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Cost Effectiveness of Screening Patients With Gastroesophageal Reflux Disease for Barrett's Esophagus With a Minimally Invasive Cell Sampling Device

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BACKGROUND & AIMS: **It is important to identify patients with Barrett's esophagus (BE), the precursor to esophageal adenocarcinoma (EAC). Patients with BE usually are identified by endoscopy, which is expensive. The Cytosponge, which collects tissue from the esophagus noninvasively, could be a cost-effective tool for screening individuals with gastroesophageal reflux disease (GERD) who are at increased risk for BE. We developed a model to analyze the cost effectiveness of using the Cytosponge in first-line screening of patients with GERD for BE with endoscopic confirmation, compared with endoscopy screening only.**

METHODS: **We incorporated data from a large clinical trial of Cytosponge performance into 2 validated microsimulation models of EAC progression (the esophageal adenocarcinoma model from Massachusetts General Hospital and the microsimulation screening analysis model from Erasmus University Medical Center). The models were calibrated for US Surveillance, Epidemiology and End Results data on EAC incidence and mortality. In each model, we simulated the effect of a 1-time screen for BE in male patients with GERD, 60 years of age, using endoscopy alone or Cytosponge collection of tissue, and analysis for the level of trefoil factor 3 with endoscopic confirmation of positive results. For each strategy we recorded the number of cases of EAC that developed, the number of EAC cases detected with screening by Cytosponge only or by subsequent targeted surveillance, and the number of endoscopies needed. In addition, we recorded the cumulative costs (including indirect costs) incurred and quality-adjusted years of life lived within each strategy, discounted at a rate of 3% per year, and computed incremental cost-effectiveness ratios (ICERs) among the 3 strategies.**

RESULTS: **According to the models, screening patients with GERD by Cytosponge with follow-up confirmation of positive results by endoscopy would reduce the cost of screening by 27% to 29% compared with screening by endoscopy, but led to 1.8 to 5.5 (per 1000 patients) fewer quality-adjusted life years. The ICERs for Cytosponge screening compared with no screening ranged from $26,358 to $33,307. For screening patients by endoscopy compared with Cytosponge the ICERs ranged from $107,583 to $330,361. These results were sensitive to Cytosponge cost within a plausible range of values.**

Abbreviations used in this paper: BE, Barrett's esophagus; BEST2, Barrett's oEsophagus Screening Trial 2; EAC, esophageal adenocarcinoma; EET, endoscopic eradication therapy; Erasmus/UW, microsimulation screening analysis model from Erasmus University Medical Center and the University of Washington; GERD, gastroesophageal reflux disease; HGD, high-grade dysplasia; ICER, incremental cost-effectiveness ratio; MGH, esophageal adenocarcinoma model from Massachusetts General Hospital; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; RFA, radiofrequency ablation; SEER, Surveillance, Epidemiology and End Results.

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CONCLUSIONS: **In a comparative modeling analysis of screening strategies for BE in patients with GERD, we found Cytosponge screening with endoscopic confirmation to be a cost-effective strategy. The greatest benefit was achieved by endoscopic screening, but with an unfavorable cost margin.**

Keywords: Barrett's Esophagus; Cost Effectiveness; Esophageal Adenocarcinoma; Cytosponge.

Since 1975, the incidence of esophageal adenocarcinoma (EAC) has increased more than 6-fold in the United States, with comparable increases in several other Western countries.[1] The prognosis for diagnosed esophageal cancer patients is poor, with 5-year relative survival rates as low as 18.8%.[1] Barrett's esophagus (BE) is a metaplastic precursor condition to EAC with an estimated prevalence of 5.6%.[2] BE can be detected via endoscopy and may be managed with surveillance to detect treatable high-grade dysplasia (HGD) or early EAC. However, more than 90% of diagnosed EACs do not arise from patients in BE surveillance programs.[3] This statistic highlights the need for better strategies for early detection to reduce the morbidity and mortality associated with EAC.

Gastroesophageal reflux disease (GERD) symptoms are a known risk factor for BE and EAC.[4–6] GERD prevalence in the Western world has been estimated at 10% to 20%.[7] Screening GERD patients for BE has the potential to reduce EAC incidence, but costs of endoscopic screening in a large population may be prohibitively high.

As a potential alternative to standard endoscopic screening, we consider a novel minimally invasive screening method, the Cytosponge (Medtronic, Dublin, Ireland) which allows tissue to be sampled from the surface of the esophagus nonendoscopically. A biomarker, Trefoil factor 3, currently is used to diagnose BE from the collected tissue.[8–10] Cytosponge screening may be available at a significantly lower cost than endoscopy and can be administered in a primary care setting without the need for sedation.

A large clinical trial, Barrett's oEsophagus Screening Trial 2 (BEST2), to assess Cytosponge performance was published, and we incorporated these latest data into our modeling approach. We used a comparative modeling approach with 2 previously validated models both calibrated to high-quality US population Surveillance, Epidemiology and End Results (SEER) data on EAC incidence and mortality.

Methods

Cancer Intervention and Surveillance Modeling Network–Esophageal Adenocarcinoma Models

Analyses were conducted using 2 independent microsimulation models of the natural history of EAC: the EAC model from Massachusetts General Hospital (Boston, MA) (MGH model), and the microsimulation screening analysis model from Erasmus University Medical Center (Rotterdam, The Netherlands) and the University of Washington (Seattle, WA) (Erasmus/UW model). Both models incorporate the full natural history of EAC, starting from normal health and progressing through nondysplastic BE, low-grade dysplasia, and HGD before reaching cancer. Both models have been calibrated previously to SEER data on EAC incidence and mortality, stratified by age, year, and historic stage.[11] During the calibration process, the MGH model approximated the BE prevalence for males and females, respectively, in 2010 to be approximately 2.6% and 1.1%; the Erasmus/UW model estimation was 1.4% and 0.5%.[11] In addition, both models were extended in a previous comparative modeling exercise to incorporate detailed simulations of BE surveillance and treatment of HGD using endoscopic eradication therapy (EET).[12] The models were developed independently and incorporate different parameters and structural assumptions regarding the natural history of EAC. However, the models are part of the National Cancer Institute's Cancer Intervention and Surveillance Modeling Network consortium and have undergone extensive comparative modeling validation exercises. Full details of the respective models are available online.[13,14]

Population of Interest

We simulated a 1950 birth cohort of US men starting at age 20. At age 60, the population of interest was restricted to those who had shown GERD symptoms and had not been diagnosed with EAC. This group then was screened for BE according to 1 of 3 strategies: Cytosponge-first screening, endoscopy-only screening, or no screening. Patient cohorts in all strategies were followed up until death or age 100. Quality-adjusted life-years, EAC cases, EAC deaths, endoscopies, EET sessions, and total lifetime costs of treatment and surveillance were recorded starting from the time of the initial screen.

Screening Strategies

Three strategies were included in this analysis. In the natural history or no-screening strategy, no intervention took place until patients were found to have cancer because of symptoms, at which point they received standard treatment. In the Cytosponge screening strategy, patients with GERD symptoms were given a 1-time Cytosponge screen for BE at age 60. Patients with positive screening results were subject to confirmation by endoscopy. The false-negative and false-positive

probabilities for the initial Cytosponge screen, conditional on dysplastic grade, were derived from the BEST2 trial (Table 1). If either the Cytosponge test or the confirmation endoscopy was negative, there was no further follow-up evaluation. In the endoscopic screening strategy, GERD-symptomatic patients were given an immediate diagnostic endoscopy at age 60. Performance characteristics for endoscopy were estimated from the literature (Table 1). Negative results received no follow-up evaluation.

Management of Barrett's Esophagus

Detailed clinical aspects of BE surveillance and endoscopic eradication therapy were incorporated into our models in a previous analysis.[12] For this analysis, we assumed all patients diagnosed with HGD were treated with endoscopic eradication that included possible endoscopic mucosal resection and radiofrequency ablation (RFA) therapy; touch-up RFA treatment was given to patients who had dysplasia recurrence after initial treatment. Possible outcomes of initial treatment were complete eradication of BE (including dysplasia), eradication of dysplasia only, and treatment failure. Patients with diagnosed low-grade dysplasia or nondysplastic BE were not treated immediately, but underwent surveillance at regular intervals (every year for low-grade dysplasia, and every 3 years for nondysplastic BE), with treatment administered after a diagnosis of HGD. This treatment and surveillance strategy is consistent with recent American Gastroenterological Association guidelines.[15] Key parameters governing endoscopic eradication treatment in the models can be found in Table 1.

Table 1. Common Input Parameters

Parameter/model inputs	Value	Reference
Endoscopy parameters		
BE ND false-negative rate	0.125	23
BE false-positive rate	0.075	23
Complication rate	0.00013	24,25
Endoscopy cost	$745	26
Cytosponge parameters		
Bleed rate	0.002	20*a*
BE false-negative rate (ND)	0.21	20
BE false-negative rate (LGD)	0.195	20
BE false-negative rate (HGD)	0.158	20
BE false-positive rate	0.076	20
Cost of Cytosponge	$182	16*b*
Key RFA treatment parameters		
RFA initial treatment cost	$5630	26
RFA touch-up treatment cost	$1012	26
Post-treatment recurrence rate	0.10	27,28
Eradication rate of dysplasia with persistence of intestinal metaplasia		
HGD	0.17	27,28
LGD	0.19	27,28
Eradication rate of dysplasia and intestinal metaplasia		
HGD	0.68	27,28
LGD	0.72	27,28
ND	0.81	27,28

LGD, low-grade dysplasia; ND, no dysplasia.
[a]Bleed rate estimated from adverse events reported in BEST2.
[b]Personal communication with Medtronic representative Terry Davison, June 29, 2016.

Costs

A cost-effectiveness analysis was conducted from a societal perspective. Costs for cancer treatment were derived from the literature. Costs for endoscopy and for EET of BE with HGD were estimated using Medicare reimbursement rates (Table 1). Because the Cytosponge is a new technology and not yet available commercially, there are little empiric data to inform its cost in a clinical setting. For the base case we estimated an expected cost of $182 based on a combination of direct communication with Medtronic representatives regarding the cost of the device itself (estimated as $55) as well as Medicare facility payments for comparable diagnostic tests.[16] Given the uncertainty of this parameter and its importance to our analysis, we conducted a pivotal sensitivity analysis using a wide range of plausible estimated Cytosponge costs from $0 up to $1000.

Quality-of-Life Adjustments

Quality-of-life utilities for EAC by stage were estimated from the literature, as were decrements for endoscopy, EET, and complications including stricture or perforation.

Outcomes

For each strategy we recorded the number of clinical EAC cases developed, the number of EAC cases detected by the initial screen or by subsequent targeted surveillance, and the number of endoscopies needed. In addition, we recorded the cumulative costs (including indirect costs) incurred and quality-adjusted years of life lived within each strategy, discounted at a rate of 3% per year, and computed incremental cost-effectiveness ratios (ICERs) between the 3 strategies. All outcomes were computed per 1000 GERD-symptomatic patients at the start of screening.

Sensitivity Analyses

We performed 1-way sensitivity analyses on several key parameters, including Cytosponge cost, Cytosponge performance characteristics, initial effectiveness of EET, rates of recurrence after EET, sex, and age at initial screening. In addition, we performed a cost-effectiveness analysis from an alternative perspective in which patient time spent undergoing screening or treatment was incorporated into the total cost. A detailed description of

the parameters used in these analyses can be found in the Supplementary Materials and Methods section and Supplementary Tables 1 and 2.

Finally, in the MGH model, a probabilistic sensitivity analysis (PSA) was performed, simultaneously varying a large number of parameters including performance characteristics of Cytosponge and endoscopy, complication rates, recurrence rates, direct costs, and utilities. Distributions for each parameter were estimated from the literature. 1000 runs of 10 million patients each were performed using parameter sets sampled from the estimated distributions via a Metropolis algorithm. A distribution for Cytosponge cost was not included in the PSA, instead the Cytosponge cost was varied across the full $0 to $1000 range for each PSA run. Full details of the probabilistic and 1-way sensitivity analyses can be found in the Supplementary Materials and Methods section.

Results

Base Case

Detailed base-case results are shown in Table 2. The natural history (no screening) strategy resulted in the worst health outcomes, with 13.75 to 16.25 total cancers and 15,076 to 15,078 quality-adjusted life-years (QALYs) (ranges reflect differences between models). Endoscopic screening offered the largest benefit, with 6.8 to 12.44 total cancers and 15,101 to 15,116 QALYs. The Cytosponge-first screening showed results that were in-between, with 8.18 to 13.15 cancers and 15,099 to 15,110 QALYs. However, greater benefits were accompanied by higher total costs. Costs were $703,690 to $762,043 using the natural history strategy, $1,485,205 to $1,597,713 using the Cytosponge strategy, and $2,089,549 to $2,185,741 using the endoscopy strategy.

Both models found the Cytosponge to be cost effective compared with no screening in the base-case analysis, with an ICER of $26,358 to $33,307 (Figure 1). Both models found that endoscopic screening was not cost effective when Cytosponge-first screening was available as an alternative; the ICER for endoscopic screening compared with the Cytosponge was $107,583 to $330,361 greater than our willingness-to-pay threshold of $100,000. The large cost difference between the Cytosponge and endoscopic screening was driven primarily by the total number of endoscopies needed. The models predicted 757 to 1197 screening or surveillance endoscopies would be needed using the Cytosponge strategy, compared with 1826 to 2296 using the endoscopic screening strategy.

Sensitivity Analyses

Results of a 1-way sensitivity analysis on the Cytosponge cost are shown in Figure 2. Endoscopic screening becomes cost effective (given a $100,000 willingness-to-pay-threshold) when the total cost of the Cytosponge exceeds $604 (MGH) or $224 (Erasmus/UW). Furthermore, endoscopic screening is a dominant strategy when the Cytosponge cost exceeds $684 (MGH) or $565 (Erasmus/UW). Thus, our results are sensitive to the Cytosponge cost within the range deemed plausible for this analysis; it is notable, however, that the Cytosponge remains cost effective over a majority of this range.

Results of all other 1-way analyses are provided in the Supplementary Materials and Methods section and Supplementary Tables 3 and 4. In an analysis of screening for 60-year-old women with GERD symptoms, the Cytosponge remained cost effective (ICER, $86,850–$89,674 compared with natural history) despite the lower incidence of EAC in women. Endoscopic screening was strictly dominated in this analysis. Our findings were somewhat sensitive to estimates of the performance characteristics of the Cytosponge and RFA characteristics. With low estimates of Cytosponge sensitivity and specificity, the Cytosponge remains cost effective (ICER, $29,172–$34,758). However, comparing endoscopy with the Cytosponge we found an ICER of $64,031 to $191,076, therefore endoscopy may be a viable strategy given a willingness-to-pay threshold of $100,000 if the diagnostic accuracy of the Cytosponge is sufficiently poor. In addition, endoscopy may be viable if the recurrence rates after EET are low or if the effectiveness is high, with endoscopy to Cytosponge ICERS of $83,686 to $314,574 and $98,227 to $303,055, respectively. Our findings were robust to inclusion of indirect costs, sex, and choice of initial screening age (ages, 50,

Table 2. Main Results of the Simulation Models

	MGH			Erasmus/UW		
	Natural history	Cytosponge	Endoscopy	Natural history	Cytosponge	Endoscopy
Total clinical EAC	16.25	8.82	7.09	13.75	5.13	3.06
Total screen-detected EAC	0.00	4.33	5.35	0.00	3.05	3.74
Total EAC	16.25	13.15	12.44	13.75	8.18	6.8
Endoscopies	0	757	1826	0	1197	2296
Cost (discounted)	$762,043	$1,485,205	$2,089,549	$703,690	$1,597,713	$2,185,741
QALY (discounted)	15,078	15,099	15,101	15,076	15,110	15,116

NOTE. All results are reported per 1000 GERD patients at the start of screening.

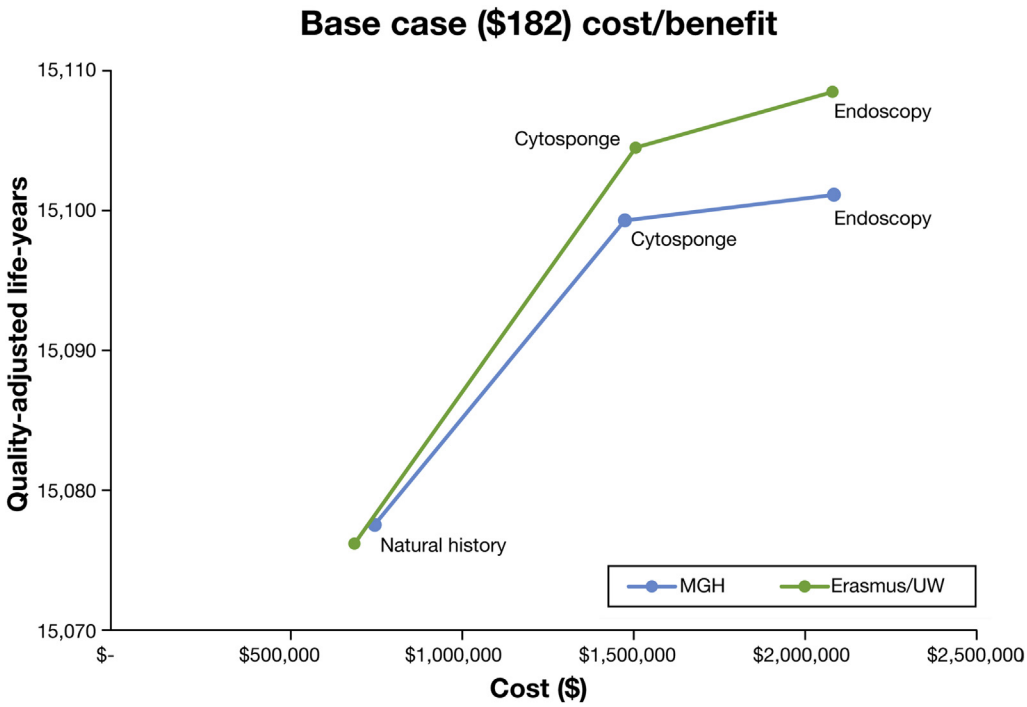

Figure 1. Cost/benefit curves for the (*A*) MGH (blue) and (*B*) Erasmus/UW (green) models. All numbers are reported per 1000 GERD patients at the start of screening. NH, natural history.

60, or 70 y); in each analysis, the Cytosponge remained cost effective whereas endoscopic screening exceeded the willingness-to-pay threshold.

Finally, a probabilistic sensitivity analysis was performed using the MGH model. With a fixed Cytosponge cost of $182 and a willingness-to-pay threshold fixed at $100,000, our results were consistent across all runs. The Cytosponge was found to be cost effective with an ICER ranging from $32,567 to $36,353 compared with natural history; endoscopic screening was not cost effective with an ICER ranging from $234,762 to $423,809 compared with the Cytosponge. When the Cytosponge cost was increased to $500, the strategy remained cost effective in all PSA runs, with an ICER ranging from $47,326 to $51,822 compared with natural history. The ICER for endoscopic screening compared with the Cytosponge remained greater than the willingness-to-pay threshold in all runs, ranging from $106,630 to $206,272. Further details including alternate analyses with other willingness-to-pay thresholds and Cytosponge costs can be found in the Supplementary Materials and Methods section, Supplementary Tables 2 and 3, and Supplementary Figures 1 to 4.

Discussion

Our comparative modeling analysis found that, for 60-year-old men with GERD symptoms, an initial Cytosponge screen may be a cost-effective way to reduce the incidence and mortality of esophageal adenocarcinoma. Cytosponge screening could result in significant cost savings compared with screening with endoscopy. These findings are consistent with those of a previous UK modeling analysis that used preliminary Cytosponge data.[17]

This cost savings is driven in part by the large difference in the estimated cost of a single endoscopy compared with administration of a Cytosponge screen. An additional driver of cost reduction in the Cytosponge strategy is the reduction in the number of false-positive results; although the estimated false-positive rate for the Cytosponge was higher than that of endoscopy, the combined false-positive rate for the Cytosponge with endoscopic confirmation was lower than that of a single endoscopy. This lead to a reduction in the number of people who entered surveillance and thus to the total number of endoscopies and EET sessions.

A significant strength of our analysis was the comparative modeling approach. Although the 2 models shared a number of common inputs (including costs of all procedures, test performance characteristics, estimates of EET effectiveness, and SEER incidence and mortality as calibration targets), they were developed and calibrated independently, used different mathematic methods, and made different quantitative and structural assumptions regarding the natural history of EAC development. For example, the models relied on different estimates of BE prevalence, and the Erasmus/UW model incorporated regression whereas the MGH model did not. Although both models were calibrated to SEER incidence data, this constrained only the overall progression rate to EAC in the total population, leaving room for differences in the relative risk of BE or cancer development associated with GERD symptoms. Detailed profiles of both models as well as a broad comparative overview are available online.[13,14]

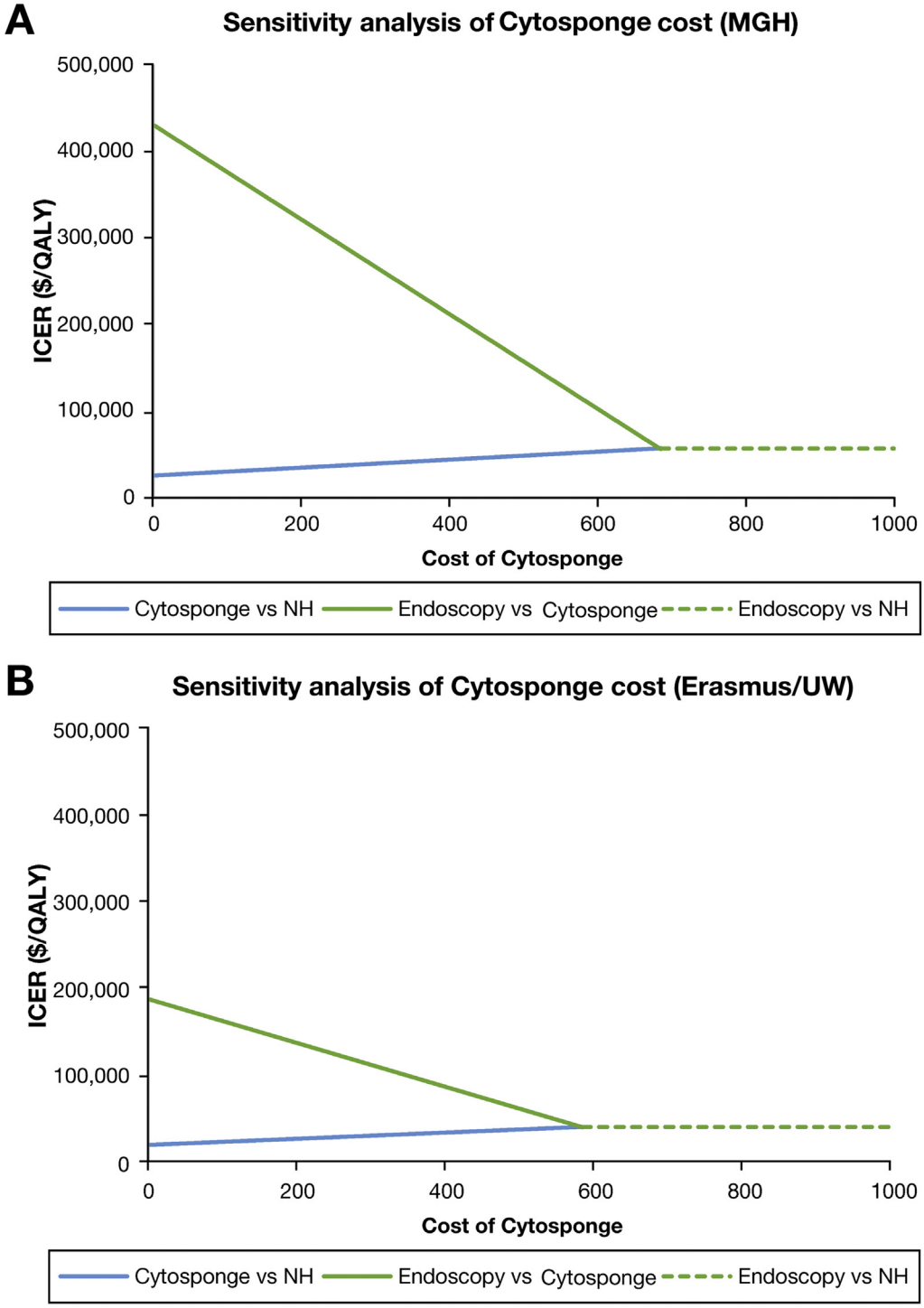

Figure 2. Sensitivity analysis of the Cytosponge cost performed with the MGH and Erasmus/UW models. ICERs corresponding to the efficiency frontier are shown at each point.

The consistency of our model results in this analysis suggests a degree of robustness in our findings to the uncertainties that these model differences represent.

In our analysis we have considered use of the Cytosponge only as a method of first-line screening for BE using the Trefoil factor 3 biomarker. We did not consider Cytosponge-based surveillance strategies because BE surveillance requires discrimination between nondysplastic BE, low-grade dysplasia, and HGD to determine appropriate surveillance intervals and treatment options. Currently, this level of detail requires an endoscopic diagnosis. However, with additional biomarkers or panels, Cytosponge tissue collection potentially could allow for the accurate identification of dysplasia, which could alter the role of the Cytosponge significantly in EAC prevention.

We chose to compare the Cytosponge with no screening or endoscopic screening because endoscopy with biopsy is the current standard for BE diagnosis.

Other low-cost, minimally invasive alternatives to conventional endoscopy such as unsedated transnasal endoscopy and tethered capsule endoscopy are promising and potentially disruptive technologies that are accruing clinical evidence and may be viable options in the future.[18,19]

A significant limitation of our analysis was the dependence of our results on estimates of uncertain parameters, including screening-related test performance characteristics, complications, quality-of-life adjustments, and parameters governing the natural history of EAC such as the independently optimized estimates of BE prevalence during the development of each model. To mitigate this limitation, we used the most reliable and up-to-date parameter estimates available in the literature, and performed both 1-way sensitivity analysis and probabilistic sensitivity analysis. Furthermore, our use of a comparative modeling approach provided a check against structural uncertainty in our knowledge of EAC natural history.

Another limitation was the uncertainty regarding the cost of the Cytosponge. It is possible that the cost of the Cytosponge could be significantly different from our base-case estimate once implemented in clinical practice. We addressed the limitation with multiple sensitivity analyses, both 1-way and probabilistic (MGH only). However, results continued to be robust at twice the cost of the base-case estimate of $182; it is not until the cost of the Cytosponge exceeds $684 (MGH) or $565 (Erasmus/UW) that endoscopy would become the dominant strategy.

Our analysis did not incorporate adherence rates; we assumed perfect compliance with the specified screening strategies as well as with all follow-up surveillance and treatment. Thus, the effectiveness of both the Cytosponge and endoscopic screening likely were somewhat exaggerated in our models. In measures of acceptability, the Cytosponge generally has outperformed endoscopy in trials conducted to date.[20–22] In addition, Cytosponge screening can be performed in a brief outpatient visit, compared with endoscopy, which in the United States typically is performed with sedation. The Cytosponge therefore may have higher adherence rates compared with endoscopy, particularly among patients who have difficulty taking time off from work or arranging postprocedure transportation. Thus, in practice, the differences in effectiveness between the Cytosponge and endoscopic screening may be smaller (or more favorable to the Cytosponge) than estimated by our models.

Our analyses focused on cohorts of men with GERD symptoms. Limited numbers of female patients in the BEST2 study made it difficult to inform the performance characteristics of the Cytosponge for this cohort. Nonetheless, we conducted a sensitivity analysis that indicated that Cytosponge screening would be cost effective for 60-year-old women with GERD symptoms. This finding should be read as provisional until adequate data become available to inform a more robust analysis.

In conclusion, our comparative modeling analysis found that a Cytosponge-first strategy may be a cost-effective way to screen for BE and reduce the harms associated with esophageal adenocarcinoma in patients with GERD symptoms. In addition, both models found endoscopic screening to be a non–cost-effective approach. These findings were consistent in both models but were sensitive to the cost of the Cytosponge.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2017.02.017.

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Conflicts of interest
The authors disclose no conflicts.

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Supplementary Materials and Methods

Probabilistic Sensitivity Analysis

Overview. A PSA was conducted to assess the robustness of our findings to uncertainty in model parameters. Parameter distributions were estimated from the literature and expert opinion. Sets of parameters were generated jointly from these distributions using the Metropolis–Hastings algorithm[1] to avoid parameter sets with low combined probability. Ten thousand parameter sets were generated; the last 1000 were used as inputs to the MGH model for runs of 10 million patients each. Cost-effectiveness calculations were performed for each run, at various values of Cytosponge cost and willingness-to-pay.

Estimation of parameter distributions. The distributions used in the PSA are listed in Supplementary Table 1. Distributions are specified as Beta(α, β) or normal(mean, SD).

The Barrett's oEsophagus Screening Trial 2 (BEST2) trial provided data that allowed us to fit beta distributions for Cytosponge performance characteristics directly. For the performance characteristics of endoscopy, we used point estimates found in the literature as means, and fitted distributions with variances based on the analogous Cytosponge parameters. Distributions for utility adjustments were based similarly on point estimates from the literature, with variance calculated based only on the order of magnitude of the point estimate.

We used conditional beta distributions for parameters such as postrecurrence histology in which exactly one of several possibilities must occur. This allowed us to generate random values for the relevant probabilities that are guaranteed to sum to 1.

Costs (with the exception of the Cytosponge) were calculated based on Medicare reimbursement rates. We assumed the variation in reimbursement rates was small and used a SD of $25.

Results. Given a base-case price of $182 for the Cytosponge and a willingness-to-pay threshold of $100,000/QALY, the Cytosponge was cost effective and endoscopy was beyond the willingness-to-pay threshold in 100% of runs. The ICER for the Cytosponge compared with natural history remained in a relatively small range ($32,567–$36,354), indicating that our results were robust to the estimated uncertainties in the included parameters. The ICER for endoscopy compared with the Cytosponge ranged from $234,762 to $423,809.

For each PSA run, we chose a best strategy by first identifying the set of strategies that were cost effective (ie, on the efficiency frontier with an ICER less than the willingness-to-pay threshold), then selecting among those the strategy that yielded the greatest number of QALYs. By using these criteria, the Cytosponge was the best strategy in 100% of runs with the fixed values of the Cytosponge cost and willingness-to-pay threshold mentioned earlier.

We conducted a further sensitivity analysis in which the PSA was repeated at values of a Cytosponge cost between $0 and $1000; for each cost point, we determined the proportion of runs in which the Cytosponge endoscopy, or natural history was the best strategy. These proportions are plotted in Supplementary Figure 1. The Cytosponge was the best strategy in all runs for every value of a Cytosponge cost less than $519. If a Cytosponge cost more than $671, then endoscopy was always the best strategy. Between these 2 values the Cytosponge/endoscopy comparison was subject to heightened uncertainty.

All previous analyses were conducted with a fixed willingness-to-pay threshold of $100,000. We examined the impact of this threshold choice by varying the willingness-to-pay threshold from $0 to $250,000, and performing PSA at values in between. We plotted the proportion of runs favoring each strategy at each point in Supplementary Figure 2. Natural history was the favored strategy if the willingness-to-pay threshold was very low, between $0 and approximately $50,000. Between $52,000 and $106,000 the Cytosponge was favored in all PSA runs, whereas at greater than $206,000 endoscopy always was favored, leaving a sizable range of varying degrees of uncertainty. For instance, at a willingness-to-pay threshold of $125,000, the Cytosponge was favored 83% of the time, and endoscopy was favored 17% of the time. At $150,000, endoscopy was favored in a majority of runs (63%) compared with the Cytosponge (37%). Thus, if the societal willingness-to-pay threshold is higher than estimated in our base-case analysis, our findings may be subject to considerable uncertainty.

One-Way Sensitivity Analyses

In addition to the PSA we performed multiple 1-way sensitivity analyses on selected parameters, including choice of screening cohort (male or female GERD patients; ages 50, 60, or 70 y), Cytosponge performance characteristics, effectiveness and recurrence rates associated with endotherapy, and inclusion or exclusion of indirect patient time costs in total cost estimates. For each analysis the effect on the ICERs of the Cytosponge compared with natural history, endoscopy compared with natural history, and endoscopy compared with the Cytosponge are shown in Supplementary Tables 2 and 3.

Cytosponge and endoscopic eradication therapy parameters. For Cytosponge specificity the upper and lower bounds were taken from the 95% confidence intervals reported by the BEST2 trial.[2] The exact parameter values used for this analysis as well as for the probabilities of recurrence after EET and of initial EET effectiveness are shown in Supplementary Table 4. In the Erasmus/UW model, we found our results to be sensitive to Cytosponge performance characteristics and EET effectiveness and recurrence; endoscopy became cost effective when the model was run with low estimates of

Cytosponge sensitivity and specificity, low estimates of EET recurrence, and high estimates of EET effectiveness. In the MGH model, results were robust for all Cytosponge and EET parameters.

Choice of screening cohort. The base-case population cohort began by screening men with GERD symptoms at age 60; we performed additional analyses of men at ages 50 and 70, and women at age 60, in each case screening those with GERD. The Cytosponge remained cost effective for screening male GERD patients regardless of the screening age considered, and endoscopy remained non–cost effective. Both models concluded that for female GERD patients, implementing Cytosponge screening at age 60 would be cost effective. The ICER for the Cytosponge compared with natural history in this analysis was substantially higher (range, $86,850–$89,674) than in the all-male base case, but remained less than the willingness-to-pay threshold. This result should be read as provisional because the data used to inform the Cytosponge performance characteristics were based on a predominantly male cohort.

Indirect costs. Large-scale screening efforts can impose considerable time costs on patients (and potential escorts after sedation), including travel time, wait time, the time of the procedure itself, and recovery time. To capture the total burden of the interventions under consideration more fully, we performed an alternative analysis in which we incorporated estimates of patient time costs for endoscopic screening, Cytosponge screening, endoscopic eradication therapy, and treatment for EAC. Time costs then were converted to US dollars by multiplying by the US median wage of $17.40 per hour.[3]

Because estimates of EAC time cost are not directly available, we used comparable estimates for gastric and colorectal cancer as proxies. The patient time cost of gastric cancer has been estimated at 351.3 hours in the first year after diagnosis and 512.2 hours in the final year of life; we adopted these as costs for the first and last year of EAC.[4] For the time cost of care between the first and final year of cancer, we followed a previous analysis that assumed a monthly time cost equivalent to $27 (2007 dollars) for colorectal cancer.[5] Adjusting for inflation to the year 2015 yielded a monthly continuing EAC cost of $31.16.

We assumed the time costs associated with an upper endoscopy were comparable with those of colonoscopy because the procedures are similar. A study of colonoscopy time costs found that patients spent a median of 1.1 hours in transit, 2.8 hours at the center (including wait and procedure time), and 17.7 hours from completion of the procedure until returning to normal activity.[6] It is recommended that endoscopy patients arrange for a friend or family member to transport them to and from the facility. This imposes an additional time burden that we accounted for by doubling the transit time and time at the center. Finally, the recovery time was an overestimate of patient time lost because it in some cases included time the patient spent sleeping overnight. To adjust for this, we adjusted the recovery time down by a third, arriving at a total endoscopy time cost of 19.6 hours. Finally, we assumed the time cost of endoscopic eradication therapy was the same as that of diagnostic endoscopy.

The time cost of Cytosponge screening will depend on its exact implementation within clinical practice; if offered during an annual physical, the incremental time cost may be negligible. As a conservative estimate, we assumed Cytosponge screening would be offered as a stand-alone intervention, so that the patient would spend on average 1.1 hours traveling and 1.4 hours waiting, similar to a colonoscopy patient.[6] In contrast to colonoscopy or upper endoscopy, no sedation is required for the Cytosponge procedure, therefore it is unnecessary for anyone to accompany the patient. Finally, we assumed the procedure time to be 0.3 hours, resulting in a total time cost of 2.8 hours.

Cost-effectiveness results for this alternative analysis including indirect cost are shown alongside the base-case results in Supplementary Figures 3 and 4. Despite the substantial effect this perspective has on procedure costs, our conclusions largely were unaffected; we found the Cytosponge to be cost effective with an ICER of $40,934 to $48,749 compared with natural history, whereas endoscopy was not cost effective. This was in part because the time costs of screening, surveillance, and endoscopic eradication treatment were offset partially by reductions in EAC and its heavy associated time costs.

References

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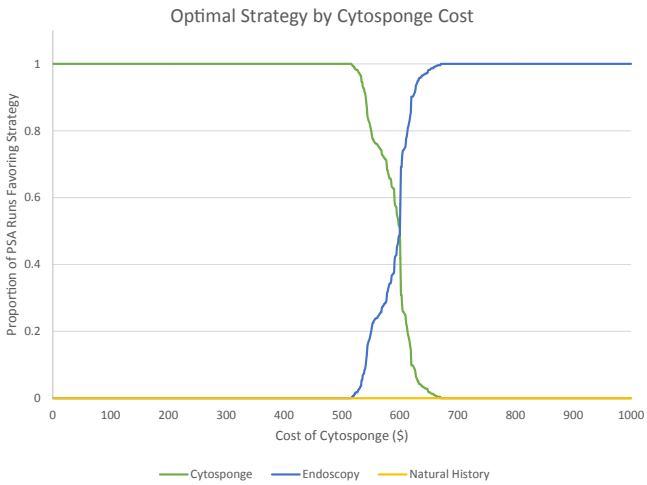
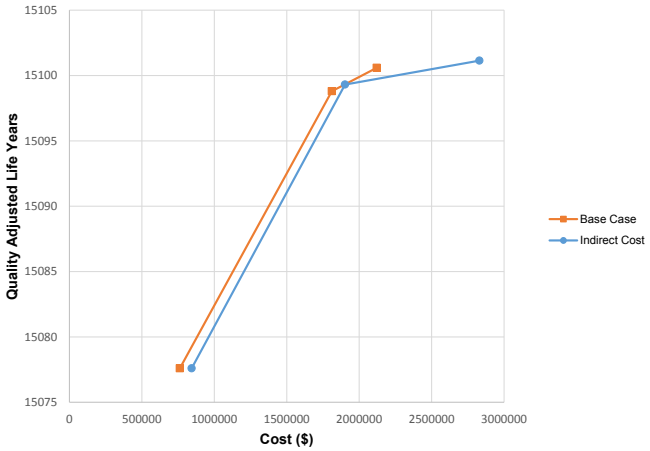
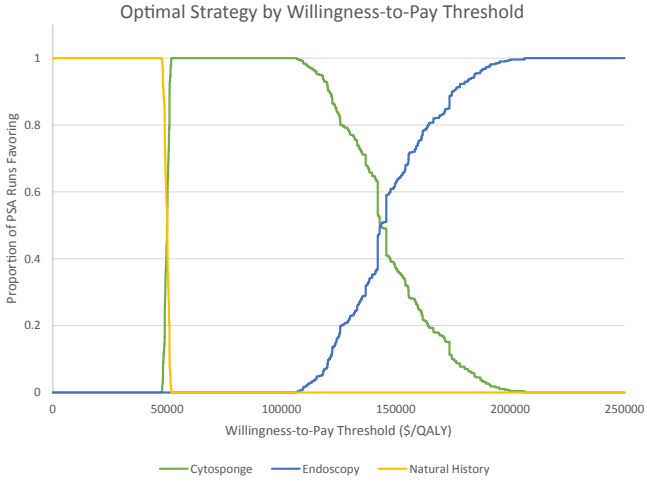


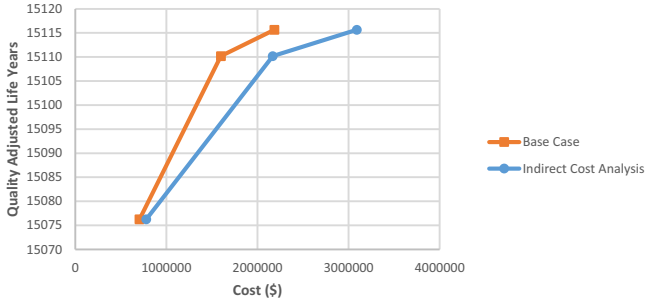
Supplementary Figure 1. Proportion of PSA runs favoring each strategy by willingness-to-pay threshold, assuming a fixed willingness-to-pay ratio of $100,000 (MGH model).



Supplementary Figure 3. Indirect cost adjustment and base-case results (MGH model).



Supplementary Figure 2. Proportion of PSA runs favoring each strategy by willingness-to-pay threshold, assuming a fixed Cytosponge cost of $182 (MGH model).



Supplementary Figure 4. Indirect cost and base case results of the Erasmus/UW model.

Supplementary Table 1. Probability Sensitivity Analysis Parameters and Distributions

	Parameter	Distribution	Reference
Cytosponge parameters	False positive	beta(34, 411)	2
	False-negative ND	beta(78, 294)	2
	False-negative LGD	beta(14, 63)	2
	False-negative HGD	beta(16, 85)	2
	Complication rate	beta(2, 998)	2
Endoscopy parameters	False negative	beta(31, 214)	
	False positive	beta(33, 405)	
	Cost	Normal(745.36, 25)	7
	Complication rate	beta(275, 211,135)	8
RFA costs	Cost of initial treatment	Normal(5630, 25)	7
	Cost of touch-ups	Normal(1012, 25)	7
Histology after post–CE-IM recurrence event by pre-RFA health state			
Pre-RFA NDBE	Postrecurrence NDBE	beta(110, 9)	9,10
	Postrecurrence LGD[a]	beta(7, 2)	9,10
	Postrecurrence HGD[a]	beta(2.5, 0.5)	9,10
	Postrecurrence EAC[a]		9,10
Pre-RFA LGD	Postrecurrence NDBE	beta(78, 17)	9,10
	Postrecurrence LGD[a]	beta(13, 4)	9,10
	Postrecurrence HGD[a]	beta(2,2)	9,10
	Postrecurrence EAC[a]		9,10
Pre-RFA HGD	Postrecurrence NDBE	beta(64, 29)	9,10
	Postrecurrence LGD[a]	beta(14, 15)	9,10
	Postrecurrence HGD[a]	beta(9, 6)	9,10
	Postrecurrence EAC[a]		9,10
Probability of recurrence event after RFA by pre-RFA health state	Pre-RFA NDBE	beta(47, 621)	9,10
	Pre-RFA LGD/IND	beta(46, 437)	9,10
	HGD	beta(42, 374)	9,10
Effectiveness by pre-RFA health state			
Pre-RFA HGD	CE-D	beta(607, 107)	11
	CE-IM given CE-D	beta(122, 485)	11
Pre-RFA LGD	CE-D	beta(581, 52)	11
	CE-IM given CE-D	beta(123, 458)	11
Pre-RFA NDBE	CE-IM	beta(941, 220)	11
Complications	Perforation rate	beta(5, 19,995)	11
	Stricture rate	beta(27, 513)	11
Quality-of-life adjustments	Local EAC utility	beta(46, 9)	
	Regional EAC utility	beta(59, 31)	
	Distant EAC utility	beta(38, 59)	
	Unstaged EAC utility	beta(59, 35)	
	Post-treatment EAC utility	beta(15, 1)	
	Endoscopy penalty	beta(15, 7642)	
	EET or stricture penalty	beta(132, 22,750)	
Cancer costs	Localized: first year	Normal(46,752, 2806.1224)	12
	Localized: last year	Normal(51,274, 3207.1428)	12
	Regional: first year	Normal(59,667, 3835.7)	12
	Regional: last year	Normal(61,606, 2534.1836)	12
	Distant: first year	Normal(45,303, 5572.9591)	12
	Distant: last year	Normal(67,526, 2826.0204)	12
	Continuing care	Normal(3102, 416.84)	12
	Unstaged	Average of local/regional/distant	12

CE-D, complete eradication of dysplasia; CE-IM, complete eradication of intestinal metaplasia; LGD, low-grade dysplasia; ND, no dysplasia; NDBE, no dysplasia Barret's esophagus.

[a]Post-recurrence histology probabilities were implemented as conditional β distributions. EAC histology probability was calculated as 1 minus the sum of probabilities of the other states.

Supplementary Table 2. Base Values and Sensitivity Parameters

	Base value			Lower value			Upper value		
	Pretreatment histology			Pretreatment histology			Pretreatment histology		
Durability of successful treatment	NDBE	LGD	HGD	NDBE	LGD	HGD	NDBE	LGD	HGD
Annual recurrence probability	7.0%	10.7%	10.0%	3.5%	5.4%	5.0%	14.0%	21.5%	20.0%
Effectiveness of the initial treatment									
Success of therapy in pretreatment HGD patients									
CE–IM and CE-D	0.680			0.644			0.889		
Non–CE-IM, CE-D	0.171			0.178			0.037		
Success of therapy in pretreatment LGD patients									
CE–IM and CE-D	0.724			0.678			0.981		
Non–CE-IM, CE-D	0.194			0.211			0.000		
Success of therapy in pretreatment ND patients									
CE–IM	0.811			0.685			0.984		
Non–CE-IM	0.189			0.315			0.016		
Cytosponge performance characteristics									
Specificity	92.4%			90.0%			95.0%		
ND sensitivity	79.0%			74.5%			83.0%		
LGD sensitivity	80.5%			69.9%			88.7%		
HGD sensitivity	84.2%			75.6%			90.7%		

CE-D, complete eradication of dysplasia; CE-IM, complete eradication of intestinal metaplasia; LGD, low-grade dysplasia; ND, no dysplasia.

Supplementary Table 3. Results of Sensitivity Analyses: MGH Model

Analysis	Cytosponge vs natural history ICER, *$*	Endoscopy vs natural history ICER, *$*	Endoscopy vs cytosponge ICER, *$*
All female	89,674	211,332	Dominated
Cytosponge performance characteristics			
Upper bound	32,168	56,391	823,979
Lower bound	34,758	56,391	191,076
Radiofrequency ablation effectiveness			
Upper bound	31,564	53,720	303,055
Lower bound	41,981	70,579	547,718
Recurrence after radiofrequency ablation			
Upper bound	34,709	58,480	346,459
Lower bound	32,380	54,952	314,574
Start: age 50	27,561	62,990	298,929
Start: age 70	45,435	74,279	722,430
Indirect costs	48,749	84,365	507,069

Supplementary Table 4. Results of Sensitivity Analyses: Erasmus/UW Model

Analysis	Cytosponge vs natural history ICER, $	Endoscopy vs natural history ICER, $	Endoscopy vs cytosponge ICER, $
All female	86,850	251,354	Dominated
Cytosponge performance characteristics			
Upper bound	24,769	37,630	215,674
Lower bound	29,172	37,630	64,031
Radiofrequency ablation effectiveness			
Upper bound	23,787	34,320	98,277
Lower bound	27,603	39,245	112,499
Recurrence after radiofrequency ablation			
Upper bound	27,583	39,056	110,470
Lower bound	25,546	35,183	83,686
Start: age 50	21,664	37,653	127,320
Start: age 70	39,576	58,548	283,514
Indirect costs	40,934	58,689	168,871