

Cost-Effectiveness of Colorectal Cancer Screening With Computed Tomography Colonography

The Impact of Not Reporting Diminutive Lesions

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Received December 14, 2006; revision received January 20, 2007; accepted January 24, 2007.

BACKGROUND. Prior cost-effectiveness models analyzing computed tomography colonography (CTC) screening have assumed that patients with diminutive lesions (≤ 5 mm) will be referred to optical colonoscopy (OC) for polypectomy. However, consensus guidelines for CTC recommend reporting only polyps measuring ≥ 6 mm. The purpose of the current study was to assess the potential harms, benefits, and cost-effectiveness of CTC screening without the reporting of diminutive lesions compared with other screening strategies.

METHODS. The cost-effectiveness of screening with CTC (with and without a 6-mm reporting threshold), OC, and flexible sigmoidoscopy (FS) were evaluated using a Markov model applied to a hypothetical cohort of 100,000 persons age 50 years.

RESULTS. The model predicted an overall cost per life-year gained relative to no screening of \$4361, \$7138, \$7407, and \$9180, respectively, for CTC with a 6-mm reporting threshold, CTC with no threshold, FS, and OC. The incremental costs associated with reporting diminutive lesions at the time of CTC amounted to \$118,440 per additional life-year gained, whereas the incidence of colorectal cancer was reduced by only 1.3% (from 36.5% to 37.8%). Compared with primary OC screening, CTC with a 6-mm threshold resulted in a 77.6% reduction in invasive endoscopic procedures (39,374 compared with 175,911) and 1112 fewer reported OC-related complications from perforation or bleeding.

CONCLUSIONS. CTC with nonreporting of diminutive lesions was found to be the most cost-effective and safest screening option evaluated, thereby providing further support for this approach. Overall, the removal of diminutive lesions appears to carry an unjustified burden of costs and complications relative to the minimal gain in clinical efficacy. *Cancer* 2007;109:000–000. © 2007 American Cancer Society.

KEYWORDS: colorectal cancer, screening, colonoscopy, computed tomography colonography, flexible sigmoidoscopy, cost-effectiveness analysis, colorectal neoplasia, colorectal polyps.

Models for colorectal cancer (CRC) screening have demonstrated that a variety of screening strategies can be cost-effective due to the prolonged, detectable preclinical phase that allows for cancer prevention. Because of wide variability in available resources, patient preferences, and program adherence, a singular solution to CRC screening is unlikely to succeed. To address this issue, a menu of effective screening strategies has long been advocated.¹ If computed tomography colonography (CTC), an emerging CRC screening tool also referred to as virtual colonoscopy,² is to be added to this list, it is important to assess the potential economic and clinical impact of this approach relative to the existing screening options.

TABLE 1
Baseline Assumption Values Applied in the Model

Variable	Base-case analysis (Range)*	References
Natural history		
Adenoma prevalence at age 50 y (%)	15 (0.15–45)	35, 36
New polyp rate (% per year)	1.9 (0.02–5.7)	37
	3.3 (0.03–9.9)	50–60 y
	2.6 (0.03–7.8)	60–70 y
		70–80 y
Annual transition rate from ≤ 5 mm to 6–9 mm (%)	2 (0.02–7.8)	17, 29–34
Annual transition rate from 6–9 mm to ≥ 10 mm (%)	2 (0.02–7.8)	17, 29–34
Annual transition rate from ≥ 10 mm to early CRC (%)	3 (0.03–13)	38
Annual transition rate from early CRC to late CRC (%)	30	39
Advanced ≥ 10 mm/advanced < 10 mm rate (%)	90	13
Polypoid/de novo rate of CRC carcinogenesis (%)	90 (70–100)	40
Annual transition rate to de novo cancer (%)	Age specific-rate, 0.010–0.093	41
Mortality rate from early cancer (% for the first 5 y)	4	39
Mortality rate from late cancer (% for the first 5 y)	4	39
Screening tests		
CTC sensitivity for ≤ 5 mm polyps (%)	48 (0–96)	11, 12
CTC sensitivity for 6–9 mm polyps (%)	70 (42–98)	11, 12
CTC sensitivity for ≥ 10 mm polyps (%)	85 (51–98)	11, 12
CTC sensitivity for CRC (%)	95 (47–99)	11, 12
CTC specificity (%)	86 (17–95)	11, 12
OC sensitivity for ≤ 5 mm polyps (%)	80 (0–96)	42, 43
OC sensitivity for 6–9 mm polyps (%)	85 (4–98)	42–45
OC sensitivity for ≥ 10 mm polyps (%)	90 (4–98)	42–45
OC sensitivity for CRC (%)	95 (47–99)	46, 47
OC specificity (%)	90 (18–100)	46, 47
FS sensitivity for ≤ 5 mm polyps (%)	45 (0–90)	36, 53
FS sensitivity for 6–9 mm polyps (%) [†]	45 (27–63)	13, 14
FS sensitivity for advanced neoplasia (%)	60–65 [‡] (36–75)	13, 14
FS sensitivity for CRC (%)	60–65 (11–68)	13, 14
FS specificity (%)	90 (18–100)	13, 14
Adherence (%) [§]	65 (1–100)	48
Compliance (%) [§]	80 (1–100)	49
OC bleeding rate (%%)	0.15	50
OC perforation (%)	0.2	51
Polypectomy bleeding (%)	2	50
Polypectomy perforation (%)	0.38	51
FS perforation (%)	0.011	52
Costs		
OC (\$)	696 (0–1530)	53
FS (\$)	401 (0–880)	53
CTC (\$)	478 (0–1052)	3
OC with polypectomy (\$)	1,139 (0–2506)	53
Bleeding (\$)	4,360 (0–9592)	53
Perforation (\$)	13,000 (0–28,600)	53
CRC treatment (\$)	45,228 (0–99,502)	53

CRC indicates colorectal cancer; CTC, computed tomography colonography; OC, optical colonoscopy; FS, flexible sigmoidoscopy.

* Range of values applied in the sensitivity analyses.

[†] Not including advanced adenomas.

[‡] Due to the association between right-sided neoplasia and aging, sigmoidoscopy sensitivity is assumed to be 65% at age 50 years and 60% at age 60 years.

[§] Adherence pertains to initial testing, whereas compliance pertains to follow-up testing.

Adapted from Hassan et al.⁵

Although the cost-effectiveness of CTC screening has been previously studied,^{3–6} these models have generally assumed that all detected polyps, including diminutive lesions (defined as ≤ 5 mm in size), would be referred to optical colonoscopy (OC) for polypec-

tomy. However, for a number of legitimate reasons, current consensus guidelines do not recommend the reporting of potential diminutive polyps at CTC,⁷ which has already translated into limited clinical practice.⁸ The purpose of the current study was to

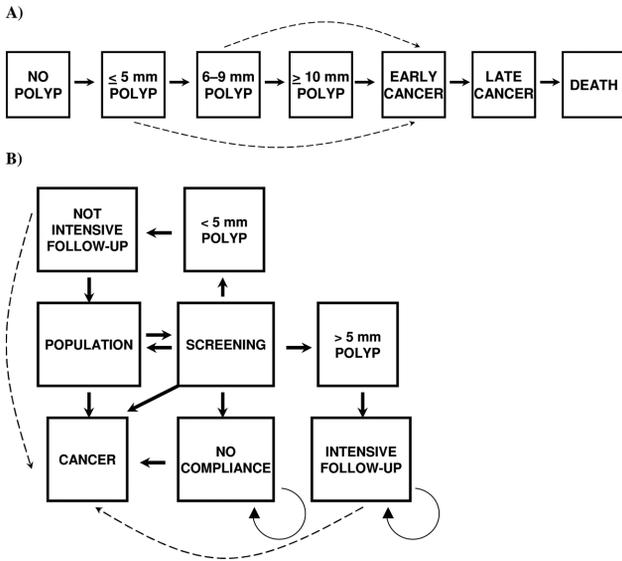


FIGURE 1. (A) The model has been constructed to simulate the progression from no lesions to colorectal cancer (CRC)-related death throughout the various phases. As shown by the broken arrows, it was assumed that early CRC could arise from sub-cm polyps. (B) The model simulates the transition of the population through consecutive yearly cycles. Patients are screened at the selected intervals, after which they may return to the initial compartment if no lesion is detected or they may enter a surveillance regimen if an adenoma is detected. Noncompliant patients are considered noncompliant until the end of the simulation. Adapted from Hassan et al.⁵

assess the clinical and economic impact of employing a reporting threshold of 6-mm polyp size at CTC screening.

MATERIALS AND METHODS

A mathematical Markov model was constructed and simulation was performed on a hypothetical cohort of 100,000 subjects at average risk for CRC. The baseline assumptions and ranges used in the model are provided in Table 1. In brief, subjects were evaluated with standard testing every 10 years beginning at age 50 years and covering 3 decades to 80 years of age. CTC screening was modelled for 2 discrete strategies: no polyp size reporting threshold and a 6-mm polyp size reporting threshold. CTC with a 6-mm reporting threshold essentially reflects nonreporting of diminutive lesions or, in effect, a 0% sensitivity for polyps measuring ≤ 5 mm; these terms will be applied interchangeably. Although some variability in polyp measurement at the time of CTC exists, given the relative operator independence and fixed spatial nature of the CT dataset, CTC likely represents the most reproducible means available for in vivo polyp assessment.⁹

Clinical efficacy of a screening test was defined according to the reduction in CRC incidence com-

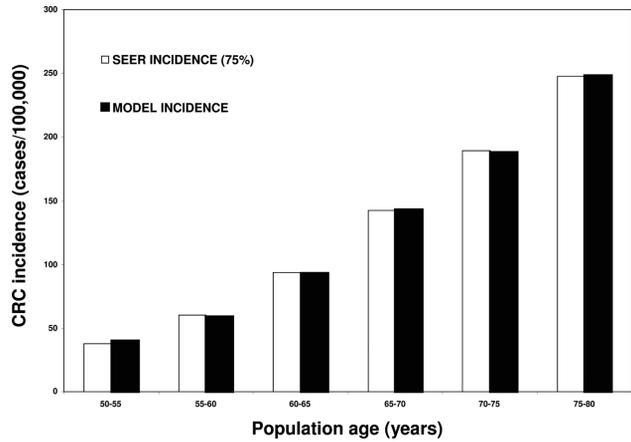


FIGURE 2. The incidence of colorectal cancer (CRC) according to age as computed by the model compared with the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) data. The SEER CRC incidence has been reduced by 25% to represent the average-risk population.

pared with no screening. The relative cost-effectiveness of a screening test was assessed based on the additional costs required to gain an additional life-year in comparison with either no screening or another screening strategy (also referred to as the incremental cost-effectiveness ratio [ICER]). One screening strategy was considered dominant over another when it was both less expensive and more clinically effective. Both future costs and future life-years saved were discounted using an annual rate of 3%.

The model simulates progression through the entire spectrum of disease, ranging from no lesions to CRC-related death, including the possibility of early CRC arising from sub-cm polyps (Fig. 1A). The model also accounts for noncompliance (Fig. 1B). The age-dependent incidence of CRC computed by the model closely simulates the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) registry data applied to average-risk adults (Fig. 2).

To project the outcomes of our simulation on the entire U.S. population, we assumed a steady state for population size and age distribution, represented by the year 2004 U.S. Census data.¹⁰

Because each age-specific output of the model was computed by simulating an average-risk population, a correction factor was introduced to reflect that approximately 75% of the population of the U.S. is at average risk for CRC. Adding the results for all ages under each strategy yielded national estimates. As previously suggested, no discounting was used in these national projections because the model outputs reflected all persons ages 50 to 80 years at a given point in time in the steady state, as opposed to

TABLE 2
Modelled Outcomes at Baseline Assumptions For The Various CRC Screening Tests

Variable	No screening	CTC 6-mm reporting threshold	CTC no reporting threshold	FS	OC
Cases of CRC prevented	–	1073	1110	924	1187
CRC prevention	–	36.5%	37.8%	31.4%	40.4%
Life-years gained	–	4266	4372	3609	4641
Procedures					
CTC	–	141,176	140,052		
FS	–			141,246	
OC	–	39,374	61,849	50,838	175,911
OC-related complications	–	351	691	610	1463
Bleeding event	–	253	525	455	1036
Perforation	–	98	166	154	427
Without advanced lesion	–	301	642	566	1415
Total cost	\$97,976,886	\$116,581,633	\$129,183,146	\$124,705,103	\$140,582,839
Cost per life-year gained*	–	\$4361	\$7138	\$7407	\$9180

CRC indicates colorectal cancer; CTC, computed tomography colonography; FS, flexible sigmoidoscopy; OC, optical colonoscopy.

* Compared with no screening.

a cohort aging from 50 years to 80 years over the course of 30 years.⁴

For sensitivity analyses, all variables of the model were broadly varied among plausible ranges (Table 1) to compensate for the lack of precise knowledge in either the natural history of colorectal polyps or the performance characteristics of the various screening tests. CTC and OC performance data for polyp detection were based in part on recent head-to-head comparison trials,^{11,12} whereas flexible sigmoidoscopy (FS) performance was derived from polyp distribution at the time of OC in conjunction with the expected reach of the sigmoidoscope.^{13,14} It is interesting to note that the baseline assumptions for CTC polyp sensitivity reflected averages based on meta-analyses^{11,12} and not the higher performance generally noted with current state-of-the-art techniques such as three-dimensional polyp detection and oral contrast tagging.^{2,8}

RESULTS

In the case of no screening, the model predicted a total of 2940 cases of CRC in the simulated population of 100,000 adults, corresponding to a loss of 16,941 CRC-related life-years and \$97,976,886 in CRC-related treatment costs.

Clinical Efficacy of the Modelled Screening Tests

At baseline conditions, the model predicted a reduction in CRC incidence ranging from 31.4% for FS screening to 40.4% for OC screening (Table 2). CTC without a polyp size threshold for reporting (ie, all detected polyps were referred for polypectomy at the time of OC) yielded a CRC prevention rate of 37.8%,

which is closer to the OC level than the FS level. It is interesting to note that by not reporting diminutive polyps (≤ 5 mm) at the time of CTC, the CRC prevention rate was 36.5%, which is only 1.3% lower than CTC without a size threshold. However, by not reporting diminutive lesions at CTC, there were 12,884 fewer “therapeutic” OC procedures with polypectomy performed compared with CTC screening without a size threshold, corresponding to a 55% reduction. The predicted CRC prevention rates for the various tests resulted in 3609 to 4641 life-years gained compared with no screening (Table 2).

The clinical efficacy of all the modelled screening tests was found to be strongly affected by the input values applied to the sensitivity for nondiminutive (≥ 6 mm) polyps (Fig. 3). CRC prevention rapidly drops off as the sensitivity for polyps measuring ≥ 6 mm decreases below baseline assumptions. Conversely, as more advanced CTC techniques yield higher sensitivities compared with the case-base analysis, the corresponding CRC prevention rates approach that of OC. In contrast to the strong influence of sensitivity for polyps measuring ≥ 6 mm, the test sensitivity for diminutive lesions appeared to have very little impact on CRC prevention rates (Fig. 1). A sensitivity of 0% for diminutive lesions, which is equivalent to simply ignoring them, generally lowered CRC prevention rates by only approximately 1%. As noted earlier, CRC prevention for CTC dropped 1.3% to 36.5% when diminutive lesions were ignored.

Cost-Effectiveness of the Modelled Screening Tests

At baseline conditions, all screening tests were found to be cost-effective compared with no screening,

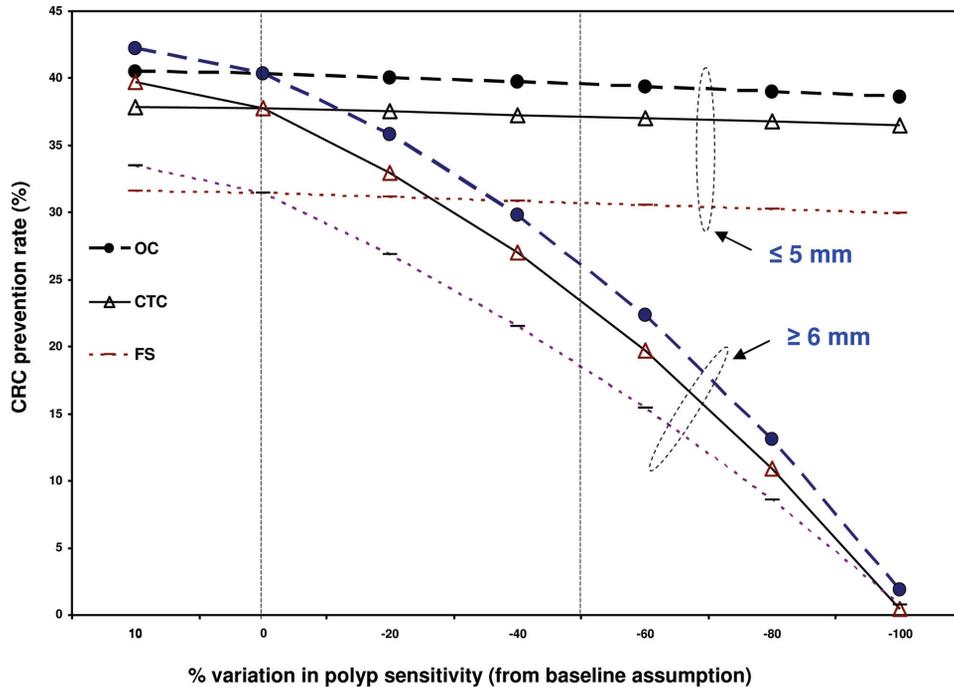


FIGURE 3. Estimated colorectal cancer (CRC) prevention rates according to variations in test sensitivity for polyps measuring ≤ 5 mm and polyps measuring ≥ 6 mm from the baseline assumptions. Percentage variation from the baseline is shown rather than absolute sensitivity to allow for the simultaneous depiction of the 3 screening tests and the 2 different polyp size categories. Note how the test efficacy plummets with decreasing sensitivity for nondiminutive polyps (measuring ≥ 6 mm), whereas ignoring diminutive polyps (ie, the equivalent of 0% sensitivity) appears to have very little effect on colorectal cancer prevention. According to the model, the cancer prevention rate would drop by only approximately 1% if diminutive lesions are ignored. OC indicates optical colonoscopy; CTC, computed tomography colonography; FS, flexible sigmoidoscopy.

amounting to $< \$10,000$ per additional life-year gained (Table 2). Primary OC was the most expensive approach at $\$9180$ per life-year gained compared with $\$7407$ for FS and $\$7138$ for CTC without a polyp size threshold. CTC with a 6-mm reporting threshold was found to be the most cost-effective approach at $\$4361$ per life-year gained. Compared with primary OC screening, this approach resulted in a 77.6% reduction in invasive endoscopic procedures, from 175,911 to 39,374 (Table 2).

Unlike the minimal effect on CRC prevention observed with nonreporting of diminutive polyps at the time of CTC (Fig. 1), the corresponding effect on cost-effectiveness was found to be much greater. By decreasing the CTC sensitivity for diminutive polyps to 0% (ie, not reporting them), the cost per life-year gained was reduced by nearly 40% from the baseline value (Fig. 4). Furthermore, the ICER for CTC without a reporting threshold compared with CTC with a 6-mm reporting threshold was large— $\$118,440$ per additional life-year gained (Table 3). Likewise, CTC screening with nonreporting of diminutive lesions was considerably less expensive than primary OC screening, with an incremental cost-effectiveness ra-

tio of $\$63,900$ per life-year gained. Finally, CTC with a 6-mm reporting threshold dominated FS screening because it was both less costly and more clinically effective. Assuming a CTC sensitivity for large polyps of 55%, as reported by Cotton et al.,¹⁵ the ICER of OC compared with CTC using a 6-mm reporting threshold improved from $\$63,900$ to $\$16,450$. However, if the CTC and OC sensitivity for large polyps as reported by Pickhardt et al. is assumed (92% and 88%, respectively), the ICER of OC increases to $\$343,878$.² For CTC with nonreporting of diminutive polyps, the sensitivity for polyps measuring ≥ 6 mm would have to drop by 46% and 24%, respectively, to match the cost-effectiveness of screening by OC and CTC without a reporting threshold.

Number of Significant Complications

Complications related to CRC screening are an important consideration because such testing is largely applied to healthy, asymptomatic adults. Compared with primary OC screening, CTC with nonreporting of diminutive lesions resulted in 1112 fewer OC-related complications from bleeding and perforation, which corresponds to a 76.0% reduction (Table 2). Few, if

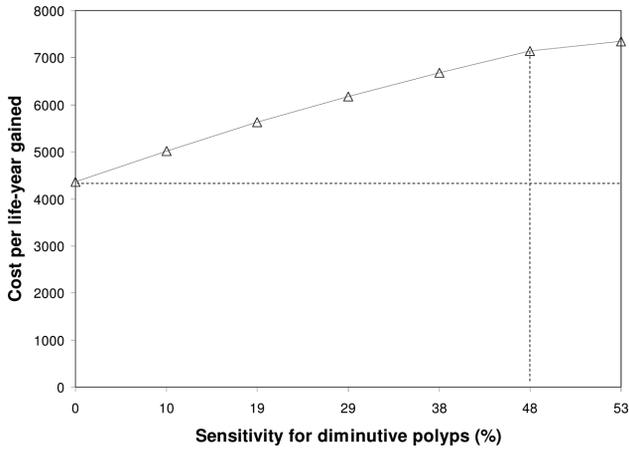


FIGURE 4. Cost-effectiveness (compared with no screening) of computed tomography colonography (CTC) according to sensitivity for diminutive polyps (≤ 5 mm). Compared with the baseline assumption (48% sensitivity; \$7138 per life-year saved), not reporting diminutive lesions at the time of CTC (0% sensitivity; \$4362 per life-year saved) results in nearly a 40% reduction in cost per life-year saved. Compare this relatively large savings with the small drop in the cancer prevention rate from Figure 1.

TABLE 3
Incremental Cost-Effectiveness Ratios of Other Screening Tests Compared With CTC With Nonreporting of Diminutive Lesions

Screening strategy	Cost per life-year gained compared with CTC using 6-mm reporting threshold
FS	CTC dominant
OC	\$63,900
CTC with no size threshold	\$118,440

CTC indicates computed tomography colonography; FS, flexible sigmoidoscopy; OC, optical colonoscopy.

any, of these patients with additional complications at the time of primary OC versus primary CTC screening would be expected to harbor advanced neoplasia, suggesting that CTC could potentially serve as a selective filter for determining those individuals who would benefit most from polypectomy. Compared with reporting and removing diminutive polyps at the time of primary CTC screening, nonreporting of these lesions resulted in a 49.2% reduction in serious OC-related complications.

U.S. Population Projection

The undiscounted annual cost of treatment for the estimated 58,452 cases of CRC in the U.S. population that would result from no screening interventions was \$2,643,663,313 (Table 4). CTC with nonreporting of diminutive polyps was the least costly screening program evaluated and was moderately effective for CRC prevention. Compared with OC screening, the

TABLE 4
Projected Annual Outcomes In The U.S. Population at Average Risk for CRC

Strategy	Cases of CRC	CRC prevention	Program costs
No screening	58,452	-	\$2,643,663,313
CTC with 6-mm reporting threshold	37,935	35.1%	\$4,117,447,801
FS	40,974	29.9%	\$4,292,477,352
CTC with no reporting threshold	37,210	36.3%	\$4,551,032,434
OC	35,586	39.1%	\$5,029,441,556

CRC indicates colorectal cancer; CTC, computed tomography colonography; FS, flexible sigmoidoscopy; OC, optical colonoscopy.

annual program cost was nearly \$1 billion less for an estimated 4% drop in relative CRC prevention. Compared with FS screening, CTC with nonreporting of diminutive lesions was less costly yet more effective (ie, dominant).

Sensitivity Analyses

The incremental cost-effectiveness of screening tests is often highly dependent on a variety of input assumptions. The effect of polyp sensitivity has already been discussed. In addition to test performance characteristics, other variables that can strongly influence results include adherence and study costs. Adherence to a screening program, defined as compliance to the initial examination, is a major determinant of ultimate efficacy. If 100% adherence is assumed, the modelled CRC prevention rates for CTC and OC rise to 56.2% and 62.1%, respectively, whereas a decrease in adherence to 35% results in CRC prevention rates of only 19.7% to 23.2%. A 10% decrease in adherence for OC reduces its efficacy to below that of CTC with nonreporting of diminutive lesions. As such, OC screening would be dominated by CTC (ie, OC would be more costly and less effective). An increase of 26% and 59%, respectively, in the cost of CTC compared with the baseline assumption would be needed to increase the cost per life-year gained (compared with no screening) to that of OC for the no reporting threshold and 6-mm reporting threshold approaches.

DISCUSSION

CRC remains the second-leading cause of cancer-related deaths in the U.S., despite the fact that it is largely preventable through effective screening.¹⁶ Given this unique opportunity to actually prevent cancer rather than just hoping to detect it after it has developed, it is not surprising that a variety of screening tests have been shown to be cost-effective

and clinically efficacious compared with no screening.¹⁷ However, given the low overall participation in CRC screening,¹⁸ driven in part by limited access and capacity with some tests, as well as by differences in patient preferences, a multipronged approach is likely needed to address the disturbingly high incidence of CRC. Simply put, the best screening test for a given individual may well be the test that they are both willing and able to undergo.

CTC is a promising screening tool that continues to rapidly evolve and may soon be added to the menu of recommended screening options. Early and somewhat disappointing performance results using older CTC techniques^{15,19,20} have been followed with more encouraging results using improved methodology.² Prior cost-effectiveness analyses in the gastrointestinal literature have compared CTC with OC.³⁻⁶ Not surprisingly, although the findings of these studies were all highly sensitive to the input variables, CTC was generally shown to be both cost-effective and clinically effective compared with no screening. However, from the base-case analyses, most studies concluded that OC was more cost-effective than CTC. It is important to note that all these cost-effectiveness analyses assumed that all CTC-detected polyps would be referred for polypectomy at the time of OC, including diminutive lesions. However, current consensus guidelines for CTC interpretation recommend 6 mm as the minimum size for polyp reporting,⁷ which also reflects actual clinical practice.⁸ This discrepancy between the existing cost-effectiveness modelling and clinical practice for CTC screening was the primary motivation for this study.

It is widely accepted that polypectomy is indicated for large polyps (≥ 10 mm) detected at the time of CTC screening because the relatively small risks of undergoing therapeutic OC are likely outweighed by the malignant potential of these lesions. Similarly, there also appears to be general agreement that diminutive lesions (measuring ≤ 5 mm) are of no practical clinical significance because only a fraction are neoplastic and, of these, $<1\%$ are histologically advanced and essentially none are malignant.^{2,21-23} In addition, the accuracy of CTC and concordance with OC for diminutive polyps is relatively low, with many lesions that either cannot be found at subsequent OC or were missed at CTC. Furthermore, the potential benefit from OC polypectomy for a CTC-detected diminutive polyp is very likely outweighed by the procedural costs and risks of the invasive procedure. To underscore this viewpoint, the American Gastroenterological Association has stated that, in the case of CTC, polyps measuring ≤ 5 mm are not sufficient cause to perform colonoscopy and polypectomy.²⁴

The current study findings showed that diminutive lesions are neither a clinically effective nor a cost-effective target for CRC screening. In fact, diminutive lesions appear to represent a heavy burden on the overall costs of screening programs, accounting for greater than half of all therapeutic OC procedures and nearly half of all OC-related complications. By not reporting diminutive polyps at the time of CTC screening, there was a large incremental gain in cost-effectiveness (ICER of \$118,440 per life-year gained), with only minimal loss in clinical efficacy (reduction in CRC prevention of 1.3%). In addition, a large number of OC-related complications were avoided in adults who would rarely, if ever, harbor advanced neoplasia, which is the widely accepted target of CRC screening.²⁵ Consideration for avoiding serious complications is critical for CRC screening because it is largely applied to healthy, asymptomatic adults (*primum non nocere*). Given the exceedingly low malignancy rate among diminutive polyps, the rare diminutive lesion with advanced histology would presumably enlarge beyond both the 6-mm and 10-mm thresholds long before developing into invasive cancer, thereby allowing for its detection at CTC.

The advantages of CTC screening would have been much more pronounced if the base-case assumptions had instead used the performance characteristics of current state-of-the-art CTC, which continues to rapidly evolve and improve.² The improved accuracy of CTC for nondiminutive polyps (≥ 6 mm) translates into improved CRC prevention by reducing false-negative results and also lowers costs related to unnecessary OC procedures and complications by reducing false-positive results. However, even at sensitivity levels for large polyps as low as 55%, as reported by earlier trials, CTC proved to be cost-effective compared with OC screening in our model.^{15,19}

The actual costs of the various screening tests will of course vary widely in actual practice and evolve over time. As such, the raw dollar figures employed and generated in cost-effectiveness modelling are perhaps less important than the general trends that are found. In fact, the charges/costs related to OC in our experience are 3 to 4 times greater than the charge/cost for CTC, which would have vastly affected our results and further separated their relative cost-effectiveness if included in the model. Other factors that were not directly addressed in the model yet nonetheless add to real-life costs include the need for recovery time after OC, the need for a second person to drive the patient home after OC, and pathology costs related to histologic

evaluation of polyps (both large and small). Costs of additional workups related to extracolonic abnormalities detected at CTC were also not included, in part because any potential benefit associated with the early detection of significant extracolonic pathology could not be addressed easily.

It must be emphasized that CTC should not be considered as a replacement for the existing CRC screening strategies but rather as an additional effective option to increase overall compliance. Although cost-effective studies generally pit 1 test against another, the overall effectiveness of population screening as a whole depends on the summed participation of all the individual screening options. It is very encouraging to note that early experience with clinical CTC screening does not appear to negatively impact the volume of parallel OC screening that is already in place.⁸ Therefore, providing additional effective yet distinct screening options such as CTC could encourage more adults to undergo screening. As nearly all cost-effectiveness models to date have shown, increasing overall compliance with screening is a critical factor for the success of a program. Compliance with CTC screening could perhaps be enhanced further by not reporting diminutive lesions because the likelihood for OC referral plummets to well under 15% in clinical practice.⁸

Although to our knowledge relatively little controversy surrounds the handling of large and diminutive polyps at the time of CTC screening, the same cannot be said for polyps measuring 6 to 9 mm (ie, "small" or "medium-sized" lesions) detected at CTC.^{26,27} Based on the available natural history data for polyps measuring 6 to 9 mm (including longitudinal OC, FS, and barium enema trials),²⁸⁻³⁴ it could be argued that short-term CTC surveillance for unresected polyps measuring 6 to 9 mm is a reasonable strategy. In addition to offering same-day polypectomy at OC for all patients with CTC-detected polyps measuring ≥ 6 mm, at least 1 clinical screening program is currently offering patients the alternative of CTC surveillance for polyps measuring 6 to 9 mm.⁸ However, at the current time, relatively few centers offer CTC screening at all, largely due to the general lack of third-party reimbursement. The economic and clinical impact of CTC surveillance for patients with polyps measuring 6 to 9 mm is uncertain because this strategy was not incorporated into our model.

In conclusion, CTC with nonreporting of diminutive lesions was found to be the most cost-effective and safest screening option evaluated. These results provide further support for the practice of a 6-mm polyp size reporting threshold at CTC screening. In

general, diminutive colorectal polyps appear to cause an unjustified cost burden and high complication rate for CRC screening, without a substantial concomitant improvement in clinical efficacy. The use of primary CTC screening as a selective filter for OC polypectomy for lesions measuring ≥ 6 mm represents a potentially powerful new approach to CRC screening.

REFERENCES

1. Smith RA, Cokkinides V, Eyre HJ. American Cancer Society guidelines for the early detection of cancer, 2006. *CA Cancer J Clin.* 2006;56:11-25.
2. Pickhardt PJ, Choi JR, Hwang I, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *N Engl J Med.* 2003;349:2191-2200.
3. Sonnenberg A, Delco F, Bauerfeind P. Is virtual colonoscopy a cost-effective option to screen for colorectal cancer? *Am J Gastroenterol.* 1999;94:2268-2274.
4. Ladabaum U, Song K, Fendrick AM. Colorectal neoplasia screening with virtual colonoscopy: when, at what cost, and with what national impact? *Clin Gastroenterol Hepatol.* 2004;2:554-563.
5. Hassan C, Zullo A, Lahgi A, et al. Colon cancer prevention in Italy: cost-effectiveness analysis with CT colonography and endoscopy. *Dig Liver Dis.* 2007;39:242-250. Epub 2006 Nov 16.
6. Vijan S, Hwang I, Inadomi J, et al. The cost-effectiveness of CT colonography in screening for colorectal neoplasia. *Am J Gastroenterol.* 2007;102:380-390. Epub 2006 Dec 11.
7. Zalis ME, Barish MA, Choi JR, et al., for the Working Group on Virtual Colonoscopy. CT colonography reporting and data system: a consensus proposal. *Radiology.* 2005;236:3-9.
8. Pickhardt PJ, Taylor AJ, Kim DH, Reichelderfer M, Gopal DV, Pfau PR. Screening for colorectal neoplasia with CT colonography: initial experience from the first year of coverage by third-party payers. *Radiology.* 2006;241:417-425.
9. Pickhardt PJ, Lee AD, McFarland EG, Taylor AJ. Linear polyp measurement at CT colonography: in vitro and in vivo comparison of two-dimensional and three-dimensional displays. *Radiology.* 2005;236:872-878.
10. U.S. Census Bureau. Annual population estimates. Available at URL: www.census.gov Accessed November 5, 2005.
11. Mulhall BP, Veerappan GR, Jackson JL. Meta-analysis: computed tomographic colonography. *Ann Intern Med.* 2005;142:635-650.
12. Halligan S, Altman DG, Taylor SA, et al. CT colonography in the detection of colorectal polyps and cancer: systematic review, meta-analysis, and proposed minimum data set for study level reporting. *Radiology.* 2005;237:893-904.
13. Lieberman DA, Weiss DG, Bond JH, et al. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. *N Engl J Med.* 2000;343:162-168.
14. Imperiale TF, Wagner DR, Lin CY, et al. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. *N Engl J Med.* 2000;343:169-174.
15. Cotton PB, Durkalski VL, Pineau BC, et al. Computed tomographic colonography (virtual colonoscopy): a multicenter comparison with standard colonoscopy for detection of colorectal neoplasia. *JAMA.* 2004;291:1713-1719.

16. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. *CA Cancer J Clin*. 2006;56:106–130.
17. Frazier AL, Colditz GA, Fuchs CS, Kuntz KM. Cost-effectiveness of screening for colorectal cancer in the general population. *JAMA*. 2000;284:1954–1961.
18. Seeff LC, Manninen DL, Dong FB, et al. Is there endoscopic capacity to provide colorectal cancer screening to the unscreened population in the United States? *Gastroenterology*. 2004;127:1661–1677.
19. Rockey DC, Paulsen EK, Niedzwiecki D, et al. Analysis of air contrast barium enema, computed tomographic colonography, and colonoscopy: prospective comparison. *Lancet*. 2005;365:305–311.
20. Johnson CD, Harmsen WS, Wilson LA, et al. Prospective blinded evaluation of computed tomographic colonography for screen detection of colorectal polyps. *Gastroenterology*. 2003;125:311–319.
21. Bond JH. Clinical relevance of the small colorectal polyp. *Endoscopy*. 2001;33:454–457.
22. Pickhardt PJ, Choi JR, Hwang I, Schindler WR. Nonadenomatous polyps at CT colonography: prevalence, size distribution, and detection rates. *Radiology*. 2004;232:784–790.
23. Odom SR, Duffy SD, Barone JE, Ghevariya V, McClane SJ. The rate of adenocarcinoma in endoscopically removed colorectal polyps. *Am Surg*. 2005;71:1024–1026.
24. van Dam J, Cotton P, Johnson CD, et al. AGA future trends report: CT colonography. *Gastroenterology*. 2004;127:970–984.
25. Winawer SJ, Zauber AG. The advanced adenoma as the primary target of screening. *Gastrointest Endosc Clin N Am*. 2002;12:1–9.
26. Rex DK. PRO: Patients with polyps smaller than 1 cm on computed tomographic colonography should be offered colonoscopy and polypectomy. *Am J Gastroenterol*. 2005;100:1903–1905.
27. Ransohoff DF. CON: Immediate colonoscopy is not necessary in patients who have polyps smaller than 1 cm on computed tomographic colonography. *Am J Gastroenterol*. 2005;100:1905–1907.
28. Pickhardt PJ. CT colonography (virtual colonoscopy) for primary colorectal screening: challenges facing clinical implementation. *Abdom Imaging*. 2005;30:1–4.
29. Hofstad B, Vatn MH, Larsen S, Osnes M. Growth of colorectal polyps: recovery and evaluation of unresected polyps of less than 10 mm, 1 year after detection. *Scand J Gastroenterol*. 1994;29:640–645.
30. Hofstad B, Vatn MH, Andersen SN, et al. Growth of colorectal polyps: redetection and evaluation of unresected polyps for a period of three years. *Gut*. 1996;39:449–456.
31. Welin S, Youker J, Spratt JS Jr. The rates and patterns of growth of 375 tumors of the large intestine and rectum observed serially by double contrast enema study (Malmö Technique). *Am J Roentgenol Radium Ther Nucl Med*. 1963;90:673–687.
32. Knoernschild HE. Growth rate and malignant potential of colonic polyps: early results. *Surg Forum*. 1963;14:137–138.
33. Hoff G, Foerster A, Vatn MH, et al. Epidemiology of polyps in the rectum and colon: recovery and evaluation of unresected polyps 2 years after detection. *Scand J Gastroenterol*. 1986;21:853–862.
34. Bersentes K, Fennerty MB, Sampliner RE, Garewal HS. Lack of spontaneous regression of tubular adenomas in two years of follow-up. *Am J Gastroenterol*. 1997;92:1117–1120.
35. Johnson DA, Gurney MS, Volpe RJ, et al. A prospective study of the prevalence of colonic neoplasms in asymptomatic patients with an age-related risk. *Am J Gastroenterol*. 1990;85:969–974.
36. DiSario JA, Foutch PG, Mai HD, et al. Prevalence and malignant potential of colorectal polyps in asymptomatic, average-risk men. *Am J Gastroenterol*. 1991;86:941–945.
37. Loeve F, Boer R, Zauber AG, et al. National Polyp Study data: evidence for regression of adenomas. *Int J Cancer*. 2004;111:633–639.
38. Stryker SJ, Wolff BG, Culp CE, et al. Natural history of untreated colonic polyps. *Gastroenterology*. 1987;93:1009–1013.
39. Ries LA, Kosary CL, Hankey BF, et al., editors. SEER Cancer Statistics Review, 1973–1994. NIH Pub. No. 97-2789. Bethesda, MD: National Institutes of Health, National Cancer Institute; 1997.
40. Chen CD, Yen MF, Wang WM, et al. A case-cohort study for the disease natural history of adenoma-carcinoma and de novo carcinoma and surveillance of colon and rectum after polypectomy: implication for efficacy of colonoscopy. *Br J Cancer*. 2003;88:1866–1873.
41. Ladabaum U, Chopra CL, Huang G, et al. Aspirin as an adjunct to screening for prevention of sporadic colorectal cancer. A cost-effectiveness analysis. *Ann Intern Med*. 2001;135:769–781.
42. Hixson LJ, Fennerty MB, Sampliner RE, et al. Prospective blinded trial of the colonoscopic miss-rate of large colorectal polyps. *Gastrointest Endosc*. 1991;37:125–127.
43. Rex DK, Cutler CS, Lemmel GT, et al. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. *Gastroenterology*. 1997;112:24–28.
44. Pickhardt PJ, Nugent PA, Mysliwiec PA, Choi JR, Schindler WR. Location of adenomas missed at optical colonoscopy. *Ann Intern Med*. 2004;141:352–359.
45. Van Gelder RE, Nio CY, Florie J, et al. Computed tomographic colonography compared with colonoscopy in patients at increased risk for colorectal cancer. *Gastroenterology*. 2004;127:41–48.
46. Bressler B, Paszat LE, Vinden C, et al. Colonoscopic miss rate for right-sided colon cancer: a population-based analysis. *Gastroenterology*. 2004;127:452–456.
47. Rex DK, Rahmani EY, Haseman JH, et al. Relative sensitivity of colonoscopy and barium enema for detection of colorectal cancer in clinical practice. *Gastroenterology*. 1997;112:17–23.
48. van Dam J, Bond JH, Sivak MV Jr. Fecal occult blood screening for colorectal cancer. *Arch Intern Med*. 1995;155:2389–2402.
49. Riff ER, Dehaan K, Garewal GS. The role of sigmoidoscopy for asymptomatic patients. Results of three annual screening sigmoidoscopies, polypectomy, and subsequent surveillance colonoscopy in a primary-care setting. *Cleve Clin J Med*. 1990;57:131–136.
50. Kirschner CG, Davis SJ, Evans D, et al. *Current Procedural Terminology: CPT*. Chicago: American Medical Association; 1999.
51. Seare S, Speirs L, Bernard SP, et al. *DRG Guide*. Salt Lake City: Medicode; 1997.
52. Garbay JR, Suc B, Rotman N, et al. Multicentre study of surgical complications of colonoscopy. *Br J Surg*. 1996;83:42–44.
53. Sonnenberg A, Delco F, Inadomi JM. Cost-effectiveness of colonoscopy in screening for colorectal cancer. *Ann Intern Med*. 2000;133:573–584.

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Cost-Effectiveness of Colorectal Cancer Screening With Computed Tomography Colonography: The Impact of Not Reporting Diminutive Lesions

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Prior cost-effectiveness models analyzing computed tomography colonography (CTC) screening have assumed that patients with lesions measuring ≤ 5 mm will be referred to optical colonoscopy for polypectomy. However, consensus guidelines for CTC recommend reporting only those polyps that are ≥ 6 mm in size. The purpose of the current study was to assess the potential harms, benefits, and cost-effectiveness of CTC screening without the reporting of diminutive lesions compared with other screening strategies.