Small and Diminutive Polyps Detected at Screening CT Colonography: A Decision Analysis for Referral to Colonoscopy

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OBJECTIVE. The objective of this study was to assess the clinical and economic impact of colonoscopic referral for small and diminutive polyps detected at CT colonography (CTC) screening.

MATERIALS AND METHODS. A decision analysis model was constructed incorporating the expected polyp distribution, advanced adenoma prevalence, colorectal cancer (CRC) risk, CTC performance, and costs related to CRC screening and treatment. The model conservatively assumed that CRC risk was independent of advanced adenoma size. The number of diminutive (≤ 5 mm), small (6–9 mm), and large (≥ 10 mm) CTC-detected polyps needed to be removed to detect one advanced adenoma or prevent one CRC over a 10-year time horizon was calculated. The cost-effectiveness of polypectomy was also assessed.

RESULTS. The estimated 10-year CRC risk for unresected diminutive, small, and large polyps was 0.08%, 0.7%, and 15.7%, respectively. The number of diminutive, small, and large polyps needed to be removed to avoid leaving behind one advanced adenoma was 562, 71, and 2.5, respectively; similarly, 2,352, 297, and 10.7 polypectomies would be needed, respectively, to prevent one CRC over 10 years. The incremental cost-effectiveness ratio of removing all diminutive and small CTC-detected polyps was $464,407 and $59,015 per life-year gained, respectively. Polypectomy for large CTC-detected polyps yielded a cost-saving of $151 per person screened.

CONCLUSION. For diminutive polyps detected at CTC screening, the very low likelihood of advanced neoplasia and the high costs associated with polypectomy argue against colonoscopic referral, whereas removal of large CTC-detected polyps is highly effective. The yield of colonoscopic referral for small polyps is relatively low, suggesting that CTC surveillance may be a reasonable management option.

Keywords: colorectal cancer, colorectal polyps, CT colonography, CT colonography screening, health care costs

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Colorectal cancer (CRC) is a major cause of morbidity and mortality in Western societies, and its therapeutic costs are a substantial economic burden [1]. According to the widely accepted adenoma–carcinoma sequence, most cancers develop from a small subset of benign adenomatous polyps over a long period of time [2]. Thus, CRC screening of average-risk adults based on polyp detection and cancer prevention has been universally accepted [3]. Among the available screening options, 3D CT colonography (CTC) is an emerging test that has shown good performance for the detection of advanced neoplasia [4–7] and offers the potential for selectively and noninvasively identifying those patients who would clearly benefit from therapeutic colonoscopy [8, 9]. Instituting a polyp size threshold for colonoscopic referral at screening CTC is somewhat analogous to using a 10-mm size threshold for colonoscopic referral at screening flexible sigmoidoscopy, as advocated by some investigators [10].

Some authors have proposed that large polyps (≥ 10 mm) detected at CTC should trigger an immediate polypectomy, small polyps (6–9 mm) could either be referred for colonoscopy or undergo CTC surveillance, and potential diminutive polyps (≤ 5 mm) should be ignored [11–13]. However, there is still some controversy surrounding the validity of this approach [7, 14]. Although the full natural history of colorectal polyps is still incompletely understood, both the prevalence of neoplastic lesions in the general population and the distribution of advanced neoplasia according to polyp size have been established. The aim of this decision analysis was to assess the relative yield of referring

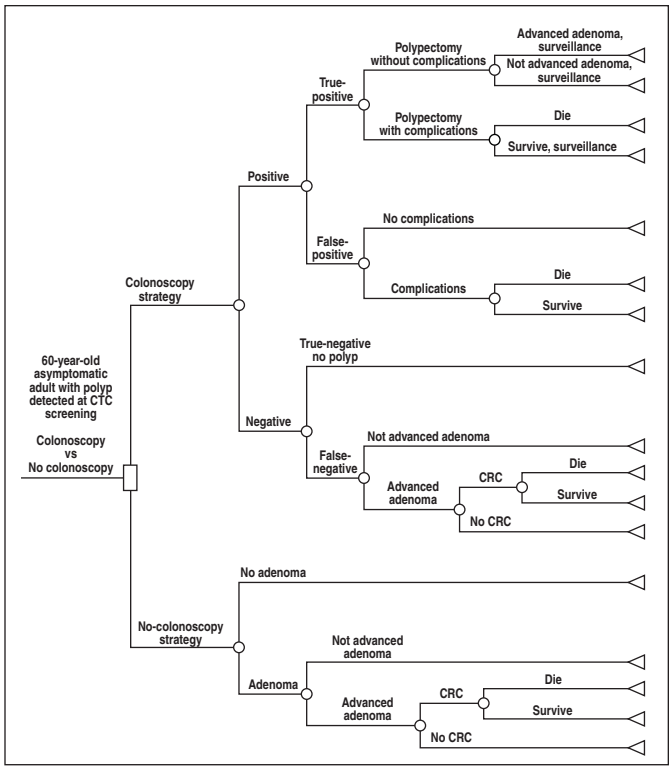


Fig. 1—Decision tree that models decision of whether to remove polyp detected in 60-year-old asymptomatic adult undergoing CT colonography (CTC) screening. Two strategies for CTC-detected polyps, colonoscopic polypectomy versus no colonoscopy, are modeled over 10-year period. No-colonoscopy strategy is equivalent to nonreporting of polyps at CTC. This decision tree applies to all three polyp size categories. Triangle at end of course signifies that patient will remain in that state until end of study period. CRC = colorectal cancer.

patients to colonoscopic polypectomy for diminutive, small, and large CTC-detected polyps. Specifically, we sought to quantify the relative benefits, harms, costs, and resource utilization of polypectomy referral for lesions detected at CTC screening.

Materials and Methods

A decision analysis model was constructed to represent the clinical and economic consequences of performing colonoscopic polypectomy after the detection of a polyp at CTC screening (Fig. 1). The polyp size categories were defined as diminutive, small, and large for polyps ≤ 5, 6–9, and ≥ 10 mm, respectively. A hypothetical U.S. screening population of 100,000 60-year-old subjects was modeled.

CRC Risk Associated with Each Polyp Size Category

To define the risk associated with each polyp size category, we related the polyp prevalence at a certain age with the risk of developing cancer in a 10-year time interval, as previously suggested [15]. Unlike the previous models, however, we assumed that all preventable CRC arose from advanced adenomas, which are defined by a size of ≥ 10 mm or by histologic features—regardless of size—of a prominent villous component or high-grade dysplasia [16].

The assumptions used for polyp prevalence in an asymptomatic screening population are shown in Table 1. The prevalence data for polyps according to both size and histology were primarily based on findings from a cohort of asymptomatic adults who underwent both CTC and same-day colonoscopy as part of a published screening trial [4, 17, 18]. Because that trial used strict exclusion criteria and used an enhanced reference standard of colonoscopy with segmental unblinding of CTC results, it more accurately reflects the true screening prevalence of disease compared with symptomatic or high-risk cohorts. The average age of this screening population was 58 years, corresponding to the assumption of patient age of 60 years in our model. The baseline assumptions for polyp prevalence were similar to the findings from recent CTC and colonoscopy screening experiences [19]. For example, the input value of 4.5% for the prevalence of advanced neoplasia in our model was slightly higher than the 3.3% prevalence rate reported in one screening cohort of more than 6,000 adults [19]. Furthermore, the input value of 0.5% for the prevalence of small advanced adenomas was similar to the 0.43% value from a large colonoscopy screening cohort of more than 13,000 adults (Moravec M et al., presented at Digestive Disease Week 2007).

Figure 2 shows the expected distribution of adenomatous and nonadenomatous polyps in a simulated screening population of 100,000 asymptomatic adults. Subjects with a polyp were categorized and modeled according to their lesion of greatest clinical significance (i.e., secondary polyps of less clinical significance were not considered in the model). On the basis of the National Polyp Study [20], we also assumed that 76% of CRC is preventable by detection and removal of advanced neoplasms, with a 24% residual risk due to de novo, fast-growing, or missed lesions or to an alternative pathway distinct from the adenoma–carcinoma sequence [21]. A baseline 10-year CRC risk of 1.4% for an unscreened 60-year-old adult was derived from Surveillance, Epidemiology, and End Results (SEER) Program data [22].

The relative frequency of advanced adenomas according to polyp size ultimately determined the 10-year CRC risk for polyps in each size category. Because of the lack of reliable data about the natural history of subcentimeter polyps, we conservatively assumed that the rate of progression to cancer of an advanced adenoma < 10 mm was the same as that for lesions ≥ 10 mm. Although this assumption likely overemphasizes the relative importance of subcentimeter advanced adenomas somewhat, caution is warranted to avoid

TABLE 1: Polyp Prevalence Assumptions

Polyp Category	Prevalence by Polyp Size (%)			Total %
	Diminutive	Small	Large	
Advanced adenomas	0.09	0.5	3.9	4.5
Nonadvanced adenomas	14.4	9.8	—	24.2
Nonadenomaotus polyps	12.2	6.4	2.0	20.6
No polyps	—	—	—	50.7
Total	26.7	16.7	5.9	100

Note—Dash (—) indicates 0%. Based on references 4, 17, and 18.

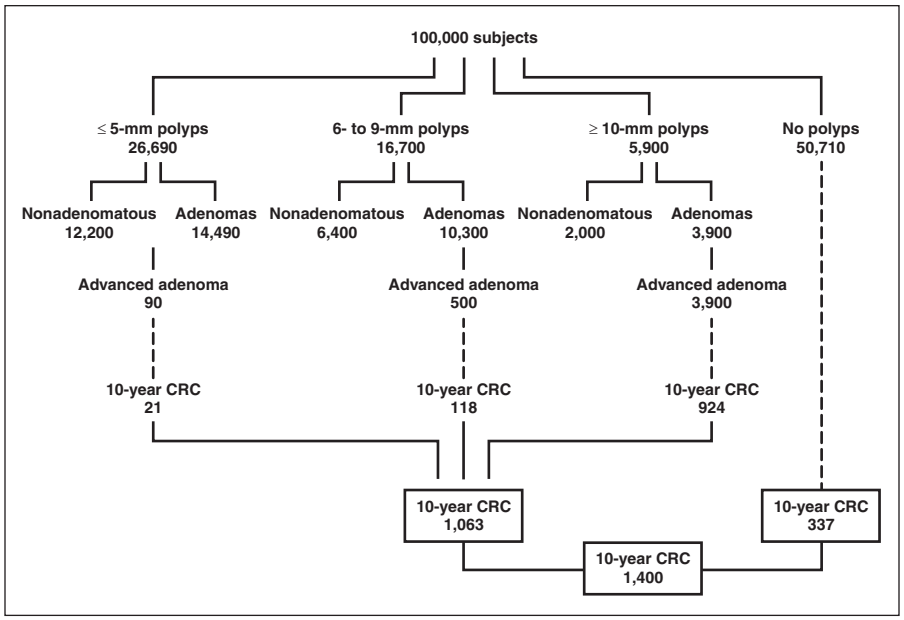


Fig. 2—Schematic representation of simulated population without CT colonography screening intervention. Expected number of advanced adenomas and colorectal cancer (CRC) cases were derived using assumptions described in text. Note that 24% of CRC is considered to be unpreventable by polyp screening based on findings from National Polyp Study [20]. Given relative paucity of firm natural history data for colorectal polyps, 10-year CRC risk for subcentimeter advanced lesions was conservatively assumed to be the same as that for large advanced lesions, which likely overestimates importance of small polyps.

undue harm until more firm longitudinal data are available. Furthermore, no distinction in CRC risk for an advanced adenoma was made with regard to the presence of high-grade dysplasia versus villous histology, which also may overemphasize the importance of small polyps. Additional baseline assumptions are listed in Table 2.

Accuracy and Costs of the Diagnostic Procedures

The performance characteristics for CTC were predicated on the use of current techniques, including 3D polyp detection and oral contrast tagging (Table 2). The performance level seen in the Department of Defense (DoD) 3D CTC multicenter trial [4] has been further validated by more recent 3D trials [23] and is therefore more representative of expected CTC performance going forward than older trials that used 2D polyp detection without tagging. Because CTC performance data for diminutive lesions were not reported in that trial, the sensitivity for those lesions was based on the meta-analysis by Mulhall et al. [5]. Furthermore, because data regarding CTC specificity for diminutive lesions are insufficient, the value for small polyps (6–9 mm) was used for all subcentimeter lesions. The simulated efficacy for reducing CRC will be somewhat less than the optimal modeled value of 76% because CTC sensitivity is less than 100% for polyp detection. In the baseline analysis, we assumed 100% compliance for colonoscopy referral after positive CTC. However, we also simulated lesser degrees of compliance in the sensitivity analysis.

The baseline costs used in this analysis are provided in Table 2. For this simulation, we assumed that one additional surveillance colonoscopy examination was performed over the 10-year period after the removal of a nonadvanced adenoma (i.e., subcentimeter tubular adenoma), which required another polypectomy in one third of the cases [15]. Two surveillance colonoscopies were simulated after removal of an advanced lesion, assuming 33% and 16% rates of polypectomy at the first and second follow-up examinations, respectively. Costs associated with colonoscopic complications of bleeding and perforation were also accounted for in the model.

The indirect costs of CRC screening are not well established, but to offer at least some societal perspective, certain additional costs were derived by a recent study [24]. Based on a median income rate of $17.76/h, costs related to lost work time from colonoscopy were estimated at $213.12, consisting of 8 hours for the patient and 4 hours for an escort. However, to allow a more direct comparison with previous cost-effectiveness analyses, which did not include indirect costs, we considered these indirect costs only in the sensitivity analysis.

Clinical Effectiveness and Cost-Effectiveness Analysis

The primary outcomes measure for assessing the yield of colonoscopic referral for CTC-detected polyps was defined as the number of polyps needed to be removed to achieve a particular goal. Two major end points evaluated in this study were the number polyps needed to be removed to detect one advanced adenoma and the number of polyps needed to be removed to prevent one CRC over a 10-year interval.

The incremental cost-effectiveness of removing polyps of a given size category (diminutive, small, or large) detected at CTC was compared with a natural history arm, which effectively corresponds to nonreporting of polyps at the various size thresholds. The cost-effectiveness was derived from a decision tree according to chance events that are determined by the assigned probabilities. The product of the probabilities along an outcome pathway determines the likelihood of each outcome. Furthermore, each outcome is associated with both direct and indirect medical costs for either diagnostic and surveillance endoscopy or CRC treatment, according to the stage of diagnosis, generated along the preceding pathway. The overall cost of an arm in the decision tree can be calculated by weighting the cost of each outcome by its probability and summing the results. The probability of CRC-related death for each arm can be obtained by summing probabilities for all terminal nodes in which the outcome is death (Fig. 1).

A key cost-effectiveness measure was the difference in cost between the post-CTC colonoscopy and no-colonoscopy arms divided by the difference in life expectancy, which represents the cost per life-year gained. Both future costs and future life-years saved were discounted using an annual rate of 3%.

Sensitivity Analysis

Sensitivity analysis was performed using two different methods. First, several inputs (CTC sensitivity, specificity, procedure costs, life-years lost from CRC, and prevalence of advanced neoplasia) were varied simultaneously and randomly for 10,000 interactions in a Monte Carlo simulation (Lumenaut version 3.4.9, Lumenaut Ltd). This provides estimates on the variability in cost-effectiveness, expressed as 10th–90th percentiles, that arise when variables in the model are allowed to take on distributions. Second, a systematic sensitivity analysis based on the prevalence of advanced adenomas and CTC performance characteristics was performed. The effect of post-CTC colonoscopy compliance, inclusion of costs related to lost work time, inclusion of a death rate at colonoscopy (set at one in 50,000), and different patient ages at CTC evaluation were also evaluated.

The prevalence of advanced adenomas in patients 50 and 70 years old was based on the same asymptomatic screening cohort [4]. Specifically, the prevalence of advanced adenomas at age 50

TABLE 2: Model Characteristics and Parameters Used in the Cost-Effectiveness Analysis

Characteristic or Parameter Used in Cost-Effectiveness Analysis	
Model type	Decision tree analysis
Hypothetical screening cohort	100,000 U.S. subjects
Screening age (y)	
Mean (range)	60 (50–70)
Time horizon (y)	10 and 20
Intervention	CTC screening
Variable	**Reference Value (range) [reference no.]**
CRC risk (%)	
10 y	1.4 [22]
20 y	3.4 [22]
Life expectancy (y)	22 (8.6–29.8) [48]
Preventable CRC (%)	76 [20]
Mortality from unpreventable CRC (%)	50 (30–70) [49]
CTC sensitivity (%)	
Polyps ≤ 5 mm	48 (20–100) [5]
Polyps ≥ 6 mm	89 (50–100) [4]
Polyps ≥ 10 mm	94 (80–100) [4]
CTC specificity (%)	
Polyps ≤ 5 mm	80 (70–100) [4]
Polyps ≥ 6 mm	80 (70–100) [4]
Polyps ≥ 10 mm	96 [4]
Post-CTC colonoscopy compliance (%)	100 (80–100)
CTC ($)	478 [50]
Colonoscopy ($)	696 (400–1,000) [48]
Colonoscopy with polypectomy ($)	1,139 (680–1,600) [50]
Colonoscopy perforation rate (%)	0.06 (0.3–0.8) [51]
Polypectomy bleeding (%)	0.48 (2.9–6.7) [51]
Polypectomy perforation (%)	0.11 (0.6–1.5) [51]
Colonoscopy-related death (%)	0.002 (0–0.03) [52]
Bleeding ($)	4,360 (2,500–6,000) [48]
Perforation ($)	13,000 (7,000–18,000) [48]
CRC treatment ($)	45,228 (27,000–63,000) [50]
Discounting (%)	3 (0–5)

Note—CRC = colorectal cancer, CTC = CT colonography.

was set at 3.4%, with a size-dependent prevalence of 0.07%, 0.37%, and 2.9% for diminutive, small, and large polyps, respectively. For the 70-year-old cohort, prevalence was set at 6.0%, with a size-dependent prevalence of 0.12%, 0.67%, and 5.2%, for diminutive, small, and large polyps, respectively. Life expectancy for these two cohorts was also adjusted accordingly.

Results

Simulation Without Screening Intervention

In this hypothetical asymptomatic population of 100,000 60-year-old subjects, largely based on prior screening results, nearly half (49.3%) will harbor a polyp. Given the underlying assumptions that the overall 10-year CRC risk of this unscreened population is 1.4%, that 76% of all CRC relates to advanced neoplasms that would be potentially preventable by screening for polyps, and that the relative risk of developing CRC is independent of the size of the advanced neoplasm, Figure 2 depicts the estimated number of CRC arising from each patient subgroup. The estimated risk that an individual polyp will progress to CRC over 10 years was found to be 0.079% (21/26,690) for diminutive lesions, 0.71% (118/16,700) for small polyps, and 15.7% (924/5,900) for large polyps. Note that 337 cases of CRC (24%) are assumed to be unpreventable by screening for polyps by currently available means. If CTC can be shown to increase detection of advanced neoplasia over colonoscopy alone, the true number of "unavoidable" CRC cases may be less in actual practice.

CTC Screening Simulation

The number of CTC-detected polyps needed to be removed to achieve the goals of advanced adenoma detection (and removal) and CRC prevention are summarized in Table 3. Specifically, the estimated number of CTC-detected diminutive, small, and large polyps that would need to be removed at colonoscopy to avoid leaving behind a single advanced adenoma was 562, 71, and 2.5, respectively. Despite the large differences in the utilization of colonoscopy for polypectomy, the overall detection rate of advanced adenomas with CTC screening was quite similar when using no polyp size threshold (92.7%), a 6-mm size threshold (91.8%), or a 10-mm size threshold (82.2%) for referral. The number of CTC-detected diminutive, small, and large polyps that would need to be removed at colonoscopy to prevent one CRC over 10 years was 2,352, 297, and 10.7, respectively.

When projecting the base case CTC sensitivity on the simulated population, a 10-year CRC risk reduction of 69.42% was predicted if no polyp size threshold for colonoscopy referral is assumed. This corresponds to 91.7% of the potentially preventable CRC according to the model. The residual absolute 10-year CRC risk was 0.428%, compared with the baseline absolute risk of 1.4% for the unscreened population. However, 0.34% of this residual absolute risk is due to CRC that was assumed to be unpreventable by screening for polyps. If a 6- or 10-mm polyp size threshold is used for polypectomy referral, the 10-year CRC risk reduction decreases only slightly to 69.36% and 62.1%, respectively, and the residual absolute risk rises only slightly to 0.429% and 0.530%, respectively.

The number of patients undergoing endoscopic procedures over a 10-year interval in this hypothetical screening population of 100,000 when using no size threshold, a 6-mm threshold, and a 10-mm threshold for colonoscopy referral differed substantially at 43,400, 35,900, and 9,300, respectively. In addition, the estimated numbers of colonoscopic complications when using no size threshold, a 6-mm threshold, and a 10-mm

TABLE 3: Number of CT Colonography (CTC)-Detected Polyps Needed to Be Removed at Colonoscopy and the Associated Cost Implications

Polyp Size Category	No. of Polypectomies		Estimated 10-Year CRC Risk of Unresected Polyp (%)	Incremental Cost-Effectiveness Ratio (cost [$] per life-year gained)
	Per Advanced Adenoma Removed	Per CRC Prevented over 10 Years		
Diminutive (≤ 5 mm)	562	2,352	0.08	464,407
Small (6–9 mm)	71	297	0.7	59,015
Large (≥ 10 mm)	2.5	10.7	15.7	–151 per person (cost savings)

threshold for colonoscopy referral was estimated to be 202, 129, and 34, respectively.

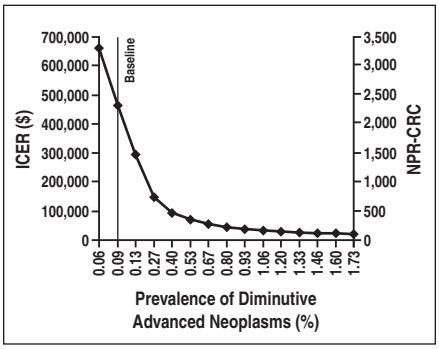
Cost-Effectiveness Analysis

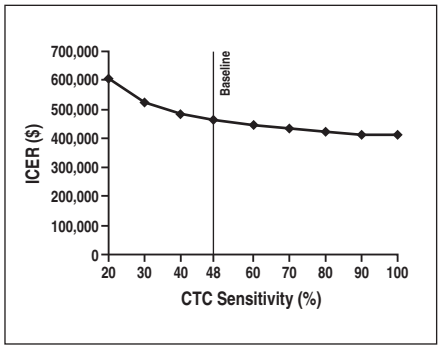
The incremental cost-effectiveness ratio (ICER) of removing CTC-detected polyps for a given size category versus not referring them to colonoscopy was based on the underlying assumptions leading to the values reported earlier, the costs associated with the post-CTC colonoscopy, and the life-years gained by the prevention of CRC. ICER results from the base case analysis are shown in Table 3.

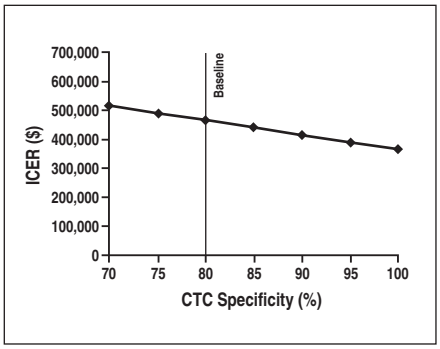
Diminutive polyps—The ICER of sending all patients with CTC-detected diminutive polyps to colonoscopic polypectomy was $464,407 per life-year gained from CRC prevention. The high cost was due to the large number of endoscopic procedures needed to detect diminutive advanced neoplasms, which represent only 0.3% of all diminutive polyps, and the relatively small gain in life expectancy (110 undiscounted life-years for the hypothetical population of 100,000 subjects). At systematic sensitivity analysis (Figs. 3A–3C), the prevalence of advanced adenomas among the diminutive polyps appeared to be the major variable, whereas CTC accuracy had relatively little impact.

Regarding CTC sensitivity, even assuming a 100% value, the ICER of removing diminutive polyps (as compared with ignoring them) was $415,887, which corresponds to 1,810 polypectomies for each prevented CRC (Fig. 3B). Similarly, assuming an increase in CTC specificity to 100%, 1,310 polypectomies would be needed for each CRC, with an ICER of $371,525 (Fig. 3C). At Monte Carlo analysis, the 10th and 90th percentiles were $370,092 and $574,502, respectively (Fig. 3D).

A reduction of post-CTC colonoscopy compliance from 100% to 80% would further reduce the undiscounted number of life-years gained with the post-CTC colonoscopy strategy to 89 (from 110) per 100,000 subjects without altering the incremental cost-effectiveness because compliance influences







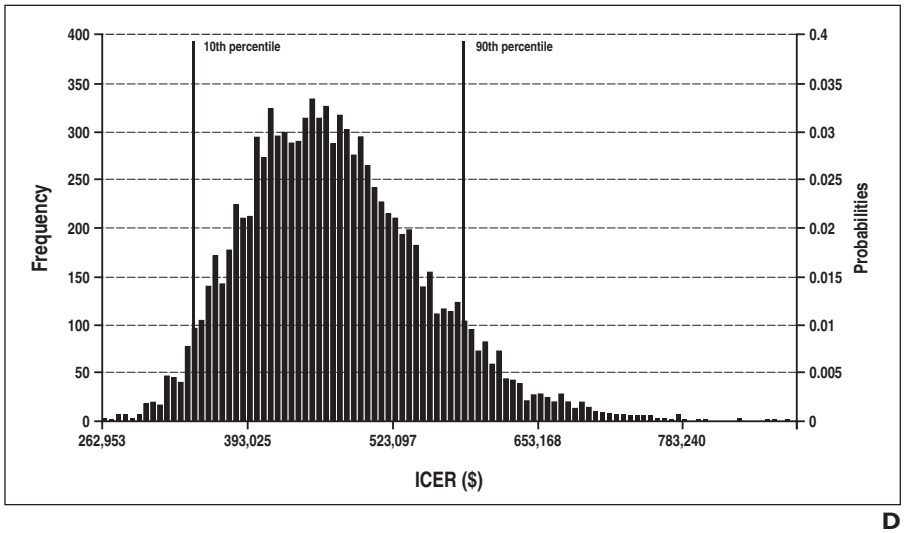


Fig. 3—Sensitivity analysis and Monte Carlo simulation for diminutive polyps (≤ 5 mm).
A, Graph shows incremental cost-effectiveness ratio (ICER) and number of CT colonography (CTC)-detected polyps needed to be removed to prevent one colorectal cancer over 10 years (NPR-CRC), according to prevalence of diminutive advanced neoplasms.
B and **C,** Graphs show ICER relative to variations in CTC sensitivity (**B**) and specificity (**C**). Baseline refers to case base assumption.
D, Graph shows distribution of frequencies of ICER when simulating 10,000 simultaneous variations of baseline values at Monte Carlo analysis. Vertical lines refer to 10th and 90th percentiles. See text for additional discussion.

the overall number of cancers prevented and the total costs in a linear fashion. Inclusion of costs related to lost work for colonoscopy results in an ICER of $594,087 compared with ignoring diminutive lesions. A death rate of one in 50,000 patients undergoing colonoscopy would result in 0.25 deaths in the colonoscopy arm of the study population, increasing the incremental cost-effectiveness of removing diminutive polyps to $534,740. Post-CTC colonoscopy would clearly become a harmful procedure without any survival benefit if the death rate approached the number of polypectomies needed to prevent one CRC. Regardless, the overall complication rate for therapeutic colonoscopy greatly exceeds the number of diminutive polypectomies needed to achieve some benefit.

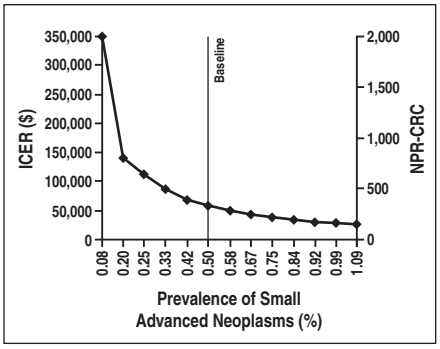
For screening 50-year-old subjects, the ICER for removing diminutive lesions was slightly decreased at $360,114 and was slightly increased for screening 70-year-old subjects at $585,370, compared with the ICER for screening 60-year-old subjects. These changes in the ICER are related to the counter effects of changing advanced adenoma prevalence and life expectancy.

Small polyps—The ICER of sending all patients with small polyps (6–9 mm) detected at CTC screening to colonoscopic polypectomy was $59,015 per life-year gained from CRC prevention, corresponding to a gain of 1,155 life-years in this hypothetical cohort of 100,000 adults. The relatively high cost was largely due to the fact that only 3% of small polyps harbor advanced histology. A systematic sensitivity analysis (Figs. 4A–4C) showed that the prevalence of advanced neoplasia among small polyps had a major influence on cost-effectiveness, similar to the case for diminutive lesions.

With regard to CTC accuracy, increasing sensitivity to 100% only reduced the ICER to $57,399 (Fig. 4B), which corresponds to 281 polypectomies per CRC prevented. Increasing CTC specificity to 100% resulted in an ICER of $44,121 (Fig. 4C), corresponding to 146 polypectomies per CRC prevented. As was the case for diminutive lesions, even relatively broad variations in CTC performance for small polyps did not meaningfully alter the results of our analysis. At Monte Carlo analysis, the 10th and 90th percentiles were $57,120 and $84,641, respectively (Fig. 4D).

A reduction of post-CTC colonoscopy compliance from 100% to 80% would reduce the undiscounted number of life-years gained to 924 (from 1,155) per 100,000 subjects without altering the marginal cost-effectiveness between the two strategies. The inclusion of lost work costs from colonoscopy would increase the ICER between the two strategies from $51,943 to $71,419. A colonoscopy death rate of one in 50,000 would result in 0.29 deaths in the colonoscopy arm, increasing the ICER for removing small polyps to $60,043. The incremental cost-effectiveness of removing all small CTC-detected polyps as compared with no polypectomy is slightly reduced at age 50, being $43,105, and is increased at age 70, being $74,781.

Large polyps—Because of the relatively high CTC accuracy for large polyps (≥ 10 mm) and the greater probability for advanced neoplasia, referral of large polyps to colonoscopic polypectomy was shown to be a cost-saving procedure compared with a policy of not removing them, yielding a savings of $151 per person screened and 9,554 life-years gained from CRC prevention in the study population.



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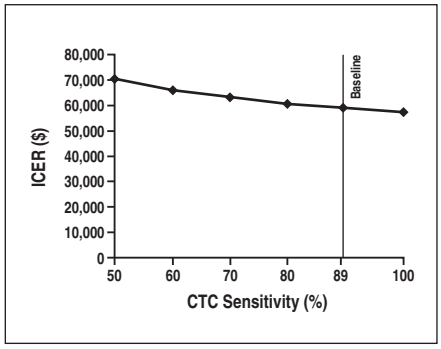

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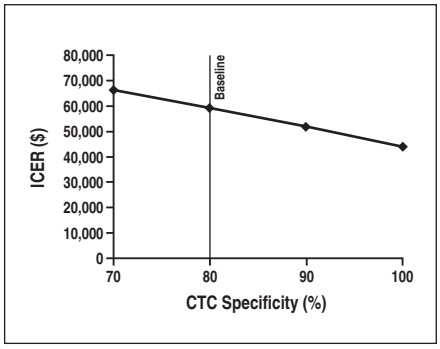

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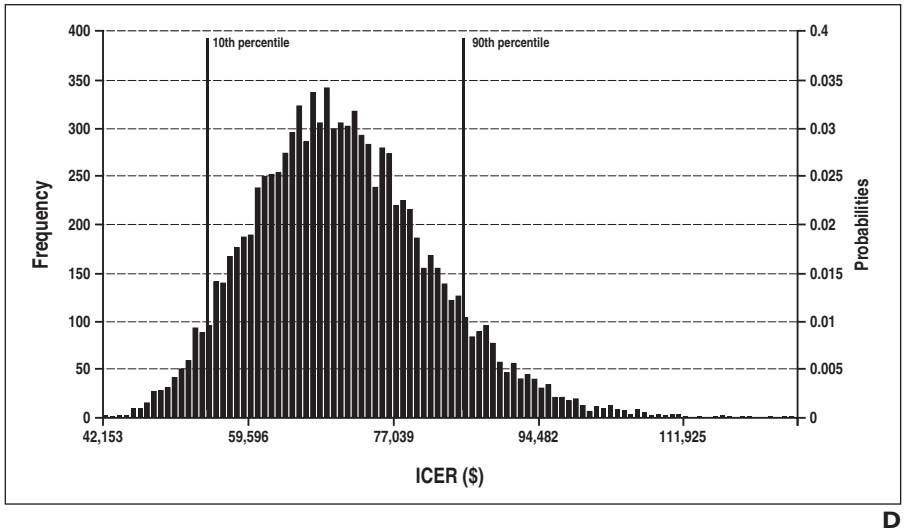

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Fig. 4—Sensitivity analysis and Monte Carlo simulation for small polyps (6–9 mm).
A, Graph shows incremental cost-effectiveness ratio (ICER) and number of CT colonography (CTC)-detected polyps needed to be removed to prevent one colorectal cancer (CRC) over 10 years (NPR-CRC), according to prevalence of small advanced neoplasms.
B and **C,** Graphs show ICER relative to variations in sensitivity (**B**) and specificity (**C**). Baseline refers to case base assumption.
D, Graph shows distribution of frequencies of ICER when simulating 10,000 simultaneous variations of baseline values at Monte Carlo analysis. Vertical lines refer to 10th and 90th percentiles. See text for additional discussion.

Discussion

Our findings suggest that the very low likelihood of advanced neoplasia and the relatively high costs associated with polypectomy argue against colonoscopic referral for diminutive polyps detected at CTC screening. In contrast, our findings also underscore the clinical effectiveness and cost-effectiveness of polypectomy for large CTC-detected polyps. Not surprisingly, the results for small polyps (6–9 mm) are intermediate between those of diminutive and large lesions. Therefore, the decision of whether to perform colonoscopy to remove small polyps detected at CTC screening (vs CTC surveillance) may ultimately become an individualized choice that incorporates a variety of patient-related factors, perhaps both clinical and nonclinical in nature.

The actual risk of developing CRC from small and diminutive colorectal polyps has not been established, but this issue has particular relevance to patient management at CTC screening. A recent consensus proposal from the Working Group on Virtual Colonoscopy, termed the "CT Colonography Reporting and Data System (C-RADS)," suggested that small polyps (6–9 mm) could either be referred for polypectomy at colonoscopy or undergo CTC surveillance and that potential diminutive polyps (≤ 5 mm) should be ignored [12]. In contrast, polypectomy is generally indicated for all large polyps (≥ 10 mm) identified at CTC.

Although C-RADS has been generally well received, with early adoption seen in the radiology community [13], this approach to subcentimeter lesions remains more controversial in the gastroenterology community [7, 14]. The debate primarily centers around the potential risks of a patient developing or even harboring a malignancy from an unresected lesion and the potential ethical and medicolegal concerns over the practice of not reporting possible diminutive lesions. A prior study by Glick et al. [25] showed the relative cost-effectiveness of the double-contrast barium enema for CRC screening, particularly when a 10-mm polyp size threshold was used.

When addressing the small-polyp dilemma, most studies have focused on the prevalence of unfavorable histology (i.e., high-grade dysplasia or villous component) [26–31], whereas relatively few longitudinal studies have actually followed up unresected colorectal lesions [32–34]. However, the prevalence of advanced neoplasia, which represents the accepted target for CRC screening and prevention [35], is unfortunately only an indirect measure of actual CRC risk because the relative frequency and timing of progression to cancer are unknown. Furthermore, one must realize that potential polyps detected at CTC do not confer a uniform cancer risk for the patient. In particular, most suspected subcentimeter colorectal lesions are nonadenomatous polyps, nonadvanced adenomas, or false lesions or cannot be found at subsequent colonoscopy. Therefore, it is important to consider whether the potential benefits of removing subcentimeter lesions detected at CTC screening outweigh the costs and risks associated with therapeutic colonoscopy. This is especially true given the limited endoscopic resources that are available.

Our study shows that the expected yield of colonoscopic referral for polyps detected at CTC screening is strongly related to polyp size, even though we made a conservative assumption that small advanced adenomas had the same CRC risk as large advanced adenomas, which very likely overemphasizes the importance of small lesions. Our model predicted that the number of diminutive, small, and large CTC-detected polyps that would have to be removed at colonoscopy to achieve similar goals in terms of advanced adenoma detection and CRC prevention were each separated by roughly an order of magnitude. For large polyps, the yield for polypectomy referral was high, needing only 2.5 lesions removed for each advanced adenoma and 10.7 lesions removed for each CRC prevented. In comparison, more than 500 diminutive lesions would need to be referred to detect one advanced lesion and more than 2,300 diminutive polypectomies would be needed to prevent one case of CRC.

Despite only minimal gains in projected CRC prevention, the large number of polypectomies for diminutive lesions corresponded to much higher procedural costs and higher complication rates due to the increased utilization of colonoscopy. In fact, the accepted perforation rate for therapeutic colonoscopy clearly exceeds the projected number of procedures needed to prevent one CRC over a 10-year time horizon by removing diminutive polyps and even approaches the rate for small 6- to 9-mm polyps.

Not surprisingly, the yield of colonoscopic referral for small (6–9 mm) CTC-detected polyps was intermediate between large and diminutive lesions, with 71 polypectomies needed for each advanced adenoma and 297 polypectomies for each CRC prevented. Although the clinical effectiveness of colonoscopy referral for small polyps is debatable, this approach was found to be rather expensive, with an ICER of $59,015 per life-year gained—more than double the upper limit of most CRC screening tests [36]. However, such a value may still be acceptable when compared with other more expensive cancer screening interventions, such as for breast or cervical cancer, which cost on average more than $100,000 per life-year gained [37]. In comparison with the ICER for the practice of removing small polyps, the ICER for the practice of removing diminutive polyps was nearly an order of magnitude higher at $464,407 per life-year gained, whereas polypectomy for large polyps was actually a cost-saving measure because of the high rate of expected CRC prevention.

The calculation of the number of polypectomies needed to achieve a certain goal used in this analysis provides a useful way to assess the therapeutic yield for the hybrid screening approach of CTC polyp detection and colonoscopic polypectomy. Previous studies have looked at analogous measures, such as the "number needed to endoscope" to detect large polyps or advanced neoplasia by screening colonoscopy [38, 39]. Lieberman et al. [38] reported that the number of subjects needed to endoscope for detecting one patient with a large polyp in an asymptomatic screening population 50–59 years old was 28 for women and 18 for men. The number needed to endoscope decreased to 16 for women and 11 for men in the setting of a positive fecal occult blood test result and positive family history for CRC. Similarly, Regula et al. [39] found the number needed to endoscope in a 50- to 54-year-old screening population to detect one patient with advanced neoplasia was 28 for women and 17 for men. Imperiale et al. [40] regarded a value for the number needed to endoscope for detecting advanced neoplasia of 24 or lower as a satisfactory threshold for which to recommend colonoscopy after sigmoidoscopy. The value of 71 polypectomies for small CTC-detected lesions for each advanced adenoma in our study is well above these values for the number needed to endoscope, suggesting that exclusion of large polyps at CTC screening places patients in a very low risk category. However, the value of 2.5 polypectomies for large CTC-detected polyps is well below the reported values for number needed to endoscope, representing a high-yield referral.

At sensitivity analysis, we found that the size-specific prevalence of advanced neoplasia was

the key variable in our study. Our baseline assumptions for the frequency of advanced histology in small and diminutive adenomas were 4.9% (500/10,300) and 0.6% (90/14,400), respectively, based primarily on findings from an asymptomatic screening cohort [4, 17, 18] (Table 1). These assumptions are similar to our current experience and those reported by other investigators in a number of previous studies [26–28]. However, somewhat higher rates of advanced histology in subcentimeter adenomas have been reported by others [36, 37]. Possible explanations for the disparate rates of advanced histology include differences in patient populations [38, 39], variations in subjective pathologic evaluation [41], or both. In contrast to the prevalence of advanced neoplasia, CTC sensitivity and specificity had relatively little effect on outcome at sensitivity analysis. Even with large shifts in CTC performance, the ICER variations were rather small. However, if less optimistic CTC performance was assumed, the ICER for referring subcentimeter polyps to colonoscopy would have increased further, making this policy even less attractive.

There are a number of limitations in the present analysis. The constructed model represents an unavoidable simplification of the adenoma–carcinoma sequence and of CRC screening in general. However, similar models have been broadly used in the past to compare the cost-effectiveness of different workup strategies after a positive screening test [42]. A number of conservative assumptions regarding a polyp's natural history were applied because of the relative paucity of established longitudinal data. Perhaps most noteworthy was the assumption that advanced adenomas carry the same CRC risk regardless of size. This assumption likely overestimates the actual risk of small and diminutive lesions, given that large size is considered by some to be the most important criterion [38]. In addition, the presence of either a villous component or high-grade dysplasia in subcentimeter adenomas was considered to carry the same CRC risk, although some have suggested that the latter may be more important [35, 43]. This assumption may also overestimate the risk of small and diminutive advanced lesions because villous histology is typically the defining feature, with high-grade dysplasia only rarely seen [18]. The assumption that 26% of CRC would not be preventable by screening for polyps was based on findings from the National Polyp Study [20]. Because colonoscopy is an imperfect reference standard [44], there could be more cases of preventable CRC if the hybrid approach of CTC with colonoscopic polypectomy leads to higher overall detection rates.

This work was not intended to compare different CTC surveillance strategies and intervals but rather to assess the clinical and economic impact of referring patients with CTC-detected polyps of varying sizes to colonoscopy. Therefore, for the purposes of this study, the cost-effectiveness of colonoscopy referral was essentially being compared with a 10-year natural history arm with no screening intervention or, equivalently, nonreporting (ignoring) polyps below a given size threshold. The 10-year time horizon served as the defined time period over which CRC may develop from an unresected polyp and should not be misconstrued as the CTC follow-up interval. Although CTC screening and surveillance intervals are important considerations, a more complex model would be required to adequately address these issues, which we hope to address in the future.

Regarding the natural history of large polyps (≥ 10 mm), the CRC-progression rate assumed in our study—nearly 16% over 10 years (1.6%/year)—represents a twofold increase over that reported by Stryker et al. [45]. However, we speculate that in that retrospective uncontrolled study only those patients in whom the progression rate of large polyps was initially slow enough to allow a sequential follow-up with more than one barium enema would have been eventually included, resulting in a population bias. Moreover, the 24% CRC-progression rate of large polyps at 20 years (1.2%/year) in that study was higher than that computed in the first 10 years and is quite close to our assumption. Of note, the 10-year CRC risk used in our model is much closer to the rate reported by Stryker and colleagues than the 5%-per-year assumption used in several previous models [46, 47], suggesting greater biologic plausibility of this analysis.

In conclusion, our analysis shows that colonoscopic referral for small (6–9 mm) and diminutive (≤ 5 mm) polyps detected at CTC screening is an inefficient strategy in terms of advanced adenoma removal and CRC prevention. Specifically, polypectomy referral for possible CTC-detected diminutive lesions is an extremely inefficient policy, whereas detection and removal of large polyps is a highly effective strategy. Our results for handling small polyps detected at CTC screening suggest that CTC surveillance may be a reasonable alternative to immediate polypectomy, given the relatively high costs associated with polyp removal and low yield for CRC prevention. Further investigation of the natural history of small colorectal polyps may provide more robust input data and lead to greater insight into this critical management issue.

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