and with each other, in both GERD-based and GERD-independent population scenarios.
- ✓ Screening individuals aged 50 years old in a GERD-independent manner with minimally invasive nonendoscopic tests is cost effective compared with no screening.
- ✓ Nonendoscopic swallowed capsule sponge + biomarker-based strategies were the favorable strategies in both GERD-based and GERD-independent scenarios compared with other endoscopic BE screening modalities.

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