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Cost Effectiveness Analysis Evaluating Real-Time Characterization of Diminutive Colorectal Polyp Histology using Narrow Band Imaging (NBI)

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Abstract

Background: Endoscopists and new computer-aided programs can achieve performance benchmarks for real-time diagnosis of colorectal polyps using Narrow-Band Imaging (NBI), though do not perform as well as endoscopists with expertise in advanced imaging. Previous cost-effectiveness studies on optical diagnosis have focused on expert performance, potentially over-estimating its benefits.

Aim: Determine cost-effectiveness of an NBI 'characterize, resect and discard (CRD)' strategy using updated assumptions based on non-expert performance.

Methods: Markov model was constructed to compare cost-effectiveness of the CRD strategy, where diminutive polyps characterized as non-adenomas with high confidence are not resected and adenomas are resected and discarded, versus standard of care (SOC) in which all polyps are resected with histologic analysis. Rates related to NBI performance, missed polyps, polyp progression, malignancy, and complications, as well as quality-adjusted life years (QALYs) were derived from the literature. Costs were age and insurer-specific. Mean QALYs and costs were calculated using first order Monte Carlo simulation. Deterministic and probabilistic sensitivity analyses were conducted.

Results: The mean QALY estimates were similar for the CRD (8.563, 95% CI: 8.557-8.571) and SOC strategy (8.563, 8.557-8.571), but costs were reduced ($2,693.06 vs. $2,800.27, mean incremental cost savings: $107.21/person). Accounting for colonoscopy rates, the CRD strategy would save $708 million to $1.06 billion annually. The model was sensitive to the incidence of tubular adenomas; the results were otherwise robust in all other one-way and probabilistic analyses.

Conclusions: An NBI CRD strategy is cost-effective when compared to the SOC, even when employed by non-experts. The appreciated benefit is primarily due to cost savings of the CRD strategy.

Abbreviations

Colorectal Cancer (CRC), Narrow Band Imaging (NBI), American Society for Gastrointestinal Endoscopy (ASGE), Negative Predictive Value (NPV), Positive Predictive Value (PPV), Preservation and Incorporation of Valuable Endoscopic Innovation (PIVI), First Order

Monte Carlo Simulation (FOMCS), Standard of Care (SOC), Characterize, Resect & Discard (CRD), Quality Adjusted Life Year (QALY), Incremental Cost Effectiveness Ratio (ICER), Sessile Serrated Polyp (SSP), Willingness to Pay (WTP), Adenoma Detection Rate (ADR)

Introduction

The increased utilization of colonoscopy and polypectomy has in large part contributed to the reduction in CRC incidence and mortality in the United States (US) over the last several decades.[1] Although colonoscopy is cost-effective[2] when considering the high cost of cancer care, there is still a high cost associated with colonoscopy as more individuals in the US are being screened and entered into polyp surveillance programs. Diminutive polyps (≤ 5 mm) are the most commonly diagnosed polyps during routine colonoscopy[3] and removal and pathologic assessment of these polyps contributes to cost. It is estimated that $2.7 to $4.3 billion are spent annually in the US for polypectomy and pathology assessment of diminutive polyps alone based on annual US colonoscopy volume,[4] proportion of colonoscopies that have at least one diminutive polyp,[5-7] and costs associated with polypectomy and pathology review.[8-10] Diminutive polyps have a low risk of advanced histology (0-3.4%)[11-14] or cancer (0-0.08%),[3,13,15,16] but are routinely removed and sent for pathology to determine appropriate surveillance intervals. If real-time polyp diagnosis can be made without the expense polypectomy for non-neoplastic polyps and histology for all diminutive polyps, there is a potential for significant cost savings without compromising efficacy.

Narrow band imaging (NBI) is an optical endoscopic imaging technology available on Olympus endoscopes (Olympus America, Center Valley, PA)[17] that, with training, can allow for real-time histologic diagnosis of colorectal polyps. If accurate, optical diagnosis can support leaving left-sided hyperplastic polyps in situ and resecting and discarding diminutive adenomas. The American Society for Gastrointestinal Endoscopy (ASGE) Preservation and Incorporation of Valuable Endoscopic Innovation (PIVI) statement[18] recommends that a 'characterize, resect and discard' strategy can be put in place for diminutive polyps characterized with "high confidence" in combination with histologic confirmation of all other polyps if endoscopists achieve (i) a ≥ 90% agreement between surveillance intervals predicted by optical diagnosis and surveillance intervals based on histology and (ii) a ≥ 90% negative predictive value (NPV) for adenomatous polyps in the rectosigmoid.

Multiple studies have shown that experts in advanced endoscopic imaging can exceed these thresholds.[5,7,19,20] Experts in these studies have achieved 93 to 98% agreement in surveillance intervals and 80-90% of their diagnoses are characterized with 'high-confidence.' Until recently, it was unclear if endoscopists without expertise in advanced imaging could achieve the thresholds set forth by the ASGE.[21-24] We recently showed that with appropriate training, endoscopists without prior experience with advanced imaging can also achieve performance thresholds.[13] Overall, 74.3% of optical diagnoses were made with 'high-confidence' in this study. More recently, there is promising data on the use of computer-aided analysis using deep neural networks to determine colorectal polyp histology. Studies using still images have shown that these computer models perform similarly to the trained endoscopists from our recent study (NPV of 91.5%-93.7%)[25,26] and real-time assessment is feasible.[27]

Prior cost-effectiveness analyses evaluating optical diagnosis for diminutive colorectal polyps have estimated cost savings ranging from 33 million dollars annually[28] to over a billion dollars annually of upfront savings.[29] However, it is unclear if these cost savings can be generalized to widespread application of a CRD strategy as these prior analyses relied on assumptions about NBI optical diagnostic performance among advanced imaging experts.[5,19,20] Non-experts have a lower proportion of high-confidence diagnoses (74%[13] vs 80-90%[5,20]) and a lower agreement in surveillance intervals compared to experts (91%[13] vs 93-98%[5,7,20]). With increasing application of real-time diagnosis (either by trained endoscopists or with implementation of computer-aided diagnosis), and an optical diagnostic strategy starts to gain traction in routine practice, it is important to confirm that the strategy will be cost-effective with updated assumptions about real-world performance.

The primary aim of this study was to determine the cost effectiveness of the NBI CRD strategy for diminutive polyps compared to the standard of care (SOC) using updated assumptions based on non-expert performance. We hypothesize that, even with reduced accuracy compared to expert performance, this NBI-based CRD strategy is more cost-effective than SOC colonoscopy where all polyps are resected and sent for histologic analysis.

Methods

A Markov simulation model was created to compare two strategies. In the standard of care (SOC) strategy, all detected polyps were removed and sent for histologic analysis. Surveillance interval recommendations were based on pathology and current polyp surveillance guidelines. Ten year surveillance was recommended if only non-adenomas were found (minimal risk), 5 year surveillance was recommended if 1-2 small (<10 mm) adenomas were found (low risk), and 3 year surveillance was recommended if three or more adenomas were found, or if an adenoma ≥ 10 mm or an adenoma with HGD or

villous architecture was detected (high risk).[30] Though current guidelines[30] recommend 5-10 years follow up for low-risk findings, we used a 5-year surveillance interval based on conventional practice.

The SOC was compared to the previously described CRD approach.[18] In this strategy, NBI optical diagnosis was applied to all diminutive polyps. Polyps characterized with high confidence were either left in place if characterized as non-adenomas (no resection or pathology cost) or resected and discarded if diagnosed as adenomas (resection cost, no pathology cost). Surveillance interval recommendations were made based on a combination of predicted histology for high confidence diminutive polyps and pathology of all other polyps. The same polyp surveillance guidelines[30] were applied to determine minimal (10 years), low (5 years) and high risk (3 years) surveillance intervals. **Figure 1** summarizes the linear decision tree for the SOC vs CRD strategies.

The outcomes after the initial colonoscopy are described in **Figure 2**. The base case for this model was a 50-year-old individual undergoing screening colonoscopy, in which a diminutive polyp was found. The time horizon for primary analyses was 10 years. In both the SOC and the CRD strategy, at model initiation, individuals underwent their first screening colonoscopy. With this procedure, individuals were at risk for procedure related complications, such as perforation and gastrointestinal hemorrhage. Individuals could either have a detected polyp or have had a polyp

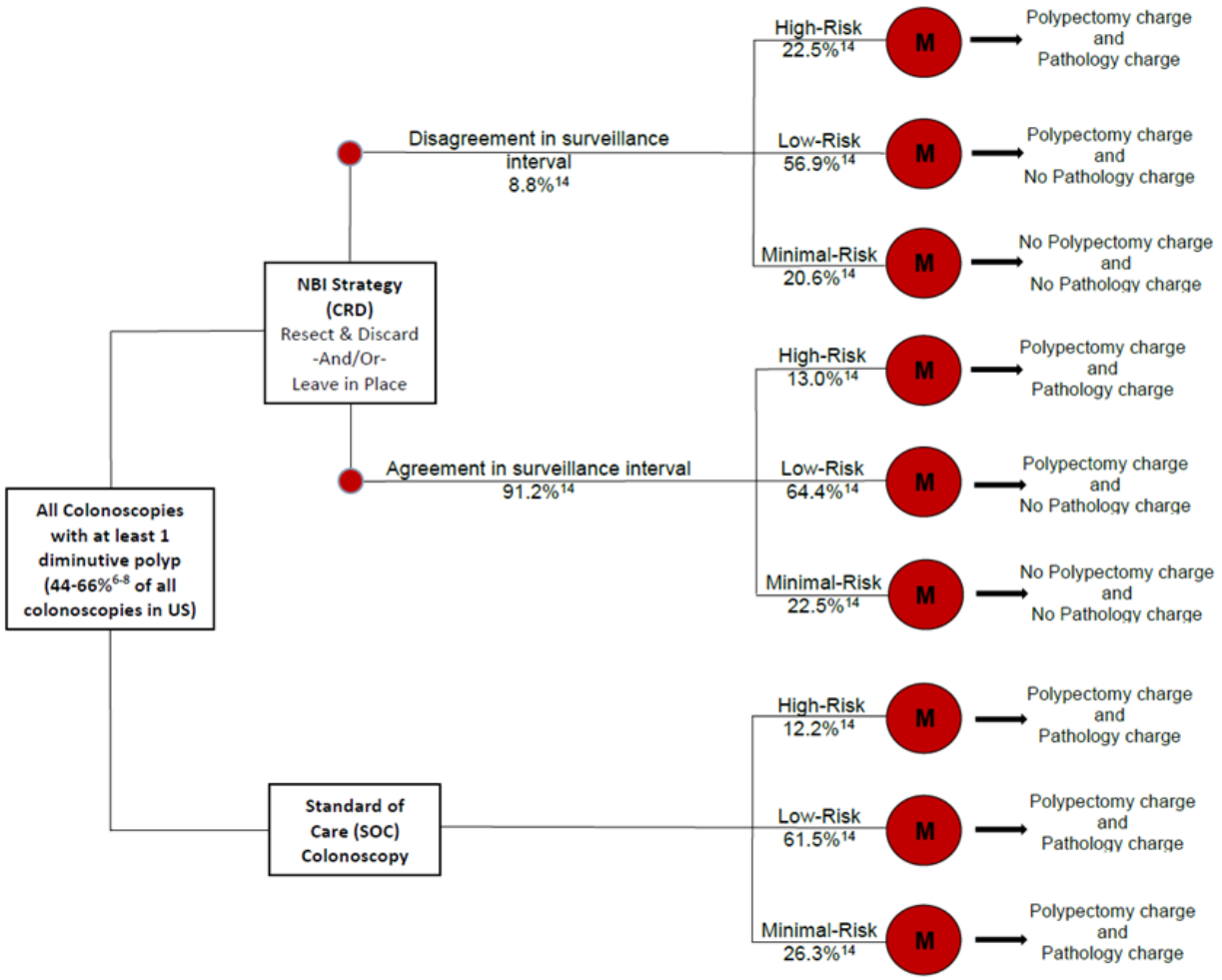

Figure 1: Model structure of initial colonoscopy polyp-related outcomes for standard of care strategy versus characterize resect and discard strategy. If only non-adenomas are found, the patient undergoes surveillance in 10 years (minimal-risk). If 1-2 tubular adenomas are found, the patient undergoes surveillance in 5 years (low-risk). If there are three or more tubular adenomas, adenoma > 1 cm or advanced histology (villous, high-grade dysplasia) the patient undergoes surveillance in 3 years. In the standard of care arm, all diminutive polyps are removed and a surveillance interval is determined based on histology. For the CRD strategy, diminutive polyp histology is characterized using NBI and surveillance intervals are determined based on high-confidence NBI predictions for diminutive polyps in combination with histology for all other polyps. Estimates surveillance interval agreement between NBI vs histology and proportion of patients with minimal, low and high-risk findings for both strategies were derived from our recent multi-center prospective study examining real-world application of a 'characterize, resect and discard' strategy.'[13]

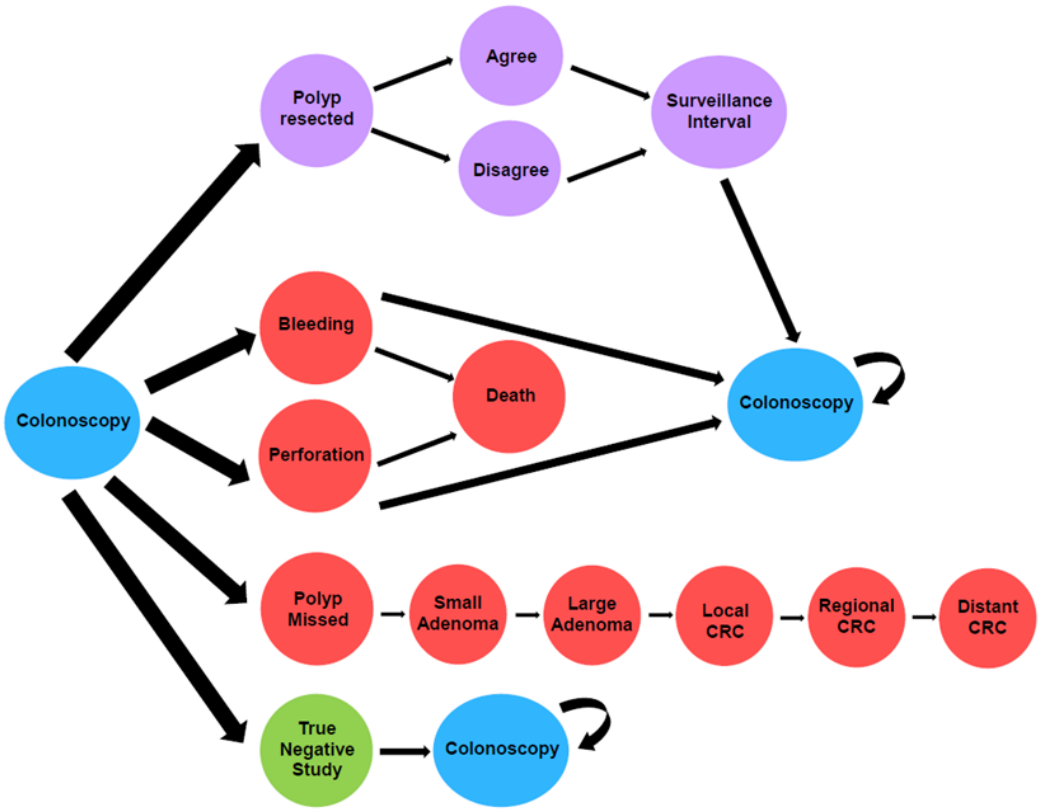

Figure 2: Model structure after index colonoscopy with at least one diminutive polyp. The model takes into account potential colonoscopy outcomes including: a true negative study wherein a patient undergoes repeat screening in 10 years and re-enters the model, a polyp is found and the patient re-enters the NBI resect and discard strategy with either agreement or disagreement in surveillance interval or potential complications (bleeding, perforation, missed polyp).

missed on this initial exam. Subsequent colonoscopies also had similar risks.

Model Assumptions

Several key assumptions were made to construct the model. We assumed that there was no difference in colonoscopy quality (quality of bowel preparation, completion rates, withdrawal times, complication rates, adenoma detection rates) or miss rates for polyps, masses or other lesions between the two strategies. The baseline risk of initial polyps was assumed to be similar between groups. For the CRD strategy, estimates of accurate vs inaccurate surveillance interval recommendations and the proportion of patients accordingly undergoing 10 year, 5 year or 3 year surveillance were derived from our recent multicenter study evaluating this strategy (**Figure 1**).[13] Subsequent polyp detection rates were assumed to be independent of the prior exam, with increased risk instead reflected by the subsequent surveillance interval. For the initial colonoscopy, the false omission rate was assumed to be zero for both strategies, i.e. all polyps for the initial screening exam were detected. Subsequent colonoscopies included the potential for missed polyps based on previously published estimates of prevalence, sensitivity, and specificity as described below.

There is currently no guideline-based standard of care regarding how colon polyps should be grouped when submitted for pathology.[31] Similar to a cost effectiveness analysis performed by Zauber et al.,[32] we assumed that all biopsies and removed polyps are reviewed by a pathologist and that a separate jar is submitted for each colon segment. Zauber et al. estimated an average of 1.38 jars per colonoscopy. Consequently, we multiplied the pathology fee by 1.38 to obtain the average pathology cost associated with colonoscopy with polypectomy.

Transition probabilities

In the scenario that a diminutive polyp was detected on colonoscopy, the proportion of patients with minimal risk, low risk, and high-risk lesions for both strategies was derived from our recent multi-center study comparing CRD to SOC (**Figure 1**). These rates were dependent on the degree of surveillance interval agreement reported in our prior research.[13]

Polyp detection rates and missed polyp rates were similar between strategies. These rates were derived from previously published literature regarding expected polyp prevalence. Polyp miss rates were estimated based previously published data on the sensitivity and specificity

of colonoscopy (CT colonography and tandem colonoscopy studies), as well as the age-dependent risk of subsequent polyps.[15,33] These were then used to calculate the false omission rate to determine the rate of false negative examinations. For missed polyps, the annual transition rate from normal tissue to small adenomas, followed by large adenomas, and subsequent cancer (local, regional or metastatic) were derived from previously published estimates and were age-specific.[34-39] Mortality rates for various stages of cancer were derived from the literature (**Table 1**).

Our previous study[13] found an NPV of 98.3% (95% CI 95.7-100.0%) for diminutive colorectal adenomas characterized with high confidence. Although this far exceeds the performance threshold set forth by the ASGE,[18] 1.7% of diminutive polyps characterized as non-adenomas by NBI are adenomas by histology. There are minimal data regarding the natural history of diminutive adenomas left

Table 1: Transition probabilities, rewards, and costs employed in the model.

Variable	Base case value (range) & References
Clinical	
Annual growth rate of diminutive adenoma, %	3.6[40]
Annual transition from normal epithelium to diminutive adenoma, %	Age specific, 3.4-6.6%[50-52*]
Annual transition rate from diminutive adenoma to small adenoma, %	Age specific, 1.4-5.6[50-52*]
Annual transition rate from small adenoma to large adenoma, %	Age specific, 3.7-4.2[39]
Annual transition rate to cancer without polypoid precursor (assuming 15% of CRCs occur de novo),[53] %	Age specific, 0.006-0.086[34-36, 54-58†]
Annual transition rate from large adenoma to local cancer, %	Age specific, 2.6-5.2[39]
Annual probability of developing symptoms with local CRC, %	22[54-58†]
Annual probability of developing symptoms with regional CRC, %	40[54-58†]
Annual mortality rate from treated localized cancer (first 5 y), %	1.7 (1.2-2.2)[54-58†]
Annual mortality rate from treated regional cancer (first 5 y), %	8.6 (6-11)[54-58†]
Annual mortality rate from treated distant cancer (first 5 y), %	17.3[59]
Mean survival from distant cancer, y	1.9 (1.4-2.6)[54-58, 60-66†]
Test Performance	
Colonoscopy sensitivity for cancer, %	95 (90-97)[67]
Colonoscopy sensitivity for large adenoma (≥10mm), %	98 (92-99)[15, 33]
Colonoscopy sensitivity for small adenoma (6-9 mm), %	87 (80-92)[15, 33]
Colonoscopy sensitivity for diminutive (≤5mm) adenoma, %	74 (70-79)[33]
Colonoscopy major hemorrhage rate, %	0.08[68]
Colonoscopy perforation rate, %	0.04[68]-0.05[69]
Mortality rate from colonoscopy, %	0.0029[69]
Quality of life (QALY) estimates for colonoscopy	
Healthy year without colonoscopy	1
Disutility for colonoscopy	0.0055[44]
Disutility for hemorrhage or perforation	0.0384[44]
Death	0
Local CRC	0.90 per year[45]
Regional CRC	0.79 per year[45]
Metastatic CRC	0.76 per year[45]
Costs commercial payments for < 65, $ Ω	
Colonoscopy	1094.76[10‡]
Colonoscopy with intervention	1218.44[10‡]
Anesthesia cost (35% of procedures performed with anesthesia)	494[10§]
Pathology payment	272[10]
Major hemorrhage after colonoscopy€	8506.04[9, 10, 70]
Perforation after colonoscopy€	23,152.86[9, 10, 70]
Localized CRC care, initial€	45,417.04[10, 71]
Localized CRC care, continuing yearly€	3,614.10[10, 71]
Localized CRC death€	81,415.89[10, 71]
Regional CRC care, initial€	76,419.08[10, 71]
Regional CRC care, continuing yearly€	4,814.66[10, 71]

Regional CRC death€	85,544.71[10, 71]
Distant CRC care, initial€	99,789.98[10, 71]
Distant CRC care, continuing yearly€	11,557.11[10, 71]
Distant CRC death€	114,808.01[10, 71]
Costs Medicare payments for ≥65, $Ω	
Colonoscopy	590.40[32, 71‡]
Colonoscopy with polypectomy	769.48[32, 71‡]
Tissue exam by pathologist per jar Tissue exam by pathologist per colonoscopy±	76[8] 104.88[32]
Anesthesia	166.17[9, 72§]
Major hemorrhage after colonoscopy	6300.77[9, 54-57, 70†]
Perforation after colonoscopy	17,150.27[9, 54-57, 70†]
Localized CRC care, initial	33,642.25[54, 71†]
Localized CRC care, continuing yearly	2,677.11[54, 71†]
Localized CRC death	60,308.07[54, 71†]
Regional CRC care, initial	56,606.73[54, 71†]
Regional CRC care, continuing yearly	3,566.41[54, 71†]
Regional CRC death	63,366.45[54, 71†]
Distant CRC care, initial	73,918.50[54, 71†]
Distant CRC care, continuing yearly	8,560.82[54, 71 †]
Distant CRC death	85,042.97[54, 71†]

*Estimate from Japanese literature. Citations include cost-effectiveness analysis using these estimates as well as source citations from which estimates were derived.

†Citations include cost-effectiveness analyses using these estimates as well as source citations from which estimates were derived.

‡Mean weighted cost based on whether procedure is performed in office, outpatient hospital or ambulatory surgical center setting.

§Assuming 30 minute colonoscopy

±Assuming 1.38 jars per routine colonoscopy[32]

Ω2017 inflation adjusted cost. CPI derived from All Urban Consumer, first half of each year interest, with base of 100 in 1982

€As done in prior cost-effectiveness analyses[54] based on ratio of reimbursement of colorectal tests by Medicare versus commercial insurance,[10] CRC care and complications costs for those < 65 were estimated to be 1.35 times Medicare payment rates.

in situ.[40,41] In the study with the longest follow-up (mean 7.8 years) of diminutive adenomas left in situ,[40] 2% of the polyps studied disappeared, the remaining grew by an average of 3.6% per year. Based on this data, if a 5 mm polyp was missed on index examination, it would be approximately 6.6 mm in size 10 years later. Thus, for our analysis, we assumed that diminutive adenomas left in situ do not progress to clinically significant neoplasia (requiring surgery or cancer treatment) by follow-up.

All individuals were continuously exposed to age-specific all-cause mortality, which was calculated using baselines rates of death per US census data.[42]

QALY estimates and costs associated with colonoscopy screening, detection, and malignancy

Outcomes were calculated using quality-adjusted life year estimates (QALY estimates), which represent the utility of a specific health state, accounting for an individual's preference for that state in comparison to perfect health (QALY=1) and mortality (QALY=0).[43] QALY estimates were derived from previously published estimates of the disutility of undergoing colonoscopy and colonoscopy-related complications, applied each time an individual within the model underwent a procedure.[44] CRC-related QALY estimates were derived from previously published estimates of CRC-specific health-related quality of life by Ramsey and colleagues.[45] It was assumed that those with local or regional CRC who had not experienced symptoms and who were not undergoing CRC treatment or diagnosed with CRC were in perfect health, i.e. they experienced no disutility related to their asymptomatic CRC.

Direct and indirect costs associated with colonoscopy (including sedation), polypectomy, pathology examination, complications and CRC treatment were derived from previously published estimates on commercial payer rates as well as Medicare reimbursement data from 2015 (**Table 1**).[38,40,41] Employed costs were age-dependent: commercial insurer rates were used for those individuals under the age of 65, whereas Medicare rates were subsequently employed when individuals reached 65 years of age in the model.

Statistical Analyses

Analyses were conducted using TreeAge Pro 2016 (TreeAge Software, Inc., Williamstown, MA) and Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA). Expected outcomes in QALYs and costs were calculated for both the SOC and the CRD strategies using

deterministic analysis as well as first order Monte Carlo simulation (FOMCS) of 100 trials of 100,000 individuals. The incremental cost-effectiveness ratio (ICER) was calculated comparing the CRD strategy to the SOC strategy with a willingness-to-pay (WTP) threshold of $100,000 USD. Cohort analyses were conducted using FOMCS with tracker variables to determine the cumulative number of procedures and mortality for a simulated cohort of 100,000 entering each treatment strategy. A discounting rate of 3% was applied for each year after the first year of follow-up for all analyses.

Sensitivity analyses

One-way sensitivity analyses varying all transition probabilities by 25% of their original value and reward estimates (both QALYs and costs) by 15% were conducted for all model inputs. Probabilistic analyses were also conducted using a cohort of 50,000 individuals. For this analysis, all deterministic inputs were converted to distributions with random sampling for each iteration of the model using available published estimates in the literature. Gamma distributions were employed for costs and beta distributions were utilized for QALY estimates.[46] Dirichlet distributions, which are the multinomial extension of the beta distribution, were employed for transition probabilities with multiple possible outcomes.[46]

We also conducted several sensitivity analyses assessing assumptions made in our model. These analyses were conducted using first order Monte Carlo Simulation. In order to assess the impact of age on increasing mortality, progression rates, and costs associated with surveillance, we performed a sensitivity analysis examining the impact of modifying the age at the start of the model from 50 to 70. To better understand the impact of time horizons longer than 10 years on the preferred strategy, we repeated our analyses with a 15-year and 20-year time horizon.

To assess the impact of missed polyps during the first exam, we repeated our analysis allowing for missed polyps that could progress from small to large adenomas, and then to cancer as in subsequent colonoscopies in our primary model. We conducted a sensitivity analysis to evaluate the impact of mischaracterizing all SSPs (1.5% of all 3,012 polyps in our original study[13] were SSPs) as non-neoplastic. To account for right-sided sessile serrated polyps (SSPs) that may have been mischaracterized as 'hyperplastic' by NBI *and* histology (deemed to be an 'accurate' diagnosis the CRD strategy) and thus left in situ, we assumed progression rates similar to typical tubular adenomas. The rate of potential diminutive SSPs mischaracterized by NBI and histology as hyperplastic was derived from our previously published study.[13]

Results

At the end of 10 years, both strategies yielded similar estimates for quality of life [SOC: 8.563 QALYs, 95% Confidence interval (CI): 8.557-8.571; CRD 8.563 QALYs, 95% CI: 8.557-8.571]. On average, the CRD strategy saved $107.21 dollars per person compared to the SOC strategy. Due to the similar clinical efficacy and cost savings of the CRD strategy, the SOC strategy was strongly dominated (ICER not reported). This was primarily driven by significant differences in costs over 100 iterations of 100,000 individuals (**Figure 3**).

In a simulated cohort of 100,000 individuals, the mean number of colonoscopies was slightly higher in the CRD strategy compared to the SOC strategy (CRD 1.78 colonoscopies per person over 10 years, SOC 1.74 colonoscopies per person over 10 years). Mortality rates were similar between the two groups (**Table 2**), as was the overall number of CRCs that developed.

Sensitivity analyses

The model was sensitive to two variables in one-way sensitivity analyses (**Supplementary figure**). If the prevalence of low-risk adenomas requiring 5-year follow-up in the CRD strategy increased above 67.2%, thereby decreasing the number of minimal risk lesions not requiring resection or histologic evaluation, and increasing the number of resections, the SOC strategy became preferred (**Figure 4a**). Similarly, if the prevalence of low risk adenomas in the SOC strategy fell below 55.9%, then SOC became the preferred strategy (**Figure 4b**). This may be because as the proportion of 'minimal risk' findings increase (in lower adenoma prevalence populations), the standard of care accurately assigns individuals to 10 year follow up. In the CRD strategy, however, a percentage of these 'minimal risk' colonoscopies will undergo surveillance sooner than 10 years, thus contributing to cost. The model was not sensitive to 25% variation of any other transition probability or QALY input.

Table 2: Summary of clinical and economic outcomes in First-Order Monte Carlo simulation in the Markov Cohort analysis

	Standard of Care Strategy	Characterize, Resect, and Discard strategy
Mean Cost per person	2800.27	2693.06
Mean QALYs per person	8.563 (8.577-8.571)	8.563 (8.557-8.571)
Mean number of colonoscopies per person	1.74	1.78
Total number of CRC cases	20 (0.02%)	28 (0.03%)
Overall mortality	5298	5304

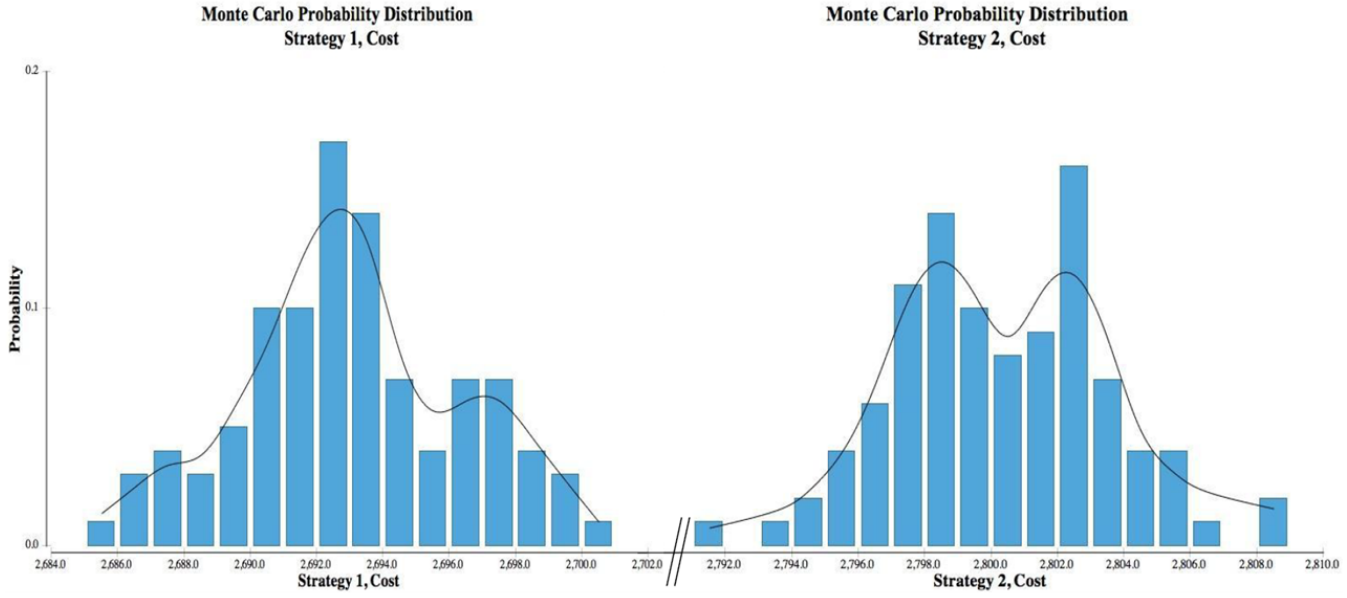

Figure 3: First-order Monte Carlo Simulation Cost Distributions. Comparison of the distribution of cost at 10 years for the two strategies for 100,000 people when the model is run 100 times. In this figure, Strategy 1 represents the CRD strategy and Strategy 2 represents the SOC strategy. The standard colonoscopy is significantly more costly in all 100 model iterations.

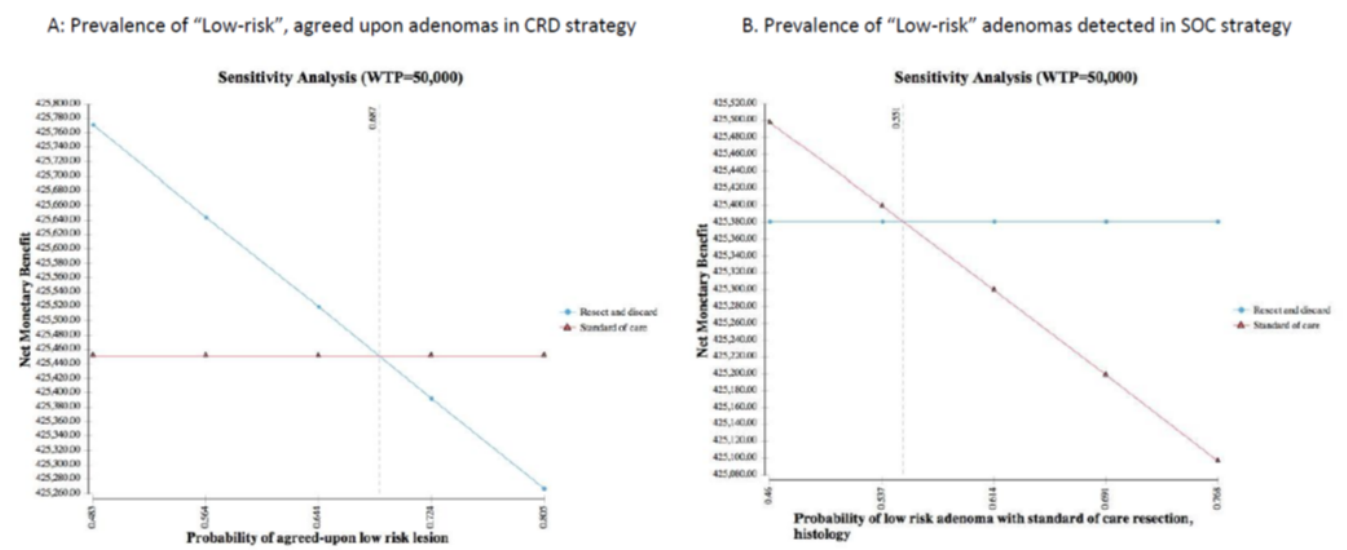

Figure 4: One-way sensitivity analyses of key variables to which the model was sensitive. The model was sensitive to adenoma prevalence both in the CRD strategy as well as the standard of care strategy. A) As the prevalence of low-risk adenomas increases (x-axis), the CRD strategy yields less net monetary benefit (y-axis). The standard of care becomes favored if the prevalence of low-risk findings exceeds 67.2% in the CRD strategy. B) As the prevalence of low-risk adenomas decreases, the SOC yields more net monetary benefit. The SOC becomes favored if the prevalence of low-risk findings falls below 55.9% in the SOC strategy.

In probabilistic sensitivity analyses, CRD remained the preferred strategy, with similar QALY estimates at the end of 10 years (CRD: 8.5622 QALYS, 95% CI 8.548-8.567; SOC: 8.5623 QALYs, 95% CI: 8.549-8.567, mean incremental difference 0.0001 QALYs) and reduced costs (CRD $2693.59, 95% CI $2251.96-3180.76; SOC: $2798.76, 95% CI $2362.40-3278.65). The ICER was $1,587,691.90, with CRD being the preferred strategy at a WTP threshold of $100,000. The preferred strategy was driven primarily by cost savings with the majority of model iterations (**Figure 5**).

We appreciated similar results in our analyses assessing our assumptions in the model. When assessing the impact of increasing the age at the start of the simulation (from 50 to 80 in 10 year increments), the impact of longer time horizons (15 years, 20 years), assuming all SSPs were mischaracterized as non-neoplastic and accounting

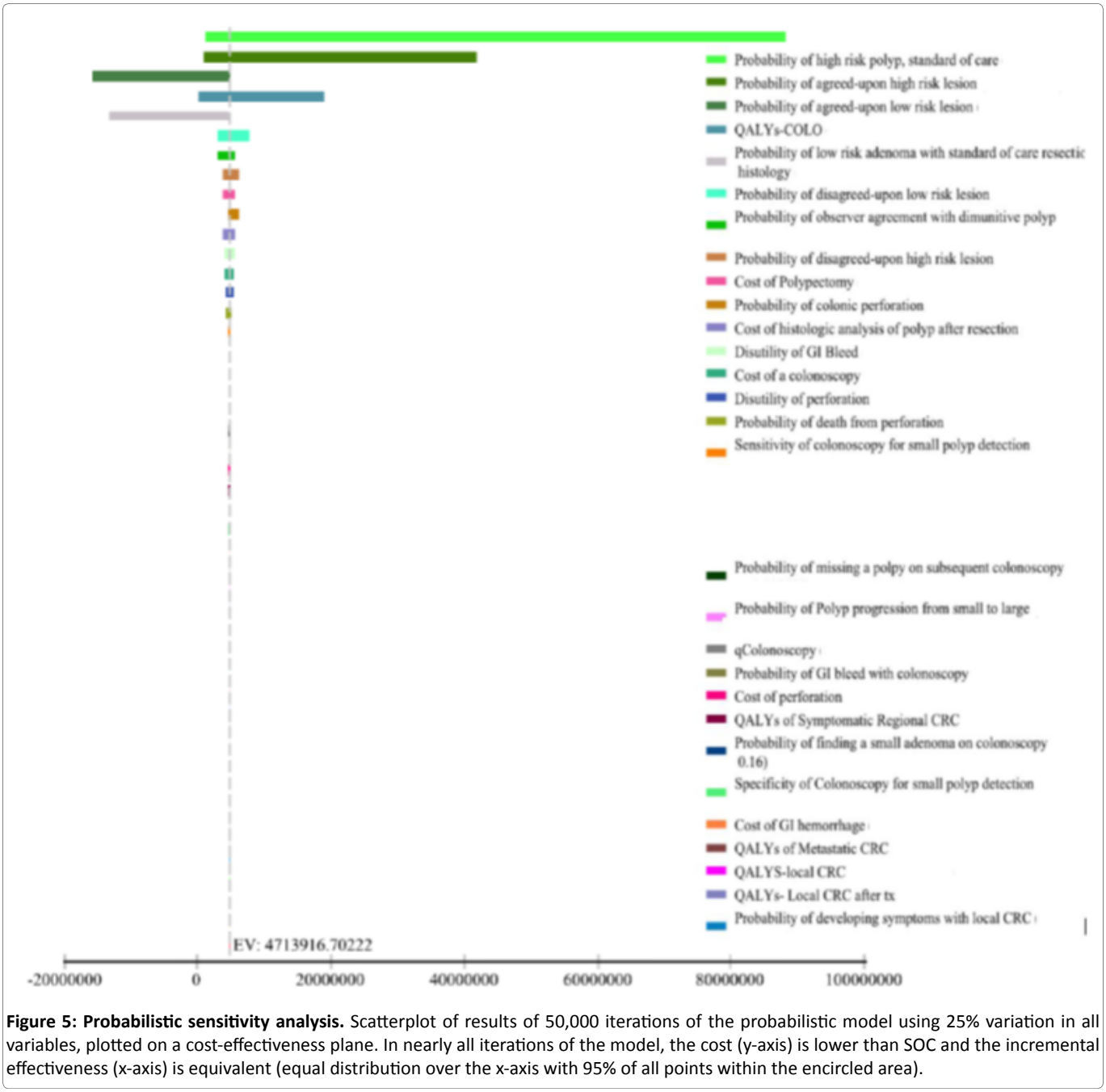

Figure 5: Probabilistic sensitivity analysis. Scatterplot of results of 50,000 iterations of the probabilistic model using 25% variation in all variables, plotted on a cost-effectiveness plane. In nearly all iterations of the model, the cost (y-axis) is lower than SOC and the incremental effectiveness (x-axis) is equivalent (equal distribution over the x-axis with 95% of all points within the encircled area).

for progression of possible SSPs left in situ due to being mischaracterized as hyperplastic by NBI and histology, the CRD strategy remained preferred over SOC with similar QALY estimates and continued cost savings (**Supplemental Table 1 and Supplemental Table 2**).

Discussion

With appropriate training, endoscopists naïve to advanced imaging can meet the clinical performance thresholds set forth by the ASGE for a CRD strategy for diminutive colorectal polyps. Recent data on computer-aided diagnosis performs similarly to trained endoscopists. Previous analyses[28,29] have shown significant cost savings with this strategy, however they have relied on a higher level of diagnostic performance by advanced imaging experts.

Using updated performance levels for endoscopists naïve to advanced imaging, this study demonstrates that there are still significant cost savings with a CRD strategy without a significant change in QALYs compared to SOC. Although there was a marginal increase in CRC cases in the CRD strategy (0.02% vs 0.03%), this did not impact mortality or quality of life. Costs were reduced in the CRD strategy at ten years (CRD: $2,693.06, SOC: $2,800.27, Mean Incremental cost savings: $107.21/person). Based on an estimated 15 million colonoscopies performed

annually in the US[4] and an estimated 44%[5,6] to 66%[7] of colonoscopies in which at least one diminutive polyp is found, this amounts to an estimated net annual savings of 708 million to 1.06 billion dollars. This study assumed a conservative 5-year surveillance interval for 1-2 small tubular adenomas. Current guidelines[30] in fact recommend 5 to 10 years for these low-risk findings, thus cost-savings would likely be amplified if surveillance examinations are not performed as frequently in this low-risk group.

The model was sensitive to low-risk adenoma prevalence. In the CRD strategy, when the low risk adenoma prevalence exceeded 68.7%, the SOC strategy became preferable. This is likely due to a relative decrease in proportion of colonoscopies in which only non-adenomas are found where polypectomy and pathology cost is deferred. In the SOC strategy, if low risk adenoma prevalence falls below 55.1%, SOC is preferable. This is likely due to fewer colonoscopies performed in the SOC since all non-adenoma colonoscopies are given a 10-year surveillance whereas the inaccurately characterized non-adenomas in the optical strategy are brought back sooner. In fact, when running the model as the base case with low risk adenoma rate of 0.615, the mean number of colonoscopies per person over 10 years in the SOC arm is 1.74. When the absolute rate of low risk adenomas is decreased by 10% to 0.515 and the model is re-run, thereby increasing the number of no risk adenoma exams by 10%, the mean number of colonoscopies per person drops to 1.64. Thus, the cost is likely significantly influenced by performing more colonoscopies. The CRD otherwise strongly dominated the SOC and was not altered in one-way sensitivity analyses.

Hassan *et al.*[28] evaluated the cost-effectiveness of this strategy in 2010 based on expert performance,[5,19,20] which was the only available published data at that time. This study assumed that 84% of predictions were made with 'high-confidence,' (thus did not require histologic analysis), assumed a 94% sensitivity and 89% specificity of NBI for detection of adenomas. The analysis was restricted to screening procedures with only diminutive polyps and potential surveillance was simplified to either five or ten years. Based on these assumptions and applied to the narrow population of screening procedures in which only diminutive polyps are found (approximately 28%[3] of all screening procedure), Hassan et al estimated an annual savings of 33 million dollars if a CRD strategy is applied. Kessler *et al.*[29] also examined cost-effectiveness of this strategy in 2011. They also used assumptions based on expert performance. In contrast to Hassan et al, Kessler et al included all colonoscopies with at least a diminutive polyp (and varying combinations of additional diminutive, small-5-9 mm and large ≥ 10 polyps). They drew upon a large database to estimate the prevalence of various combinations of polyp size/histology/number and resultant proportions of patients who fell into different surveillance intervals (3, 5 or 10 years). They applied the per-polyp NBI optical diagnostic accuracy reported in the literature at that time (all based on experts) and accordingly determined downstream cost savings of forgoing pathology and costs of inaccurate surveillance intervals for each of the possible surveillance interval outcomes. Kessler et al concluded that a CRD strategy would results in an annual cost savings of over 1 billion dollars.

There are several limitations to the generalizability of the widely variable results from these analyses when considering the potential application of a 'characterize, resect and discard' strategy. As mentioned, both studies used assumptions of performance by experts, who characterize a significantly higher proportion of polyps with high confidence (80-90% vs 74% in our study), thus fewer diminutive polyps sent for pathology. Experts also have better accuracy in predicting surveillance intervals (93-98% vs 91%), thus less costs incurred by more frequent surveillance or missed neoplasia progressing to cancer from delayed surveillance. Furthermore, the analysis by Hassan was restricted to only screening procedures with only diminutive polyps, which may have underestimated the cost savings given that the strategy can be applied to colonoscopy for any indication (diagnostic, screening or surveillance) where a diminutive polyps is found and can be applied to procedures in which larger polyps are found. Although the analysis by Kessler et al aimed to overcome this restrictive application of CRD and include all procedures in which a diminutive polyp was found, they extrapolated proportions of surveillance intervals (and thus consequences of deviation from histology-based surveillance intervals) from a complex permutation of polyp findings (size/number/histology).

Our study attempted to overcome these limitations by drawing assumptions from a recent multi-center study specifically aimed at examining the CRD strategy amongst newly trained endoscopists. We demonstrated that with appropriate training, endoscopists without prior expertise in NBI were able to achieve a 91.2% (95% CI 89.7-92.7) agreement in surveillance interval predictions (using a combination of high-confidence NBI predictions for diminutive polyps in combination with histology for all other polyps) and a 94.7% NPV (95% CI 92.6-96.8) for adenomatous histology in the rectosigmoid colon.[13] This study more accurately reflected performance of NBI-naïve endoscopists, thus avoiding inflation of cost savings when applying expert performance to routine practice. This study also directly reported the proportion of individuals with at least one diminutive polyp who fell into three, five and ten year surveillance recommendations based on histology, as opposed to extrapolating these groups based on complex permutations of possible polyp size/

histology/number as was done by Kessler et al. Since one of the primary aims of our prior work[13] was to evaluate the accuracy of surveillance intervals based on NBI optical diagnosis compared to histology, we were able to directly estimate the repercussions of patients getting earlier or later surveillance in a CRD strategy.

Using assumptions based on non-expert performance and evaluating direct and indirect costs associated with deviations from histology-based surveillance intervals, this study demonstrates that a CRD strategy using NBI is cost effective without compromising quality adjusted life years. With increasing volume of colonoscopy performed in the United States, this translates to significant cost savings to the health care system.

There are several limitations to this analysis. The model assumes that low-risk lesions will be surveyed in 5 years, even though current guidelines recommend 5-10 year surveillance. Extending surveillance to 10 years is likely associated with even more cost-savings given fewer number of colonoscopies performed. This analysis does not include the potential costs of monitoring/auditing NBI performance and maintaining new ways to track quality metrics [such as adenoma detection rate (ADR)], though photo-documentation has been shown to be a reliable way to monitor ADR.[47] These costs would likely be absorbed at the institutional level even though the cost savings would be for the healthcare system as whole. Additionally, this analysis does not take into account physician[48] or patient[49] acceptance of a CRD strategy. It is possible that individuals may be willing to bear the differential in cost over 10 years for a minimal potential benefit or increased peace of mind; future research is required to assess these preferences.

There have been recent developments in computer-aided diagnosis of diminutive colorectal polyps.[25-27] Early studies suggest that they perform similarly to the results from our recent multi-center study which were used as assumptions for this cost-effectiveness analysis. Although wide-spread application of computer-aided diagnosis is not currently in place, it may be incorporated into clinical practice in the near future. Although there would likely be an up-front cost associated with acquiring the technology needed, adoption of computer-aided diagnosis can eliminate the costs of auditing endoscopists' performance in optical diagnosis and endoscopist variability in performance and acceptance of the strategy. Cost-effectiveness analyses may need to be updated with once exact costs associated with adopting this technology are available.

The model was sensitivity to adenoma prevalence. Thus, in patient populations with a particularly high prevalence of adenomas, a CRD strategy may not be cost-effective (such as fecal immunochemical test positive patients or Veterans). The ten-year time horizon may not predict future changes in the incremental cost-effectiveness ratio, though we appreciated similar results in our sensitivity analyses examining a longer time horizon. The analysis also assumed perfect health upon entry into the model which is an unrealistic assumption (though without impact on the choice of the favored strategy).

Inherent to the design of the study, our results are based on assumptions derived from the literature. In particular, though the natural history of diminutive adenomas seem to be quite indolent based on available data, there is no long-term follow up data available. Our assumptions regarding optical diagnosis performance were derived from a recent multi-center study including advanced imaging naïve endoscopists to best reflect real world application. Furthermore, the sensitivity analyses utilized a robust 25% variation in estimates. Despite these strengths, validation of our findings in other prospective cohorts would add further support to the robustness of our findings in this simulation.

Another potential limitation to this analysis is that there may have been sessile serrated polyps in the right colon that were optically classified as "hyperplastic" and also histologically called as "hyperplastic." This would have resulted in a "correct" NBI prediction, however may represent in situ neoplasia that has the risk of progression. Of the 3,012 diminutive polyps included in our original study,[13] 73 polyps in the right colon were diagnosed as "hyperplastic" by pathology with a concordant prediction of hyperplastic by NBI. This raises the concern that these 73 polyps were in fact SSPs and if left in place may have had the risk of progression. To take this into account for our cost-effectiveness analysis, we incorporated this risk in the "low-risk" arm of the CRD strategy in our structural sensitivity analysis examining the impact of missed polyps on the first exam. Future use of this or other models could assess this risks of not resecting these lesions as we better understand the natural history of these lesions.

To account for SSPs in the right colon that may be mischaracterized as non-neoplastic, we performed a sensitivity analysis where all of these polyps were left in situ. There was no significant difference in QALY between the CRD and SOC. This is likely because of the low prevalence of diminutive SSPs (1.5% of all diminutive polyps from our original study).

In summary, this study demonstrates marked cost savings associated with a CRD strategy for diminutive colorectal polyps found on routine diagnostic, screening and surveillance colonoscopy, even when applied by advanced imaging naïve (though trained) endoscopists. There was no difference in quality adjusted life years or mortality between CRD and the SOC strategies.

We now have robust data that with appropriate training, routine endoscopists can achieve the performance thresholds set forth by the ASGE and that even at their level of performance, the strategy remains highly cost effective compared to the current standard of care. The data supports widespread implementation of optical CRD for diminutive, non sessile serrated polyps if the strategy can be endorsed by professional societies and embraced by medical institutions, endoscopists and patients.

Author Contributions

S. Patel: Study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding; , technical, or material support; study supervision

F. Scott: Study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; technical, or material support; study supervision

A. Das: Study concept and design; Analysis and interpretation of data; critical revision and final approval of the manuscript

D. Rex: Study concept and design; Analysis and interpretation of data; critical revision and final approval of the manuscript

S. McGill: Study concept and design; Analysis and interpretation of data; critical revision and final approval of the manuscript

T. Kaltenbach: Study concept and design; Analysis and interpretation of data; critical revision and final approval of the manuscript

D. Ahnen: Study concept and design; Analysis and interpretation of data; critical revision and final approval of the manuscript

A. Rastogi: Study concept and design; Analysis and interpretation of data; critical revision and final approval of the manuscript

S. Wani: Study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding; , technical, or material support; study supervision

Conflicts Of Interest

SGP - None

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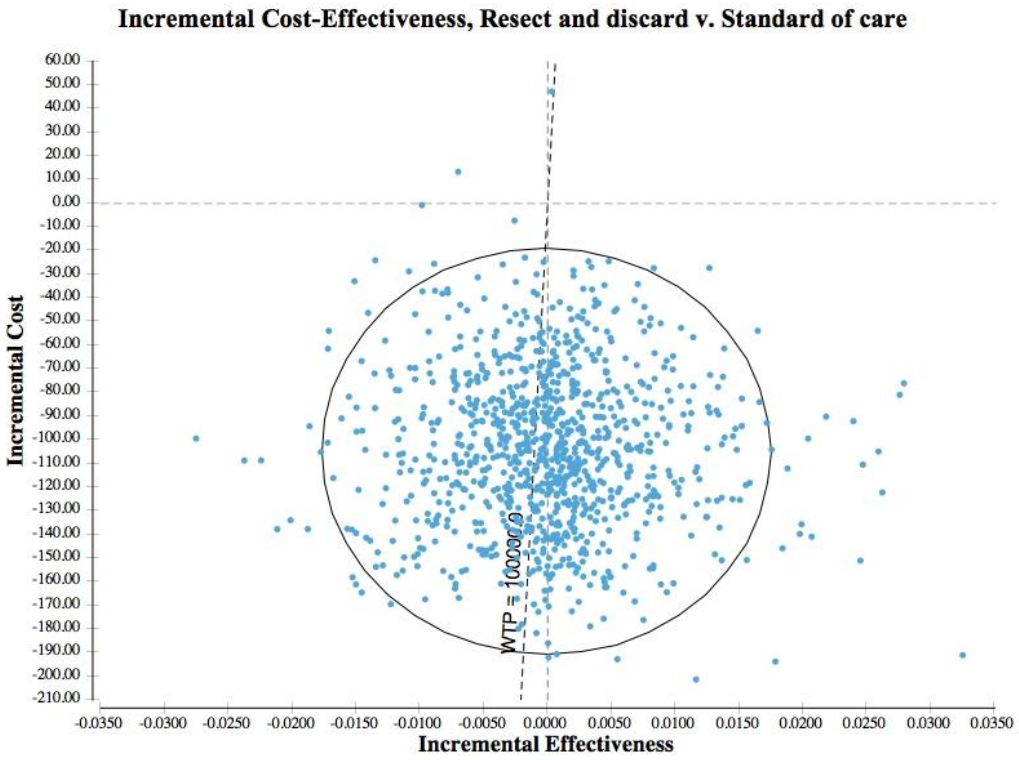

Supplemental Figure: Incremental cost-effectiveness ratio (ICER) Tornado Plot of key transition probabilities. Of all the transition probabilities evaluated, the model was sensitive to two variables (where horizontal bar crosses 0 on the x-axis): the probability of 'low-risk' findings in the CRD strategy and the probability of 'low-risk' finding in the SOC strategy.

Supplemental Table 1: Sensitivity analyses examining time horizon and risk of missed polyps during initial exam

Analysis	CRD strategy		SOC strategy	
	Mean QALYs (95% CI)	Mean Cost (95% CI)	Mean QALYs (95% CI)	Mean Cost (95% CI)
Increased time horizon				
15 years	11.8432 (11.8329, 11.8577)	$3138.23 ($3129.40, 3148.86)	11.8431 (11.8331, 11.8582)	$3272.54 ($3261.26, 3283.04)
20 years	14.5966 (14.581, 14.618)	$ 3721.86 ($3706.36, 3737.70)	14.5965 (14.591, 14.618)	$3,846.94 ($3835.37, 3859.26)
Potential missed adenomas on first exam	8.5626 (8.5558, 8.5711)	$ 2743.11 ($2733.18, 2753.10)	8.5625 (8.5566, 8.5712)	$2834.93 ($2826.30, 2844.72)
Progression of all SSPs	8.5911 (8.5843, 8.5979)	$ 2749.24 ($2739.15, 2759.10)	8.5912 (8.5844, 8.5980)	$ 249.25 ($2739.17, 2759.12)
Progression of mischaracterized SSPs	8.5626 (8.5558, 8.5711)	$ 2743.11 ($2733.18, 2753.10)	8.5625 (8.5566, 8.5712)	$2834.93 ($2826.30, 2844.72)

CRD: Characterize, resect & discard; SOC: Standard of care; QALY: Quality Adjusted Life Year; SSP: Sessile serrated polyp

Supplemental Table 2. Sensitivity analyses examining age at entry into model.

	Characterize, Resect and discard (CRD) strategy		Standard of care (SOC)				
Age	Efficacy (in QALYs)	Cost	Efficacy (in QALYs)	Cost	Incremental Effectiveness	Incremental Cost	ICER
55	8.4604	$2716.71	8.4584	$2824.86	0.0020	-108.1420	*
60	8.3279	$2731.40	8.3244	$2850.72	0.0035	-119.3232	*
65	8.1237	$1583.78	8.1210	$1692.67	0.0028	-108.8943	*
70	7.8138	$1580.39	7.8120	$1693.29	0.0018	-112.8971	*

*Negative Incremental Cost Effectiveness Ratio not reported (per convention).