Cost-effectiveness of adding Endocuff® to standard colonoscopies for interval colorectal cancer screening

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Background and aims: Higher screening colonoscopy adenoma detection rates (ADRs) correlate with reduced risk of interval colorectal cancer (CRC). The Endocuff® device has been shown to improve ADRs compared to standard colonoscopy (SC). This cost-effectiveness analysis compared interval CRC screening using Endocuff®-assisted colonoscopy (EC) vs SC.

Methods: A decision-analytic Markov model followed patients through screening, CRC diagnosis, progression, remission, and death. ADRs, CRC progression, and utilities were from literature. CRC incidence, stage distribution, and mortality were from the Surveillance, Epidemiology, and End Results (SEER) and SEER-Medicare linked databases. Screening and annual patient costs were from public databases and literature. Endocuff® device average sales price was applied. Lifetime device and medical costs were evaluated separately for device purchaser, health plan, and accountable care organization (ACO) perspectives.

Results: Consistent use of EC instead of SC was expected to reduce lifetime risks of interval CRC and related death by 0.98% and 0.19%, respectively, preventing one case per 102 patients and one death per 526 patients. Survival and quality-of-life (QoL) improved by 0.025 life-years and 0.011 quality-adjusted life-years (QALYs) per patient on average. EC instead of SC led to incremental cost-effectiveness ratios to the device purchaser of $4,421 per life-year gained and $9,843 per QALY gained, and $199 or $87 average cost-savings per patient to the health plan or ACO, respectively.

Conclusion: Endocuff® for screening colonoscopies was expected to reduce interval CRC incidence and death, improve QoL, and be cost-effective to the device purchaser and cost-saving to a health plan or ACO.

Keywords: adenomatous polyps, colorectal neoplasm, colonic polyps, adenocarcinoma, interval cancer

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer among men and women, and the third leading cause of cancer-related death in the US.1 In 2018, 97,220 new cases of colon cancer and 43,030 new cases of rectal cancer were projected to be diagnosed.1 That year, CRC was projected to cause 50,630 deaths. Lifetime risk of CRC is 4.5% for men and 4.2% for women. Of incident CRC patients, 39% are diagnosed with localized disease, 35% with regional, and 21% with distant, according to data reported by the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program.2 Five-year survival for these patients is 89.9%, 71.3%, and 13.9%, respectively.
The majority of CRCs derive from adenomatous polyps (adenomas), which take over a decade on average to become malignant.\(^4\) This provides a window of opportunity to prevent CRC through early adenoma identification and removal during regular CRC screening. Most adenomas are asymptomatic, so early detection depends on effective screening modalities.\(^5\) Optical colonoscopy is the most common modality for CRC screening. The adenoma detection rate (ADR), defined as the proportion of screening colonoscopy patients in which at least one adenoma is detected, is an evidence-based quality measure for colonoscopy used by gastroenterology specialty societies and the Centers for Medicare and Medicaid Services (CMS).\(^6\) \(^7\) Conventional adenomas are the precursors to, at minimum estimates, 70% of all CRCs, emphasizing the importance of adenoma detection in effective CRC prevention.\(^8\)

Even among experienced endoscopists, the adenoma miss rate with colonoscopy was estimated to be 17%, and may be as high as 24%.\(^9\) \(^10\) Factors correlated with the miss rate include adequacy of colon preparation, adenoma location within the colon, and colonoscopy withdrawal time.\(^11\) Modifications to the basic colonoscope have been suggested to improve adenoma detection, including changing the colonoscope (eg, using a wide-angled lens or numerous lenses) and/or adding accessory devices (eg, distal attachments).\(^12\) \(^13\)

Data from an integrated healthcare delivery organization showed that a 1% increase in ADR was associated with a 3% decrease in the risk of interval CRC and a 5% decrease in the risk of interval CRC-related death.\(^14\) Endocuff\(^\text{®}\) (Arc Medical Design Ltd, Leeds, UK; US distribution by Olympus Corporation of the Americas) is a mechanical device placed on the distal end of the colonoscope, and aids in the discovery of adenomas and polyps within the colon. The device has soft flexible arms that extend from its fixed base. The arms collapse backward during colonoscopy insertion and advancement, and extend during examination and withdrawal, allowing flattening of the colon folds to reduce slippage and enhance visualization of the colon.

A meta-analysis of published studies showed Endocuff\(^\text{®}\)-assisted colonoscopy (EC) increased ADRs by 14.0% compared to standard optical colonoscopy (SC).\(^15\) \(^17\) This cost-effectiveness analysis evaluated potential CRC outcomes and costs over a lifetime with consistent interval CRC screening using EC compared to SC in the US.

### Methods

A decision-analytic Markov model was used to compare EC to SC for guideline-appropriate CRC screening for US patients over a lifetime (Figure 1A). CRC screening patients were tracked through health states representing screening (no CRC diagnosis), CRC diagnosis, metastasis, remission, and death (Figure 1B). Probabilities of transitioning between health states were applied annually. Patient outcomes included CRC incidence, CRC-related death, life-years, and quality-adjusted life-years (QALYs).

Three stakeholder perspectives were evaluated: the device purchaser, the health plan, and the fully integrated accountable care organization (ACO) responsible for both device and downstream payer-borne costs. Endocuff\(^\text{®}\) device and medical costs were considered separately and together, depending on perspective. Lifetime Endocuff\(^\text{®}\) device costs were considered for the device purchaser; lifetime medical costs were considered for the health plan. The fully integrated ACO was assumed to be responsible for device and medical costs.

Reductions in lifetime risks were evaluated using the number needed to treat (NNT) to avoid one CRC case or CRC-related death. Cost-effectiveness was evaluated using incremental cost-effectiveness ratios (ICERs): cost per life-year gained, and cost per QALY gained. Annual 3% discount rates were applied to costs and QALYs.\(^18\) This analysis was developed in accordance with guidelines for cost-effectiveness analyses.\(^19\) \(^22\)

### Modeled patient pathway

#### Screening

Patients entered the model with CRC screening initiation at age 50 based on the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines.\(^23\) At each screening over their lifetimes, patients in the SC arm of the model underwent standard optical colonoscopy, while patients in the EC arm used Endocuff\(^\text{®}\) to augment their colonoscopies. In accordance with NCCN Guidelines, time intervals between screenings were 5 years for patients with high-risk characteristics and 10 years for patients without high-risk characteristics (average-risk patients). The proportions of high-risk and average-risk screening patients with SC screening were based on the distribution of high- and average-risk screening colonoscopies (Healthcare Common Procedure Coding System [HCPCS] codes G0105 and G0121) conducted in 2016 under CMS (Table 1).\(^24\) ADRs with SC and EC (25.8% and 39.8%, respectively) were from published colonoscopy studies comparing SC and EC, and were
Increased adenoma detection with EC would also be expected to increase the proportion of patients considered high-risk due to identification of more sessile adenomas or more adenomas per patient. In the absence of data on the magnitude of that increase, it was assumed that the proportion of screening patients considered high risk with EC vs SC would increase by the same magnitude as ADR (14.0%).

Colon cancer incidence rates
CRC incidence rates by age in the screened population (ie, interval cancer) were calculated based on 2014 overall US incidence rates from the SEER database (Figure 2, grey line). The model assumed that CRC prevention benefits of screening would not be realized in the first screening year, so incidence with SC in that year was set equal to the overall population. Improved

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Table 1 Model inputs

| Description                                                                 | Value       | Range      | Source                                      |
|----------------------------------------------------------------------------|-------------|------------|---------------------------------------------|
| **CRC screening**                                                          |             |            |                                             |
| Proportion of patients undergoing screening                                 |             |            |                                             |
| Ages 50–64 years old                                                       | 57.8%       | 51.3%–73.4%| ACS 2017                                   |
| Ages 65+ years old                                                         | 68.3%       | 68.3%–81.8%| NCCN Guidelines 2017                       |
| Starting age of screening (in years)                                        | 50          | 50–65      |                                             |
| Adenoma detection rates                                                    |             |            |                                             |
| Standard colonoscopy                                                       | 25.8%       | 20.3%–31.7%| Studies of EC and SC                        |
| Endocuff®-assisted colonoscopy                                             | 39.8%       | 34.3%–45.4%|                                             |
| Proportion of patients categorized as high-risk                            |             |            |                                             |
| Standard colonoscopy strategy                                              | 50.1%       | 37.5%–62.6%| CMS PSPS file 2016                          |
| Endocuff®-assisted colonoscopy strategy                                    | 64.1%       | 50.1%–80.1%|                                             |
| **CRC diagnosis hazard ratios**                                            |             |            |                                             |
| Standard colonoscopy vs no colonoscopy                                     | 0.42        | 0.28–0.65  | Wang et al 2016                             |
| At first screening under EC vs SC strategy                                 | 1.06        | 1.03–1.11  | Pickhardt et al 2011                       |
| After the first year, per 1% increase in ADR                               | 0.97        | 0.96–0.98  | Corley et al 2014                           |
| **Stage distribution at diagnosis of interval CRC**                        |             |            |                                             |
| Stage I                                                                    | 37.4%       | 28.0%–46.7%| SEER-Medicare database                      |
| Stage II                                                                   | 25.7%       | 19.3%–32.1%|                                             |
| Stage III                                                                  | 23.5%       | 17.6%–29.4%|                                             |
| Stage IV                                                                   | 13.4%       | 10.1%–16.8%|                                             |
| **Annual progression rates**                                               |             |            |                                             |
| Distant recurrence                                                         | 1.5%        | 1.1%–2.0%  | Teloken et al 2015                          |
| Stage I                                                                    |             |            |                                             |
| Distant recurrence or death                                                | 5.3%        | 3.9%–6.6%  | Allegra et al 2013                          |
| Stage II                                                                   |             |            |                                             |
| Stage III                                                                  | 11.1%       | 8.3%–13.9% | Ramsey et al 2000                           |
| **Health state utility values**                                            |             |            |                                             |
| No CRC diagnosis                                                           | 0.87        | 0.85–0.89  | Luo et al 2005                              |
| Incident year of CRC                                                       |             |            |                                             |
| Stage I                                                                    | 0.74        | 0.69–0.78  | Ness et al 1999                            |
| Stage II                                                                   | 0.72        | 0.67–0.77  |                                             |
| Stage III                                                                  | 0.66        | 0.61–0.70  |                                             |
| Stage IV                                                                   | 0.25        | 0.20–0.31  |                                             |
| Years 2–5 following CRC diagnosis                                          |             |            |                                             |
| Stage I                                                                    | 0.84        | 0.79–0.89  | Ramsey et al 2000                           |
| Stage II                                                                   | 0.86        | 0.83–0.89  |                                             |
| Stage III                                                                  | 0.85        | 0.81–0.89  |                                             |
| Stage IV                                                                   | 0.84        | 0.77–0.91  |                                             |
| **Screening costs, mean**                                                  |             |            |                                             |
| Endocuff® device                                                           | $30.00      | $22.50–$50.00 | Average sales price                        |
| Colonoscopy procedure, serious AEs, and pathology                         |             |            |                                             |
| Standard colonoscopy                                                       | $885.58     | $664.18–$920.19 | CMS 2016 PSPS schedules; Leffler et al 2010 |
| Endocuff®-assisted colonoscopy                                             | $920.19     | $885.58–$1,150.24 |                                             |

(Continued)
visualization of the colon with EC may increase the number of CRCs detected in the short term. A systematic review and meta-analysis found that the sensitivity of SC for CRC detection was 94.7%, suggesting that 5.3% of CRCs may be undetected by SC, indicating that the maximum relative increase in CRC detection is

Table 1 (Continued).

| Description                                      | Value   | Range        | Source                                      |
|--------------------------------------------------|---------|--------------|---------------------------------------------|
| Total annual costs, mean                         |         |              |                                             |
| No CRC diagnosis                                 | $12,007.99 | $9,005.99   | $15,009.98 CMS Health Expenditures 2017  
| With diagnosed CRC                               |         |              |                                             |
| First year after diagnosis                       | $51,066.68 | $38,300.01   | $63,833.35 CMS Health Expenditures 2017  
| Stage I                                          |         |              |                                             |
| Stage II                                         | $66,097.22 | $49,572.92   | $82,621.53 Lansdorp-Vogelaar et al 2009  
| Stage III                                        | $109,284.34 | $109,115.54 | $109,453.13 Lairson et al 2014  
| Stage IV                                         | $165,832.31 | $160,792.79 | $170,883.26 Song et al 2011  
| Continuing year (excluding year of diagnosis or death) |         |              |                                             |
| Progression-free survival                        | $15,271.05 | $11,453.29   | $19,088.81 CMS Health Expenditures 2017  
| Post-progression survival                        | $135,366.79 | $131,210.33 | $139,538.48 Lansdorp-Vogelaar et al 2009  
| Last year of life                                |         |              |                                             |
| Without metastases                               | $29,315.18 | $21,986.38   | $36,643.97 Song et al 2011  
| With metastases                                  | $206,403.53 | $188,373.14 | $224,452.94 Song et al 2011  
| Annual time preference discount rate             | 3.0%    | 0.0%         | 6.0% Ramsey et al 2005  

Notes: *Default value assumes that all additional patients in whom an adenoma was found with EC vs SC would be reclassified from average-risk to high-risk. *Default value assumes that the relative increase in malignant findings with Endocuff® is proportional to the increase in ADR. *National Cancer Institute. SEER-Medicare Linked Database. Bethesda, MD, USA. *Provided by the Endocuff® US distributor. *Screening costs with EC were higher than SC due to increased ADR with EC, which was assumed to result in an equal increase in the probability of polyp removal and surgical pathology examination. 

Abbreviations: CRC, colorectal cancer; ACS, American Cancer Society; NCCN, National Comprehensive Cancer Network; CMS, Centers for Medicare and Medicaid Services; PSPS, Physician/Supplier Procedure Summary; SEER, Surveillance, Epidemiology, and End Results; EC, Endocuff®-assisted colonoscopy; SC, standard colonoscopy; ADR, adenoma detection rate; AEs, adverse events; QALY, quality-adjusted life-year.

Figure 2 Colorectal cancer incidence rates by age.

Abbreviations: SC, standard colonoscopy; EC, Endocuff®-assisted colonoscopy.
To account for this possibility, the CRC incidence with EC in the first year was assumed to be 1.06 times the incidence with SC (Table 1). This conservative assumption was selected in order to maximize the cancer treatment-related costs associated with use of EC.

In subsequent years, interval CRC incidence by age with SC was calculated using overall US incidence rates, screening prevalence, and CRC hazard ratio with SC compared to no screening (Equation 1A). Interval CRC incidence rates with EC were calculated using the incidence rates with SC, the difference in ADR with EC vs SC, and the CRC hazard ratio for ADR improvements (Equation 1B).

Equation 1. Interval CRC incidence rates in the screened population

A. Standard colonoscopy

\[
\text{Incidence rate with SC}_{\text{age}} = \frac{\text{Overall US incidence rate}_{\text{age}} \times \text{CRC hazard ratio with screening}}{1 - \text{%screened}} \times \text{ADR improvement}_{\text{EC}}
\]

B. Endocuff®-assisted colonoscopy

\[
\text{Incidence rate with EC}_{\text{age}} = \frac{\text{Incidence rate with SC}_{\text{age}} \times \text{CRC hazard ratio per 1\% ADR improvement}_{\text{ADR}}}{1 - \text{ADR improvement}_{\text{ADR}}}
\]

Stage at interval cancer diagnosis

CRC stages were defined using the American Joint Committee on Cancer (AJCC) 7th edition staging system. Stage distribution at interval CRC diagnosis was analyzed using the SEER-Medicare linked database. Approval for this analysis was obtained from the New England Independent Review Board. Patients diagnosed with CRC as their first primary cancer in 2012–2013 were identified using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes (Appendix 1: Table S1). For patients with Medicare claims data (available from 2006 on), claims preceding their diagnosis date were examined for screening colonoscopies using an approach similar to published Medicare claims analyses (Appendix 1: Figure S1).

Screening colonoscopies were identified using HCPCS and Current Procedural Terminology (CPT) codes (Appendix 1: Tables S2 and S3). Colonoscopies were not considered screening if they were conducted within 1 month following a diagnosis that may have necessitated a colonoscopy (Appendix 1: Table S4), or within 6 months preceding CRC diagnosis as those may have been diagnostic. Patients were considered high risk if their most recent screening colonoscopy included biopsy or tumor/polyp/lesion removal, or the claim included ICD-9-CM code V16.0 (family history of CRC) (Appendix 1: Table S5). Patients had interval CRC if the time between their most recent screening colonoscopy and their CRC diagnosis was within the appropriate interval for their risk group.

Disease progression

Patients diagnosed in stages I-III were assumed to undergo surgical resection in accordance with clinical guidelines. The annual rate of distant recurrence among patients diagnosed with stage I CRC was 1.5% based on the 7.1% 5-year recurrence rate from a multi-center retrospective database analysis. Annual rates of distant recurrence or death among patients diagnosed with stage II or III CRC (5.3% and 11.1%, respectively) were from 3-year progression-free survival rates in the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-08 randomized clinical trial (85.4% and 71.7%, respectively).

Remission

CRC survivors whose disease did not progress for 5 years were assumed to enter remission, based on the expectation that CRC-related risks (ie, distant recurrence and cancer-specific mortality), quality-of-life (QoL) decrements, and costs would decrease over time among surviving patients (Figure 1B). This assumption is supported by the relative survival among stage IV CRC patients in later years (Figure 3) and QoL among CRC survivors (Table 1). The same risks, QoL, and costs were applied for the remission and screening health states.

Mortality

Cancer-related and non-cancer-related mortalities were included. Non-cancer-related mortality by age was based on vital statistics published by the Centers for Disease Control and Prevention, and applied to all patients. CRC-related mortality was only applied for patients with stage IV CRC, assuming that cancer-related death would only occur after metastasis.

Cancer-related mortality was assessed in the SEER database using period analyses of relative survival with stage IV CRC compared to the non-cancer population (Figure 3; Appendix 2: Figure S2). Relative survival was analyzed by age at stage IV diagnosis and years since diagnosis. The base year was 2013 and relative survival at each year after diagnosis was determined using data from cohorts of patients diagnosed across
three calendar years. For example, 10-year relative survival was based on patients diagnosed in 2001–2003, 9-year relative survival was based on patients diagnosed in 2002–2004, 8-year relative survival was based on patients diagnosed in 2003–2005, and so on.

Quality-of-life
QoL of each health state was measured with a utility ranging from zero (death) to one (perfect health). The utility of no cancer, applied for the screening and remission health states, was from a large survey of the US adult population. Utilities for CRC by stage were from surveys of colorectal adenoma patients and CRC survivors.

Costs
Mean lifetime direct medical costs were considered from the perspective of the device purchaser (device costs), the health plan (medical costs), and the fully integrated ACO (responsible for both device and medical costs). Costs are reported in 2017 US Dollars.

CRC screening
CRC screening costs were applied in the first year of the model, and again at guideline-recommended intervals.

Screening procedures
Average SC or EC cost included the colonoscopy procedure, pathology, and serious adverse events (AEs). Colonscopy procedure cost for SC was the average 2017 CMS fee schedule cost for types of colonoscopies used for screening (Table S2), weighted by distributions of procedures and settings-of-care reported in the 2016 CMS Physician/Supplier Procedure Summary File. The additional cost of surgical pathology examination (CPT code 88305) was weighted by the proportion of colonoscopy procedures with polyp removal. For EC, the distribution of colonoscopy procedure types was shifted toward those including polyp removal by the difference in ADR from SC to EC (+14.0%). AEs cost was equal for EC and SC screening and was from an analysis of hospitalizations occurring within 14 days of screening or surveillance colonoscopy.

Endocuff® device
Endocuff® device cost was $30, based on the distributor’s average sales price. Each EC colonoscopy required one device.

Annual costs
Annual cost for patients in the screening (no CRC diagnosis) health state was the average healthcare expenditure per Medicare beneficiary reported by CMS (Table 1). Annual costs for CRC patients by stage at diagnosis and phase of disease were from retrospective claims analyses. The initial phase was the year post-diagnosis or distant recurrence, the terminal phase was the last year of life, and the continuing phase was the intervening years. Patients who experienced distant recurrence...
after diagnosis with stage I-III CRC incurred costs associated with stage IV CRC following distant recurrence. Patients in remission incurred costs equal to those in the high-risk screening population.

Sensitivity analyses

One-way sensitivity analyses evaluated the potential influence of input uncertainty on the ICER per QALY. Inputs were varied across individual ranges (Table 1). The probability of being considered high-risk may be higher with EC than SC so this was varied from equal to SC up to +25% over base case. The ADRs with EC and SC were varied simultaneously to opposite ends of their 95% CIs. CRC utility values in the year after diagnosis and in subsequent years were varied together for each CRC stage. Endocuff® device cost was varied from 75% of average sales price up to list price ($50). All other inputs were varied over 95% CIs where reported or ±25% otherwise.

Results

Consistent use of Endocuff® is expected to decrease incidence of interval CRC in the screened population (Figure 2, black line “SC screening”, and blue line “EC screening”). Lifetime risk of CRC in the screened population decreased 0.98% with EC vs SC and risk of CRC death decreased 0.19%. The NNT to avoid one case of CRC with EC vs SC was 102 patients and the NNT to avoid one CRC-related death was 526 patients. Survival and QoL were expected to improve with EC compared to SC by 0.0254 life-years and 0.0114 QALYs per patient on average due to the decreased probability of developing CRC.

Total per-patient lifetime cost from the device purchaser perspective was $112.27 with consistent EC screening compared to SC screening (Table 2). This translated to ICERs of $4,421 per life-year gained, $9,843 per QALY gained, $11,505 per avoided CRC, and $59,035 per avoided death due to CRC. From the health plan perspective, lifetime costs per patient were expected to decrease $199.22. From the ACO perspective encompassing both

| Table 2 Results |
|------------------|------------------|------------------|
| **Result**       | **Change with EC compared to SC** |
| **Effectiveness**| **** |
| Lifetime risk    | **** |
| CRC              | −0.98%          |
| CRC-related death| −0.19%          |
| Number needed to treat to avoid   | **** |
| One CRC case     | 102             |
| One CRC-related death | 526             |
| Survival per patient on average   | **** |
| QALYs gained     | 0.0114          |
| Life-years gained| 0.0254          |
| **Lifetime costs per patient on average** | **** |
| **Cost perspective** | **Device purchaser** | **Health plan** | **ACO** |
| Endocuff® device | $112.27          | N/A             | $112.27          |
| Screening        | N/A              | $377.76         | $377.76          |
| Survival without CRC diagnosis | 707.02         | N/A             | N/A              |
| Survival after CRC diagnosis | 1,283.99      | -1,283.99       | -1,283.99        |
| Total            | $112.27          | -199.22         | -86.95           |
| **Incremental Cost Effectiveness Ratio** | **** |
| Per avoided CRC case | $11,505         | N/A             | N/A              |
| Per avoided CRC-related death | 59,035         | (Cost-savings and improved outcomes) | (Cost-savings and improved outcomes) |
| Per life-year gained | $4,421          |               |                 |
| Per QALY gained   | $9,843           |               |                 |

**Note:** Perspective of an ACO that is both the Endocuff® device purchaser and the payer responsible for other medical costs like CRC screening and treatment.

**Abbreviations:** EC, endocuff®-assisted colonoscopy; SC, standard colonoscopy; QALY, quality-adjusted life-years; CRC, colorectal cancer; NNT, number needed to treat; ACO, accountable care organization; ICER, incremental cost-effectiveness ratio.
the device costs and medical costs, CRC screening using EC compared to SC resulted in overall cost-savings of $86.95 per patient over a lifetime.

Savings were largely due to avoidance of CRC-related costs. Mean per-patient CRC costs over a lifetime decreased $1,283.99 with EC compared to SC. Non-device screening costs increased by $377.76 due to projected increases in screening frequency and need for polypectomies and pathology evaluations with increased ADR with EC vs SC. Costs associated with survival without CRC diagnosis increased $707.02 as patients were less likely to be diagnosed with CRC and spent more time in the cancer-free health state with EC vs SC.

In one-way sensitivity analyses, the top-ranked most influential inputs on the ICER per QALY from the device purchaser’s perspective were 1) ADRs with EC and SC, 2) cost of the Endocuff® device, and 3) annual time preference discount rate (Figure 4A). The only scenario under the device purchaser’s perspective that showed an ICER above $20,000 per QALY gained was when the ADRs with SC and EC were varied across their 95% CIs such that the improvement in ADR was only 2.6%, resulting in an ICER of $44,029 per QALY gained. One-way sensitivity analyses showed a $50,000 ICER per QALY gained when ADR with EC was 28.1%, representing a 2.3% improvement over base case ADR with SC. When the Endocuff® device cost was set equal to list price, the ICER was $16,405 per QALY gained.

From the health plan perspective, the most influential variables were the 1) non-device cost of each EC screening, 2) cost of each SC screening, or 3) proportion of patients considered high-risk with EC screening (Figure 4B). Cost-additive results were only observed from the health plan perspective in three tested scenarios: i) when the non-device cost of each EC screening was high ($1,150 [base case $920]), ii) when the cost of each SC screening was low ($664 [base case $886]), and iii) when the proportion of patients considered high-risk with EC screening was high (80.1% [base case 64.1%]) (Figure 4). The ICERS per QALY gained in these three scenarios were $58,012, $49,830, and $7,635, respectively.

**Discussion**

This analysis found that consistent CRC screening with EC compared to SC was expected to improve patient survival and QoL and reduce risks of interval CRC and related death. Average survival and QoL per patient improved by 0.0254 life-years and 0.0114 QALYs with...
EC instead of SC, while lifetime risks of interval CRC or CRC-related death were expected to decrease by 0.98% and 0.19%, respectively. Lifetime cost to the device purchaser was expected to be $122 per patient screened consistently with EC instead of SC. The costs per life-year or QALY gained to the device purchaser were $4,421 and $9,843, respectively, well under the $50,000 willingness-to-pay (WTP) per life-year or per QALY gained threshold commonly discussed in the US, suggesting that the Endocuff® device for CRC screening and prevention would be cost-effective. One-way sensitivity analyses showed that cost-effectiveness was expected across all reasonable input ranges.

Due to reduced CRC risks and associated costs, EC was expected to be cost-saving to the health plan or fully integrated ACO. Expected average savings per patient screened consistently with EC instead of SC was $199 to a health plan not including the Endocuff® device costs, and $86 to a fully integrated ACO that pays for the Endocuff® device. To a fully integrated ACO stakeholder responsible for both the Endocuff® device cost and medical costs for CRC screening and treatment, consistent screening with EC was expected to be dominant over SC by reducing costs and improving patient outcomes.

While WTP thresholds per avoided CRC case, or avoided death due to CRC, are less commonly discussed and have not been established in the US, it appears that $11,505 per avoided CRC case and $59,035 per avoided CRC death may be considered cost-effective, especially in the context of the high per-patient costs of oncology treatments used to reduce the risk of cancer mortality. The reduction in lifetime risk of interval CRC by 0.98% with EC compared to SC corresponds to an NNT to avoid one CRC death of 526 patients, which is lower than the NNT reported for other recommended cancer preventative services. For example, biennial screening mammography as recommended by the US Preventative Services Task Force (USPSTF) was estimated in a meta-analysis of clinical trials to avoid 8 breast cancer deaths per 10,000 screened women 50–59 years of age.49 This translates to an NNT to avoid one breast cancer death with screening mammography of approximately 1,250 women, suggesting that the NNT reported in the current study to avoid one CRC death with EC instead of SC screening is within an acceptable range for cancer screening in the US.

**Limitations**

This analysis used Medicare claims data to determine the risk-group distribution in the SC screened population, the distribution of procedures used for screening colonoscopies, and to identify previously screened CRC patients to determine the incident stage distribution of interval CRC. Using claims data to identify screening colonoscopies was limited by the colonoscopy CPT procedure codes, which do not differentiate between colonoscopies performed for screening vs other purposes, or between high- and low-risk patients. Risk group distribution with SC screening was determined using HCPCS codes, which are screening-specific and differentiate high- vs low-risk patients, but these codes are only used when the screening colonoscopy was negative. Therefore, the proportion of patients who are high-risk may be underestimated. To evaluate the stage distribution of interval CRC, this study assessed older patients in the SEER-Medicare linked database using methodologies similar to previously published analyses of CRC screening colonoscopies.33,34 More research to characterize the CRC screening patient population and treatment patterns would be useful in evaluations of the progress and success of CRC screening.

Increased ADR with EC screening was expected to increase the need for polyp removals and increase the proportion of patients in the high-risk screening group, thus increasing screening costs. In the absence of robust data describing the relationship between ADR and risk designation, this analysis assumed that the increases in polypectomy use and in the proportion of patients considered high-risk were equal to the increase in ADR. The definition of a patient’s risk group is multifactorial, depending on the number, size, and type of adenomas detected. For this reason, the change in the screening risk-group distribution cannot be determined with certainty based on ADR alone, despite the metric’s established clinical significance. In particular, if EC improves detection of intermediate-to-high risk polyps, this may lead to higher proportions of patients being considered high risk.
and needing more frequent screening. The proportion of patients considered high-risk with EC is the third-most influential variable from the health plan perspective, suggesting that additional research on the impact of Endocuff® on CRC screening treatment patterns would be useful. Even so, Endocuff® was expected to be at least cost-effective in all risk-group distribution scenarios tested in the sensitivity analyses.

Potential detection of CRC at earlier stages with EC compared to SC was not included in this model. This analysis applied the same incident CRC stage distribution to both the SC and EC arms of the model. However, if EC screening was to shift the distribution of incident CRCs toward earlier stages, then this would be expected to result in larger improvements in survival and reductions in cancer-associated treatment costs. The potential for diagnosis at an earlier stage due to improved screening with EC is unclear. Larger lesions are less likely to be missed by endoscopists during SC. Previous studies demonstrating improved adenoma detection with EC suggest that detection gains are often in smaller lesions. As such, these potential benefits were not included, and this analysis may present conservative estimates of the improvements in patient outcomes and cancer-related savings with Endocuff®.

The model hinges on the relationship between improved ADR during colonoscopies and decreased CRC incidence, as demonstrated in published studies of the benefit of CRC screening. This assumes that the additional adenomas identified by EC are clinically meaningful – ie, that they would have developed into interval CRCs before being detected at later screenings. The mean ADRs observed in studies comparing SC and EC (25.8% and 39.8%, respectively) were similar to those in published studies that have demonstrated decreased CRC incidence with increased physician ADRs (median 25.7% for the 3rd physician quintile and 38.9% for the 5th quintile), suggesting that the CRC prevention benefit applies in the ADR ranges relevant to SC and EC.

Endocuff®-augmented colonoscopy screening was projected to improve patient outcomes compared to SC screening. Mean survival and QoL were expected to increase, and risks of interval CRC and CRC-related death in the screened population were expected to decrease. Adding Endocuff® to screening colonoscopies was expected to be cost-effective to the device purchaser in the US, and decrease lifetime costs per patient to a health plan or fully integrated ACO.

**Abbreviations**
ACO, accountable care organization; ADR, adenoma detection rate; AE, adverse event; AJCC, American Joint Committee on Cancer; CMS, Centers for Medicare and Medicaid Services; CPT, Current Procedural Terminology; CRC, colorectal cancer; EC, Endocuff®-assisted colonoscopy; HCPCS, Healthcare Common Procedure Coding System; ICD-9-CM, International Classification of Diseases, 9th revision, Clinical Modification; ICER, incremental cost-effectiveness ratio; NCCN, National Comprehensive Cancer Network; NNT, number needed to treat; NSABP, National Surgical Adjuvant Breast and Bowel Project; QALY, quality-adjusted life-year; QoL, quality of life; SC, standard colonoscopy; SEER, Surveillance, Epidemiology, and End Results; USPSTF, US Preventative Services Task Force; WTP, willingness-to-pay.

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Supplemental materials

SEER-Medicare Analysis of Interval CRC Incident Stage Distribution

The Surveillance, Epidemiology, and End Results Program (SEER)-Medicare Linked Database was used to evaluate the incident stage distribution of interval colorectal cancer (CRC) diagnosed between guideline-appropriate colonoscopy screenings. Data were provided by the National Cancer Institute. Institutional review board exemption approval for this protocol was granted by the New England Independent Review Board.

SEER-Medicare patients with CRC cancer diagnoses
N = 49,493

First primary cancer diagnosis in 2012-2013
N = 41,247

First primary CRC diagnosis in 2012-2013*
N = 38,197

With Medicare claims data from 2006 to CRC diagnosis date
N = 21,345

With ≥1 claim with an included colonoscopy code†
N = 2,647

With ≥1 screening colonoscopy‡
N = 2,583

With ≥1 screening colonoscopy ≥6 months preceding CRC diagnosis
N = 1,592

High risk screening§
N = 1,033

Average risk screening
N = 559

6-months ≤ screening ≤5 years prior to diagnosis
N = 874 (69%) 6-months ≤ screening ≤10 years prior to diagnosis
N = 397 (31%)

Interval CRC patients with known AJCC stage
N = 1,118

Figure S1 Patient selection flow chart.
†ICD-9-CM codes in Table S1.
‡Procedure codes in Table S2.
§Screening colonoscopy is defined as a colonoscopy without (i) any excluded colonoscopy codes on the claim (Table S3), and (ii) without the excluded ICD-9 codes on the claim or in the month prior to the colonoscopy (Table S4).
§CPT and ICD-9 codes in Table S5.

Abbreviations: SEER, surveillance, epidemiology, and end results; CRC, colorectal cancer; AJCC, American Joint Committee on Cancer; ICD-9-CM, International Classification of Diseases – Ninth Edition – Clinical Modification; CPT, Current Procedural Terminology.
### Table S1 ICD-9-CM codes used to identify CRC diagnosis

| ICD-9-CM Code | Description                              |
|----------------|------------------------------------------|
| Colon cancer   |                                          |
| 153.0          | Malignant neoplasm of hepatic flexure    |
| 153.1          | Malignant neoplasm of transverse colon    |
| 153.2          | Malignant neoplasm of descending colon    |
| 153.3          | Malignant neoplasm of sigmoid colon       |
| 153.4          | Malignant neoplasm of cecum              |
| 153.6          | Malignant neoplasm of splenic flexure     |
| 153.7          | Malignant neoplasm of other specified sites of large intestine |
| 153.8          | Malignant neoplasm of colon, unspecified site |
| 153.9          |                                          |
| Rectal cancer  |                                          |
| 154.0          | Malignant neoplasm of rectosigmoid junction |
| 154.1          | Malignant neoplasm of rectum             |

**Abbreviations:** ICD-9-CM, International Classification of Diseases – Ninth Edition – Clinical Modification; CRC, colorectal cancer.

### Table S2 Included procedure codes for routine colonoscopy screening

| Code       | Description                                                                 |
|------------|-----------------------------------------------------------------------------|
| HCPCS codes |                                                                           |
| G0105      | Colorectal cancer screening; colonoscopy on individual at high risk          |
| G0121      | Colorectal cancer screening; colonoscopy on individual not meeting criteria for high risk |
| CPT codes  |                                                                           |
| 45378      | Colonoscopy, flexible; diagnostic, including collection of specimen(s) by brushing or washing, when performed (separate procedure) |
| 45380*     | Colonoscopy, flexible; with biopsy, single or multiple                       |
| 45381      | Colonoscopy, flexible; with directed submucosal injection(s), any substance  |
| 45383*     | Colonoscopy, flexible, proximal to splenic flexure; with ablation of tumor(s), polyp(s), or other lesion(s) not amenable to removal by hot biopsy forceps, bipolar cautery or snare technique |
| 45384*     | Colonoscopy, flexible; with removal of tumor(s), polyp(s), or other lesion(s) by hot biopsy forceps |
| 45385*     | Colonoscopy, flexible; with removal of tumor(s), polyp(s), or other lesion(s) by snare technique |

**Notes:** Claims at least 6 months prior to the patient’s CRC diagnosis date with any of these codes were evaluated as potentially a screening colonoscopy. * Colonoscopy with polyp removal. When used to calculate cost, reimbursement for CPT code 88305 (surgical pathology examination) was added to the cost of each procedure. **Abbreviations:** HCPCS, Healthcare Common Procedure Coding System; CPT, Current Procedural Technology.
Table S3 Excluded procedure codes for routine colonoscopy screening

| CPT Code | Description |
|----------|-------------|
| 44388    | Colonoscopy through stoma; diagnostic, including collection of specimen(s) by brushing or washing, when performed (separate procedure) |
| 44389    | Colonoscopy through stoma; with biopsy, single or multiple |
| 44390    | Colonoscopy through stoma; with removal of foreign body(s) |
| 44391    | Colonoscopy through stoma; with control of bleeding, any method |
| 44392    | Colonoscopy through stoma; with removal of tumor(s), polyp(s), or other lesion(s) by hot biopsy forceps |
| 44393    | Colonoscopy through stoma; with ablation of tumor(s), polyp(s), or other lesion(s) not amenable to removal by hot biopsy forceps, bipolar cautery or snare technique |
| 44394    | Colonoscopy through stoma; with removal of tumor(s), polyp(s), or other lesion(s) by snare technique |
| 45355    | Colonoscopy, rigid or flexible, transabdominal via colotomy, single or multiple |
| 45379    | Colonoscopy, flexible; with removal of foreign body(s) |
| 45382    | Colonoscopy, flexible; with control of bleeding, any method |
| 45386    | Colonoscopy, flexible; with transendoscopic balloon dilation |
| 45387    | Colonoscopy, flexible, proximal to splenic flexure; with transendoscopic stent placement (includes predilation) |
| 45391    | Colonoscopy, flexible; with endoscopic ultrasound examination limited to the rectum, sigmoid, descending, transverse, or ascending colon and cecum, and adjacent structures |
| 45392    | Colonoscopy, flexible; with transendoscopic ultrasound guided intramural or transmural fine needle aspiration/biopsy(s), includes endoscopic ultrasound examination limited to the rectum, sigmoid, descending, transverse, or ascending colon and cecum, and adjacent structures |

Note: A claim with any of these colonoscopy CPT codes was not considered an instance of screening colonoscopy.

Abbreviation: CPT, Current Procedural Terminology.
### Table S4 Excluded diagnoses indicating potential non-screening colonoscopy

| ICD-9-CM Code | Description |
|---------------|-------------|
| 280*          | Iron deficiency anemia |
| 285.1         | Acute post-hemorrhagic anemia |
| 285.9         | Anemia, unspecified |
| 555*          | Regional enteritis |
| 556*          | Ulcerative colitis |
| 558.2         | Toxic gastroenteritis and colitis |
| 558.9         | Other and unspecified noninfectious gastroenteritis and colitis |
| 560.9         | Unspecified intestinal obstruction |
| 564.00        | Constipation, unspecified |
| 564.01        | Slow transit constipation |
| 564.02        | Outlet dysfunction constipation |
| 564.09        | Other constipation |
| 564.5         | Functional diarrhea |
| 569.3         | Hemorrhage of rectum and anus |
| 578.0         | Hematemesis |
| 578.1         | Blood in stool |
| 578.9         | Hemorrhage of gastrointestinal tract, unspecified |
| 787.0*        | Nausea and emesis |
| 787.3         | Flatulence, eructation, and gas pain |
| 787.6*        | Fecal incontinence |
| 787.91        | Diarrhea |
| 787.99        | Other symptoms involving digestive system |
| 789.0*        | Abdominal pain |
| 789.3*        | Abdominal or pelvic swelling, mass, or lump |
| 781.0         | Anorexia |
| 781.2         | Abnormal loss of weight and underweight |
| 781.21        | Loss of weight |
| 781.22        | Underweight |
| 792.1         | Non-specific abnormal findings in stool contents |

**Notes:** * Includes all possible codes starting with these digits. Colonoscopy claims with any of these diagnoses either on the claim or in the month prior to the claim were not considered instances of screening colonoscopy.

**Abbreviation:** ICD-9-CM, International Classification of Diseases – Ninth Edition – Clinical Modification.

### Table S5 Indicators of high-risk status after screening colonoscopy

| Code   | Description |
|--------|-------------|
| CPT    |             |
| 45380  | Colonoscopy, flexible; with biopsy, single or multiple |
| 45383  | Colonoscopy, flexible, proximal to splenic flexure; with ablation of tumor(s), polyp(s), or other lesion(s) not amenable to removal by hot biopsy forceps, bipolar cautery or snare technique |
| 45384  | Colonoscopy, flexible; with removal of tumor(s), polyp(s), or other lesion(s) by hot biopsy forceps |
| 45385  | Colonoscopy, flexible; with removal of tumor(s), polyp(s), or other lesion(s) by snare technique |
| ICD-9-CM |         |
| V16.0  | Family history of malignant neoplasm of gastrointestinal tract |

**Notes:** Patients with any of these codes on their latest screening colonoscopy claim were considered high-risk screening patients, while patients without any of these codes on their latest screening colonoscopy claim were considered average-risk.

**Abbreviations:** CPT, Current Procedural Technology; ICD-9-CM, International Classification of Diseases – Ninth Edition – Clinical Modification; CRC, Colorectal Cancer.
Figure S2 Relative survival with stage IV CRC by Age at Diagnosis and Years from Diagnosis. Dashed lines represent 95% CIs. Period analyses of relative survival conducted using the Surveillance, Epidemiology, and End Results database, base year 2013, and three-year cohorts.