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CT Colonography versus Multitarget Stool DNA Test for Colorectal Cancer Screening: A Cost-Effectiveness Analysis

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See also the editorial by Galgano and Smith in this issue.

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Background: Colorectal cancer (CRC) is largely preventable or curable with effective screening.

Purpose: To compare both the clinical efficacy and cost effectiveness of CRC screening with CT colonography (CTC) with those of multitarget stool DNA (mt-sDNA) testing.

Materials and Methods: A state-transition Markov model was constructed using updated natural history evidence for colorectal polyps applied to a hypothetical 10000-person cohort representative of the 45-year-old U.S. population. Three screening strategies were modeled with these data: mt-sDNA testing every 3 years, the conventional CTC (CTC_{conv}) strategy of immediate polypectomy for all polyps measuring at least 6 mm every 5 years, and the surveillance CTC (CTC_{surv}) strategy of 3-year CTC follow-up for small polyps (6–9 mm) and polypectomy for large polyps (≥10 mm). Multifaceted model validation was performed to confirm robustness. A detailed sensitivity analysis was performed in addition to the base-case scenario.

Results: Without screening, the cumulative incidence of CRC was 7.5% (n = 752), which was reduced by 59% (n = 310) with mt-sDNA, 75% (n = 190) with CTC_{conv}, and 70% (n = 223) with CTC_{surv} screening. The estimated programmatic costs per person for no screening, mt-sDNA, CTC_{conv}, and CTC_{surv} were $4955, $6011, $4422, and $3913, respectively. The estimated cost per quality-adjusted life year (QALY) gained for mt-sDNA testing was $8878, whereas both CTC strategies resulted in cost savings. Accordingly, CTC strategies dominated over both mt-sDNA and no screening (ie, more clinically efficacious and more cost-effective [cost-saving]). However, the CTC_{conv} strategy was not as cost-effective as the CTC_{surv} strategy, as costs related to more optical colonoscopies did not offset the corresponding small gains in QALYs. The results were similar when CRC screening began at 50 and 65 years of age.

Conclusion: Both CTC screening strategies dominated over mt-sDNA screening and no screening, yielding cost savings and increased clinical efficacy. The CTC strategy consisting of 3-year surveillance for small colorectal polyps and colonoscopy referral for large polyps achieved the best overall balance of cost and clinical efficacy.

Supplemental material is available for this article.

Colorectal cancer (CRC) remains the second leading cause of cancer-related death both in the United States and globally (1). However, CRC is largely preventable with direct visualization screening tests that can help reliably detect benign advanced adenomas, and cancers are potentially curable if detected early (2). Optical colonoscopy (OC) remains the dominant CRC screening modality in the United States, but there are also less invasive options such as multitarget stool DNA (mt-sDNA) testing and CT colonography (CTC). In 2014, the U.S. Centers for Medicare and Medicaid Services included mt-sDNA screening as a covered service for Medicare beneficiaries. As of January 2025, CTC screening will also be included as a covered Medicare benefit. There is also a disturbing trend of increasing incidence of early-age-onset CRC (ie, diagnosed before the age of 50 years) (3,4), which has prompted the U.S. Preventive Services Task Force and various medical societies to lower the recommended screening age to 45 years.

Previous cost-effectiveness analysis (CEA) studies evaluating mt-sDNA testing have demonstrated that although it is generally cost-effective relative to no screening, it is overall less clinically effective and more costly than most other screening options (5–7). Previous CEA studies focusing on CTC screening have consistently shown that it is clearly more cost-effective than no screening, with some studies showing that it is more cost-effective than primary OC screening (8). In particular, the rational practice of ignoring diminutive polyps (ie, ≤5 mm) at CTC screening greatly improves its cost effectiveness (9). Some previous studies have also attempted to model variable handling of small polyps (ie, 6–9 mm) at CTC screening (10,11), but natural history data were somewhat lacking at the time. However, more recent data elucidating the natural history of small colorectal polyps can now better inform these models (12–14).

Given the recent expansion of Medicare coverage to include CTC screening, the general lowering of the initial CRC screening age to 45 years, and the more robust small polyp natural history data, a head-to-head comparison of CTC and mt-sDNA screening, two inherently different methods, is needed. mt-sDNA testing yields a binary result (positive or negative) without providing any other details for positive cases. Furthermore, mt-sDNA is primarily a cancer detection test, as the majority of benign advanced adenomas are not detected (15). In comparison, CTC detects more than 90% of all advanced adenomas and more than 95% of all cancers (16–18), providing both effective cancer prevention and cancer detection. In addition, a positive CTC test result can also include

Abbreviations

CEA = cost-effectiveness analysis, CRC = colorectal cancer, CTC = CT colonography, CTC_{conv} = conventional CTC, CTC_{surv} = surveillance CTC, ICER = incremental cost-effectiveness ratio, mt-sDNA = multitarget stool DNA, OC = optical colonoscopy, QALY = quality-adjusted life year

Summary

Compared with both multitarget stool DNA screening and no screening, CT colonography showed cost savings and improved clinical efficacy, especially when including surveillance for small polyps.

Key Results

- In a study of 10000 modeled 45-year-old adults, colorectal cancer incidence was reduced by 59% with colorectal screening with multitarget stool DNA (mt-sDNA) testing and by 70%–75% with CT colonography (CTC) strategies.
- Compared with no screening, screening with mt-sDNA testing was more cost-effective ($8878 per quality-adjusted life year [QALY]), but the CTC strategies were actually cost-saving.
- A conventional CT strategy of polypectomy for all polyps measuring at least 6 mm was not cost-effective relative to a surveillance strategy for small (6–9-mm) polyps; the increased costs of colonoscopy did not offset the small gain in QALYs.

specific information on the size, number, morphologic characteristics, and location of reported nondiminutive lesions.

The primary purpose of this study was to compare both the clinical efficacy and cost-effectiveness of CRC screening with CTC versus mt-sDNA testing.

Materials and Methods

Modeling Methodology and Structure

The cost-effectiveness of CRC screening was analyzed via a state-transition Markov model implemented in R software (version 4.3.2; R Foundation for Statistical Computing) (19). The model structure was largely based on that described by Areia et al (20), with other input assumptions detailed in Tables 1 and S1. Certain assumptions regarding the future behavior of small (6–9-mm) polyps, including their growth and progression to advanced adenomas and CRC, were adjusted to reflect recent real-world observational data from CTC surveillance (12–14). Our analysis measures both clinical effectiveness (ie, the quality and efficacy of health care interventions) and cost-effectiveness (ie, the financial expenditure required to achieve a specific health outcome).

For the base case, CRC screening began at the age of 45 years instead of 50 years to reflect the most recent American Cancer Society screening guidelines (5). Compared with previous Surveillance, Epidemiology, and End Results data from 1990 to 1994 (21), the CRC incidence used herein was increased by 1.34-fold due to recent increases among 40-year-old persons (6). The methodology for modeling was similar to that of the National Cancer Institute Cancer Intervention and Surveillance Modeling Network model (22). In Appendix S1, we provide additional details on the baseline natural history assumption (section I), model recalibration and validation (section II), and CTC small polyp surveillance data (section III).

Table 1: Key Study Population and Test Characteristics Used for Base-Case and Sensitivity Analyses

Category	Value	Distribution
Calibrated variable		
Prevalence of polyps <5 mm at age 45 years (%)	16	
Prevalence of polyps 6–9 mm at age 45 years (%)	9	
Prevalence of polyps >9 mm at age 45 years (%)	2.8	
Screening test characteristics used in the analysis*		
mt-sDNA test		
Sensitivity for cancer (%)	91 (83.8–94.0)	Beta
Sensitivity for large polyp (%)	42.4 (38.9–46.0)	Beta
Sensitivity for diminutive or small polyp (%)	17.2 (15.9–18.6)	Beta
Specificity (%)	89.6 (88.6–90.7)	Beta
Diagnostic and/or surveillance colonoscopy		
Sensitivity for cancer (%)	95	Not varied
Sensitivity for large polyp (%)	90	Not varied
Sensitivity for small polyp (%)	85	Not varied
Sensitivity for diminutive polyp (%)	75	Not varied
CTC test		
Sensitivity for cancer (%)	94 (88–97)	Beta
Sensitivity for large polyp (%)	85 (65–98)	Beta
Sensitivity for small polyp (%)	70 (49–83)	Beta
Sensitivity for diminutive polyp (%)	Not reported	
Complication rates		
Colonoscopy major hemorrhage rate (%)	0.08 (0.05–0.14)	
Colonoscopy perforation rate (%)	0.04 (0.02–0.05)	
Mortality rate given endoscopic perforation (%)	7.5 (4.5–16)	

Note.—Numbers in parentheses are ranges. The 2017 Centers for Disease Control U.S. life tables (23) were used to estimate the age-specific probability of all-cause mortality. Compared with previous Surveillance, Epidemiology, and End Results (SEER) data from 1990 to 1994 (21), the colorectal cancer incidence used here was increased by 1.34-fold due to recent increases among 40-year-old individuals. See Table S1 for further details and source references. CTC = CT colonography, mt-sDNA = multitarget stool DNA.

The model simulates the progression of colorectal disease in the absence of screening a large population of individuals from birth to death. Clinical events are modeled as transitions of patients among a set of predefined health states, with the occurrence of each transition being governed by a probability value (Fig 1). The simulation period was divided into 1-year intervals, during which patients could transition from one state to another. The initial population was composed of 10 000 individuals representative of the 45-year-old U.S. population. Simulated individuals were assigned to health states defined by the presence or absence of a colorectal lesion: diminutive (≤5 mm), small (6–9 mm), or large (≥10 mm) polyps or invasive cancer (localized, regional, or distant). Adenomas could grow, with some transitioning to preclinical (presymptomatic) CRC. Preclinical CRC could become symptomatic, leading to clinical detection. The probability of clinical detection was given by the age-specific incidence rate. All simulated individuals, including those with CRC, could die of other causes at any age. The 2017 Centers for Disease Control and Prevention U.S. life tables estimated the age-specific probability of all-cause mortality (23). Postdiagnosis survivorship was dependent on the stage at diagnosis (21). The natural history of colorectal disease was simulated by a screening mechanism that allowed for the detection and removal of polyps and the detection and treatment of cancer. The effect of screening depended on the specific test performed (eg, sensitivity, specificity, and frequency; Tables 1, S1). The model also incorporated the risk of complications from colonoscopy with polypectomy (24,25), including the potential for death from perforation (Tables 1, S1).

Screening and Surveillance Strategies

Screening and surveillance were performed from the simulated age of 45 years to the age of 75 years, assuming perfect adherence to screening, diagnostic follow-up, and surveillance recommendations. The evaluated screening strategies included mt-sDNA testing every 3 years with immediate colonoscopy following a positive test, a conventional CTC (CTC_{conv}) strategy in which screenings were conducted every 5 years and a 6-mm threshold was applied for immediate colonoscopy referral, and a surveillance CTC (CTC_{surv}) strategy that also included 3-year surveillance for 6–9-mm polyps. For both CTC strategies, all diminutive lesions were ignored, and all large polyps (≥10 mm) were sent for polypectomy (Fig 2). The simulated behavior of small 6–9-mm polyps was based on recent in vivo surveillance data from CTC screening (Appendix S1, section III) (12–14). By performing several sensitivity analyses (see the Statistical Analysis section), the essential elements that affect the clinical outcomes of the CTC_{surv} strategy were analyzed.

For all the modeled screening strategies, polypectomy was simulated at the time of diagnostic colonoscopy. Model individuals with negative findings at follow-up colonoscopy due to a false-positive triage test resumed their original screening regimen 10 years after colonoscopy (26). Individuals with simulated adenoma detection at colonoscopy were assumed to follow established surveillance guidelines until the age of 85 years (26). Individuals whose large adenomas were removed underwent colonoscopy surveillance with a 3-year interval. Patients with low-risk adenomas (<10 mm) underwent colonoscopy surveillance every 5 years, with a return to routine screening if no adenoma was detected.

Test Characteristics for Polyp Detection

The assumptions concerning mt-sDNA accuracy were based on published findings (Table 1) (5,15). The sensitivity of CTC in the detection of adenoma was assumed to be 70% for those measuring 6–9 mm, 85% for those measuring at least 10 mm, and 94% for colorectal carcinoma (27). Notably, these baseline assumptions for CTC polyp sensitivity reflect more pessimistic values from meta-analyses that incorporated outdated two-dimensional techniques (18,28). The specificity was assumed to be 87% for CTC_{conv} (with a 6-mm polypectomy threshold) and 95% for

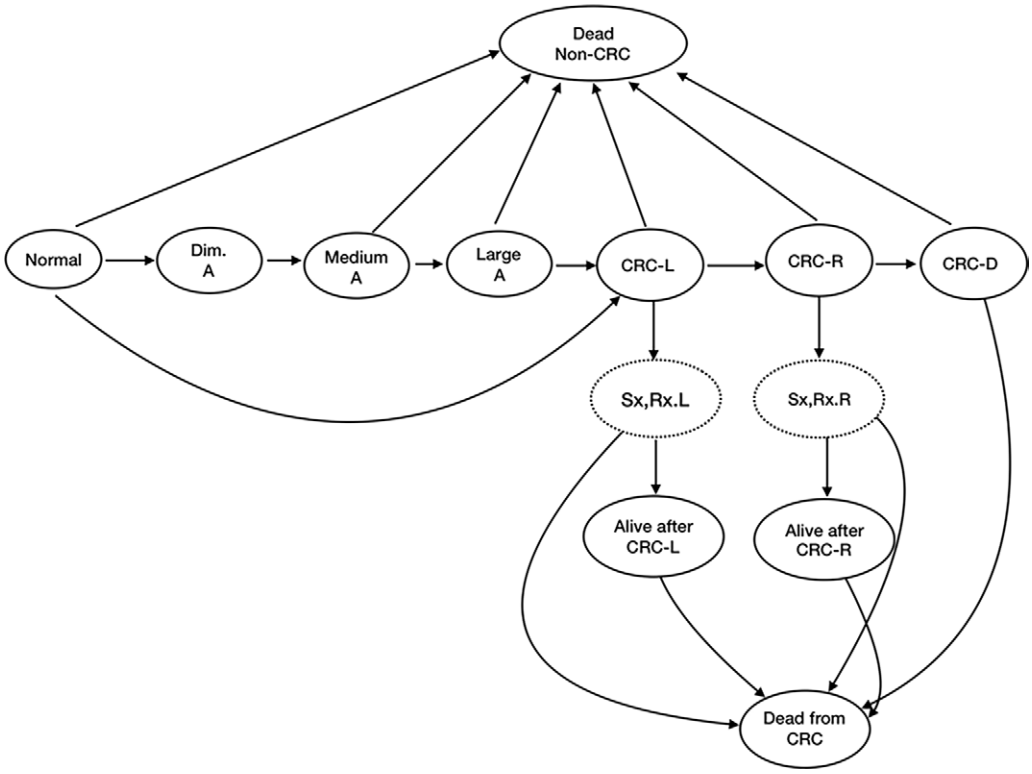

Figure 1: Schematic of the natural history model. The principal health states in the model are normal, diminutive (Dim.) (≤5 mm), small (6–9 mm), and large (≥10 mm) adenomatous polyps, as well as localized colorectal cancer (CRC-L), regional colorectal cancer (CRC-R), disseminated colorectal cancer (CRC-D), survival following symptomatic treatment of localized colorectal cancer (Sx,Rx.L), survival following symptomatic treatment of regional colorectal cancer (Sx,Rx.R), and death. Without screening, colorectal cancer (CRC) was assumed to be diagnosed and treated only after symptoms developed.

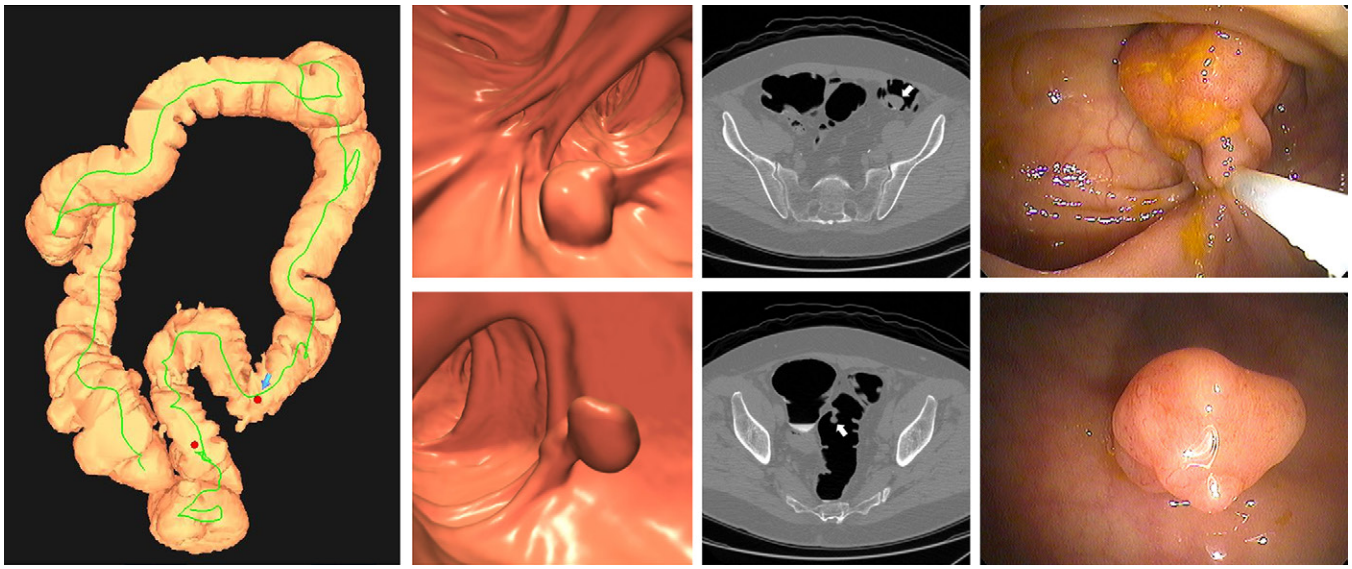

Figure 2: Images of positive CT colonography (CTC) screening examination result in an asymptomatic 67-year-old man. Three-dimensional colon map from CTC (left image) shows the location of two sigmoid polyps that were detected (red dots). Three-dimensional endoluminal and confirmatory two-dimensional transverse CTC images show a large 1.6-cm pedunculated polyp on top row (arrow) and a 9-mm pedunculated polyp in the distal sigmoid on the bottom row (arrow). Both polyps were confirmed and resected at optical colonoscopy performed the same day (right images), avoiding the need for a second bowel preparation. The larger polyp proved to be a tubulovillous adenoma (large advanced adenoma), whereas the smaller polyp was a nonadvanced tubular adenoma. Compare this level of information of a positive CTC screening test result with a positive multitarget stool DNA test result, for which no specific information is provided.

CTC_{surv} (with a 10-mm polypectomy threshold). We assumed the OC sensitivity to be 75% for diminutive (≤5 mm), 85% for small (6–9 mm), and 95% for large (≥10 mm) lesions (29).

Economic Assumptions

Tables S1 and S2 present the health state utilities (30) and costs (31) assumed in this study. Costs included screening, diagnostic and/or surveillance colonoscopy, and treatment costs. The baseline costs of mt-sDNA and CTC were assumed to be $531 and $493, respectively. The base-case scenario did not consider Medicare coverage costs. Diagnostic colonoscopy costs were incurred by those who tested positive at either mt-sDNA or CTC and those with symptom-detected CRC. Surveillance colonoscopy costs were incurred by patients with adenomas discovered at screening. The rates and associated costs of the major complications of screening were also considered (Tables 1, S1). The model did not include any risk of complications with mt-sDNA or CTC. However, simulated individuals undergoing a diagnostic or surveillance colonoscopy were considered at risk for perforation and bleeding (24,25). For the base-case analysis, the commercial payment rates for colonoscopy in patients younger than 65 years, colonoscopy complications, and CRC treatment from published literature were used (31). Following comparable CEAs (30,31), the costs of colonoscopy (and associated complications) and treatment for persons aged 45–64 years were assumed to be approximately 1.35-fold greater than those reported for persons aged 65 years and older. Health state utilities for the CRC stage (Table S1) were discounted from the screening benefit. All costs and benefits were discounted at 3% per year.

Statistical Analysis

Validation approach.—Face and internal validation were performed to review the problem formulation, data source, model structure, and results. A calibration validation was performed to ensure that the model output was consistent with data reported in the literature. In addition, cross-validation was performed to compare the model outputs with those of previously developed models. Finally, external validation was performed by comparing CRC incidence and mortality against the results from a randomized controlled trial of screening sigmoidoscopy (32,33). Details of the model validations are provided in Appendix S1, section II.

Base-case analysis and outcomes.—The base case was calculated using the expected value of each parameter, lifetime costs, and number of quality-adjusted life years (QALYs) of the different screening strategies, applying a 3% annual discount rate. Health state utilities for CRC by stage were used to calculate QALYs by applying these for 5 years after CRC diagnosis. The lifetime risk of CRC cases and deaths and the lifetime number of tests per person in a cohort of 10 000 45-year-old individuals were also estimated. An incremental cost-effectiveness ratio (ICER) was calculated as follows: (cost of strategy – cost of reference strategy)/(effectiveness of strategy – effectiveness of reference strategy), with effectiveness expressed in terms of QALYs. The strategy with the lowest costs and greatest effectiveness compared with the reference strategy was considered the best strategy. Strategies with a positive ICER below a willingness-to-pay threshold of $100 000 per QALY gained were considered to be cost-effective, corresponding to a typically used threshold in CEA studies (34,35).

Sensitivity analysis.—Sensitivity analysis was performed using two different methods. First, several inputs, including polyp characteristics (eg, percentage that are hyperplastic, advanced adenomas, and cancers), the diagnostic performance of CTC-based volumetric growth as a predictor of advanced adenomas (for CTC_{surv}), and costs, were varied (Tables 1, S1) simultaneously and randomly for 1000 interactions in a Monte Carlo simulation.

This provided estimates of the variability in cost effectiveness, expressed as the 5th–95th percentiles, that arise when variables in the model were allowed to vary (ie, probabilistic sensitivity analysis). Cost-effectiveness acceptability and expected loss curves were used as metrics for probabilistic sensitivity analysis (36).

The cost-effectiveness acceptability curves showed the probability or proportion of the simulated outcomes in which a given strategy was more cost-effective than the alternatives for a range of maximum willingness-to-pay thresholds. The cost-effectiveness acceptability frontier can be overlaid on top of the cost-effectiveness acceptability curve to summarize the uncertainty around the cost-effectiveness of the strategies compared in the study by indicating which strategy is optimal or has the highest net monetary benefit at different threshold values for cost-effectiveness (36).

Expected loss curves are graphical representations related to the forgone benefits of choosing a suboptimal strategy across willingness-to-pay thresholds (36) due to the uncertainty in model parameter values; specifically, the "optimal" strategy might not be chosen. In effect, if different parameter values are used, the choice of strategy might differ from the strategy that should ultimately be adopted. The sum of the benefits forgone for not being able to make the right decision due to this uncertainty is the expected value of perfect information, in which there is no possibility of making a wrong decision. Second, one-way sensitivity analyses were performed by varying one or two relevant variables while keeping the rest constant to assess the robustness of the conclusions against key assumptions. The variables analyzed included test performance characteristics, the diagnostic performance of the volumetric growth rate for predicting advanced neoplasia, the prevalence of advanced neoplasia in patients undergoing CTC_{surv}, and costs. The upper and lower values for all included parameters were obtained from the published literature. If not available, the mean value ± 20% was considered a reasonable range to evaluate a model parameter in the deterministic model. If the model results were sensitive to a particular parameter (ie, the conclusions could be changed by altering the parameter estimate or model input), the threshold value at which the model's predictions changed was determined. Finally, extreme case analysis, consisting of worst- and best-case analyses, was also performed.

Scenario analysis.—With respect to the age of screening initiation, for the base-case scenario, we assumed that CRC screening began at 45 years of age to match recent recommendations (22). We also simulated a sensitivity case scenario in which the starting age for screening was 50 and 65 years of age.

Results

Base-Case Scenario

Clinical outcomes.—In the absence of screening (natural history), 7.5% of the study population developed CRC and 3.0% died of it, which is consistent with published studies (22,30,31). As shown in Table 2, all three screening strategies were found to be clinically effective compared with no screening but varied in terms of CRC prevention rates and deaths. Specifically, mt-sDNA every 3 years, CTC_{surv}, and CTC_{conv} resulted in a reduction in CRC incidence by 59%, 70%, and 75%, respectively and in mortality by 72%, 80%, and 82%, when 100% adherence was assumed.

CEA.—No screening (natural history) was associated with 21.65 QALYs after 45 years of age, with a mean cost per person of $4955. All three screening options were considered cost-effective relative to no screening, with ICERs well below the willingness-to-pay threshold of $100 000. Under a program of triennial mt-sDNA screening, the simulated cohort of 10 000 45-year-old individuals experienced an estimated 310 CRC cases and 83 deaths, yielding 1196 QALYs gained per 10 000 individuals relative to no screening. The mt-sDNA strategy resulted in a cost of $8878 per QALY gained and was therefore considered a cost-effective option. CTC_{surv} and CTC_{conv} strategies resulted in costs of $3913 and $4422 per person, respectively, making both CTC strategies not only cost-effective but also cost-saving relative to no screening (Table 2).

Compared with the mt-sDNA strategy, the CTC_{conv} and CTC_{surv} strategies resulted in 241 and 195 additional QALYs, respectively. When mt-sDNA was used as the reference strategy, both CTC_{surv} and CTC_{conv} were again found to be cost-saving options, resulting in fewer cancers and lower costs (Fig 3). When comparing the two CTC strategies against each other, the higher costs of CTC_{conv} relative to CTC_{surv} were not adequately offset by the slightly greater clinical efficacy, with an ICER higher than the assumed adopted threshold for an efficient test ($110 592). This result was driven primarily by substantial differences in the numbers and costs of surveillance colonoscopies (Table 2). Specifically, for a population of 10 000 screening individuals, the number of lifetime colonoscopies was 17 765 for CTC_{conv} compared with 8485 for CTC_{surv}, whereas the number of CRCs and overall mortality rates were similar (Table 2). In comparison, a greater proportion of these patients developed and died of CRC in a triennial mt-sDNA screening scenario (Table 2).

Sensitivity Analysis

The results of the probabilistic sensitivity analysis with 1000 iterations in the base-case population are displayed in cost-effectiveness acceptability (Fig 4) and expected loss (Fig 5) curves. For 45-year-old individuals, CTC_{surv} showed the highest probability of being cost-effective, whereas CTC_{conv} was the optimal screening choice only when the willingness-to-pay threshold exceeded $121 000 per QALY. A screening strategy with mt-sDNA was never cost-effective when compared with either CTC_{surv} or CTC_{conv}, regardless of the willingness-to-pay threshold (Figs 4, 5). At a willingness-to-pay threshold of $50 000 per QALY, the probabilities of CTC_{surv}, CTC_{conv}, and mt-sDNA being cost-effective were 71%, 21%, and 0.2%, respectively (Fig 4). These results largely align with the base-case results. Additional probabilistic sensitivity analysis results are given in Table S3–S5 and Figure S5.

The results from one-way sensitivity analysis (Table 3) support that the model is robust, as they are either insensitive to parameter estimates at any value or sensitive only at extreme values well outside published ranges. In nearly all one-way sensitivity analyses, mt-sDNA every 3 years remained dominant or was not cost-effective compared with either the CTC_{conv} or CTC_{surv} strategies (Table 3). Even when assuming the best accuracy for

Table 2: Baseline Clinical Outcomes and Cost-Effectiveness of the Model

Parameter	No Screening	mt-sDNA	CTC_{surv}	CTC_{conv}
CRC cases per 100 000 persons	752	310	223	190
CRC incidence rate (per 100 000 person-years)*	212 (198–226)	86 (76–95)	62 (54–68)	52 (46–60)
Hazard ratio*†		0.41 (0.39, 0.42)	0.29 (0.28, 0.30)	0.25 (0.24,–0.26)
CRC cases prevented‡		442 (59)	529 (70)	562 (75)
CRC deaths	298	83	60	54
CRC mortality rate (per 100 000 person-years)*	82 (74–91)	23 (19–28)	16 (13–21)	15 (11–19)
Cases of CRC deaths avoided‡		215 (72)	238 (80)	244 (82)
Hazard ratio*†		0.28 (0.26, 0.30)	0.22 (0.18, 0.22)	0.18 (0.16, 0.19)
Expected screening results in the lifetime of a cohort of 10 000 persons				
Screening colonoscopies*		7045	2046	6113
Diagnostic, follow-up, and surveillance colonoscopies		9468	6440	11 653
Total no. of colonoscopies		16 513	8485	17 765
CRCs averted per colonoscopy		0.027	0.062	0.032
CRC deaths averted per colonoscopy		0.013	0.028	0.014
Overall stool tests per person		7.4		
CTC surveillance examinations per person			0.6	
Overall CTC examinations per person			6.0	5.3
Overall colonoscopies per person		1.7	0.8	1.8
Major hemorrhages at colonoscopy		13	7	14
Perforations at colonoscopy		7	3	7
Deaths from colonoscopy complications		0	0	1
Cost-effectiveness outcomes per person (compared with no screening)				
Undiscounted life years per person	36.18	36.46	36.49	36.50
Undiscounted life years gained per person		0.276	0.310	0.318
Discounted life years per person	21.69	21.79	21.80	21.80
Discounted life years gained per person		0.102	0.116	0.119
Discounted QALYs per person	21.65	21.77	21.79	21.79
Discounted QALYs gained per person		0.120	0.139	0.144
Discounted lifetime cost per person ($)	4954.77	6011	3913	4422
Incremental costs per person ($)		1057	2098	533
ICER, incremental cost per QALY gained§				
No screening		Not dominated	Dominated by CTC_{surv}	Dominated by CTC_{conv}
mt-sDNA	$8878		Dominated by CTC_{surv}	Dominated by CTC_{conv}
CTC_{surv}	Dominates over no screening	Dominates over mt-sDNA		Not dominated
CTC_{conv}	Dominates over no screening	Dominates over mt-sDNA	$110 592	

Note.—Except where indicated, numbers in parentheses are ranges. The time to the next surveillance colonoscopy was simulated on the basis of findings at the last colonoscopy examination: 3 years when a large adenoma or three or more adenomas (any size) were detected or 5 years if two or fewer subcentimeter adenomas were detected. Adherence to surveillance colonoscopy was assumed to be 100% in all modeled scenarios. CRC = colorectal cancer, CTC = CT colonography, CTC_{conv} = conventional CTC strategy, CTC_{surv} = surveillance CTC strategy, ICER = incremental cost-effectiveness ratio, mt-sDNA = multitarget stool DNA, QALY = quality-adjusted life year.

* Outcomes are age-adjusted and expressed over the lifetimes of 10 000 45-year-old individuals who start screening at age 45 years and are screened until age 75 years.

† Numbers in parentheses are 95% CIs.

‡ Numbers in parentheses are percentages.

§ Whenever the ICER could not be defined, whether the strategy was better or worse than the comparator strategy is indicated.

mt-sDNA (ie, 19% sensitivity for small adenomas, 46% for large adenomas, and 94% for CRC) and the worst accuracy for CTC (ie, 49% sensitivity for small adenomas, 65% for large adenomas, and 88% for cancer), mt-sDNA was still dominated by both CTC strategies (Table 3). When comparing CTC_{conv} with CTC_{surv}, the model was sensitive to assumptions related to the diagnostic performance of volumetric polyp growth as a predictor of advanced histology. Further details are provided in Appendix S1. Other somewhat sensitive model parameter estimates included the absolute prevalence of 6–9-mm advanced neoplasia and the 5-year incidence of CRC with the CTC_{surv} strategy (Table 3). With respect to procedural costs, a 50% reduction in

the assumed costs of the screening tests did not meaningfully alter the cost-effectiveness results (Table 3). A reduction in the baseline cost of mt-sDNA from $531 to $25 (a 95% decrease) and an increase in the baseline cost of CTC from $493 to $1234 (a 250% increase) were needed before the ICER of CTC relative to mt-sDNA exceeded $100 000 per QALY gained (Table 3).

With coverage of the screening tests by Medicare for adults aged 65 years and older, the triennial mt-sDNA screening cost was $6173 per QALY gained relative to no screening, but the CTC alternatives remained dominant, as they were less costly and more effective. For the Medicare scenario, the ICER of CTC_{conv} compared with CTC_{surv} was $112 596 per QALY gained, which remained above the chosen willingness-to-pay threshold for being a cost-effective alternative. A 50% reduction in endoscopic costs from the baseline assumption was required to decrease the ICER of CTC_{conv} compared with that of CTC_{surv} below the $100 000 threshold.

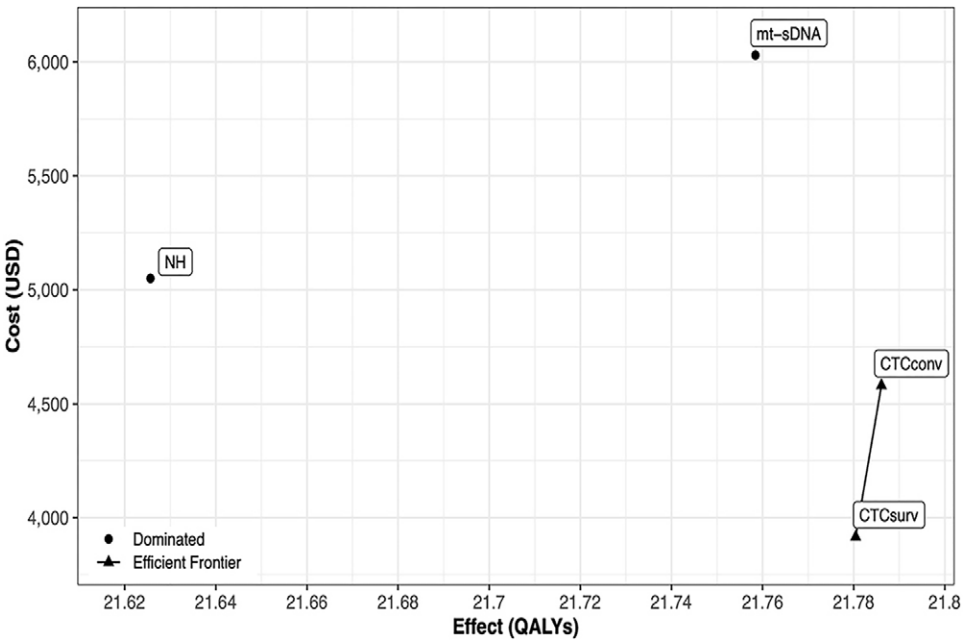

Figure 3: Graph shows clinical effectiveness versus costs for colorectal cancer screening strategies. Clinical effectiveness (discounted quality-adjusted life years [QALYs] per person) and cost (discounted dollars per person) are shown for the evaluated screening strategies on a cost-effectiveness plan. The solid line connecting surveillance CT colonography (CTCsurv), where there is 3-year CT colonography surveillance for 6–9-mm polyps and 10-mm threshold for polypectomy, and conventional CT colonography (CTCconv), where there is a 6-mm threshold for colonoscopic polypectomy, represents the efficient frontier, representing screening strategies that are not dominated by other scenarios (where "Dominated" means that a strategy is both more expensive and less clinically efficacious). The no screening (NH) and triennial multitarget stool DNA (mt-sDNA) strategies were dominated.

Scenario Analysis

A scenario analysis in which individuals 45 years old begin screening for CRC after turning 50 was also performed. The results from the analysis are provided in Table S6. We also simulated an unscreened cohort of 10 000 U.S. 65-year-olds, who were then screened with either triennial mt-sDNA testing or one of the two CTC strategies (Table S7). Neither scenario analysis yielded conclusions that differed from those of the base-case model, that is, that triennial mt-sDNA was the costliest strategy and was not a cost-effective alternative compared with either CTC_{conv} or CTC_{surv}.

Discussion

Colorectal screening with noninvasive tests has the potential to substantially reduce the population incidence of colorectal cancer (CRC), providing safer options relative to primary optical colonoscopy (OC) screening (2,37). In our state-transition Markov model simulation, multitarget stool DNA (mt-sDNA) testing beginning at 45 years of age led to a 59% reduction in CRC incidence among the screened population, whereas the CT colonography (CTC) screening strategies resulted in a 70%–75% reduction. mt-sDNA screening was found to be cost-effective relative to no screening, with an estimated cost of nearly $9000 per quality-adjusted life year (QALY) gained, well below the selected threshold of $100 000. However, both CTC screening strategies were found to be cost-saving relative to no screening. As such, CTC screening dominated over both mt-sDNA testing and no screening, being both more clinically efficacious and more cost-effective. When the conventional CTC screening strategy of sending all detected polyps measuring at least 6 mm to OC was compared with a hybrid CTC strategy that included 3-year CTC surveillance for small (6–9-mm) polyps, the former was not cost-effective relative to the latter strategy. This result was driven primarily by the higher costs related to OC referral for small polyps, which was not sufficiently offset by the corresponding small incremental gain in QALYs. As such, a CTC strategy consisting of 3-year surveillance for small colorectal polyps and colonoscopy referral for large polyps achieved the best overall balance. When our model assumed an initial screening age of 50 years and a Medicare-aged population of 65 years, neither scenario differed from the base-case model conclusions. Specifically, mt-sDNA testing remains the least effective and most costly strategy (ie, dominated) and is not a cost-effective alternative to the more efficient and effective CTC strategies.

Advanced adenomas remain the primary target for CRC prevention and are defined as polyps that are large (≥10 mm) and/or contain a villous component or high-grade dysplasia (38–41). In our experience, the vast majority of advanced adenomas (90%–95%) qualify by their large size alone, which can effectively serve as a surrogate for advanced disease (Fig 2) (39, 42). In particular, high-grade dysplasia is rare among subcentimeter polyps but is a more critical driver of malignant degeneration than villous histologic characteristics (43). Because CTC is able to help stratify polyps specifically by size (and morphologic characteristics), it is particularly well suited to selectively identify advanced neoplasia (ie, large adenomas and invasive cancer) for endoscopic referral (Fig 2). Stool-based tests largely target cancers, which may

have progressed too far for a cure in some cases. At the other end of the spectrum, the vast majority of polyps removed at primary OC screening are diminutive and benign, which substantially increases costs and complications (44,45). Therefore, CTC screening is ideally positioned in a "Goldilocks zone" that emphasizes cost-effective cancer prevention and early detection (46).

In addition to our simulations reported herein, we previously reported on a real-world screening experience in which mt-sDNA was compared with CTC at our institution (47,48). Despite an OC referral rate for positive mt-sDNA testing that was more than double that for CTC using a 10-mm size threshold (13.1% vs 5.9%), the overall yield for advanced neoplasia was significantly lower for mt-sDNA testing (2.7% vs 4.4%; $P < .001$) (48). Similarly, the yield for high-risk sessile serrated lesions was more than double that for CTC at the 10-mm referral threshold compared with mt-sDNA testing (0.7% vs 1.6%; $P < .001$) (47). Similar trends were observed in a broader meta-analysis (40). These findings underscore the inherent differences between these two CRC screening tests. The binary nature of mt-sDNA test results, which provide no specific information regarding the nature of positivity, yields a positive predictive value for cancer of only 2% (40, 48). Furthermore, because mt-sDNA testing is focused on detecting malignancy, the majority of large adenomas, the key screening targets for cancer prevention, are missed (15). In comparison, CTC results can be specifically tailored to ignore isolated diminutive lesions, provide 3-year surveillance for small polyps, and prompt referral for large polyps and masses (Fig 2). The detection of invasive cancer via CTC is typically fairly obvious, and its performance matches that of OC (18).

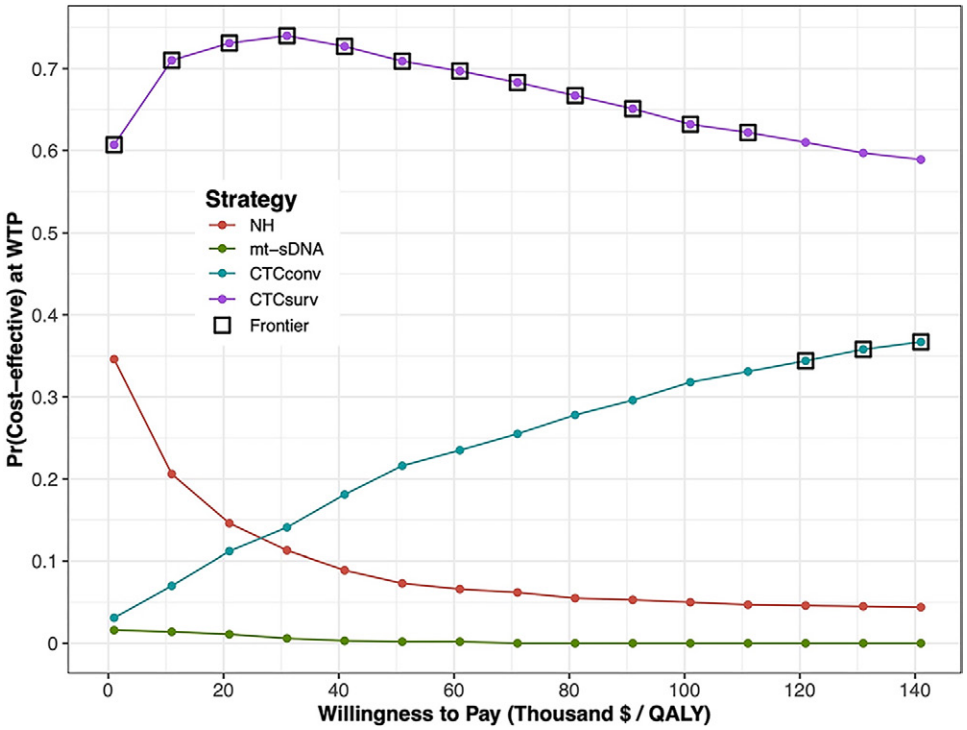

Figure 4: Cost-effectiveness acceptability and frontier from the probabilistic sensitivity analysis. Cost-effectiveness acceptability curves display the probability of each screening strategy being cost-effective across all simulations in the probabilistic sensitivity analysis and the frontier displaying the probability for the optimal screening strategy (□) being cost-effective across a range of willingness-to-pay (WTP) thresholds. The optimal strategy was chosen as the one that provided the highest monetary benefit on average across all samples of probabilistic sensitivity analysis at the willingness-to-pay value being considered. For each willingness-to-pay value, the sum of the probabilities of all screening strategies equals 1. CTCconv = CT colonography with a 6-mm threshold for colonoscopy referral, CTCsurv = 3-year CT colonography surveillance for 6-mm polyps and 10-mm threshold for colonoscopy referral, mt-sDNA = triennial multitarget stool DNA, NH = no screening, QALY = quality-adjusted life year.

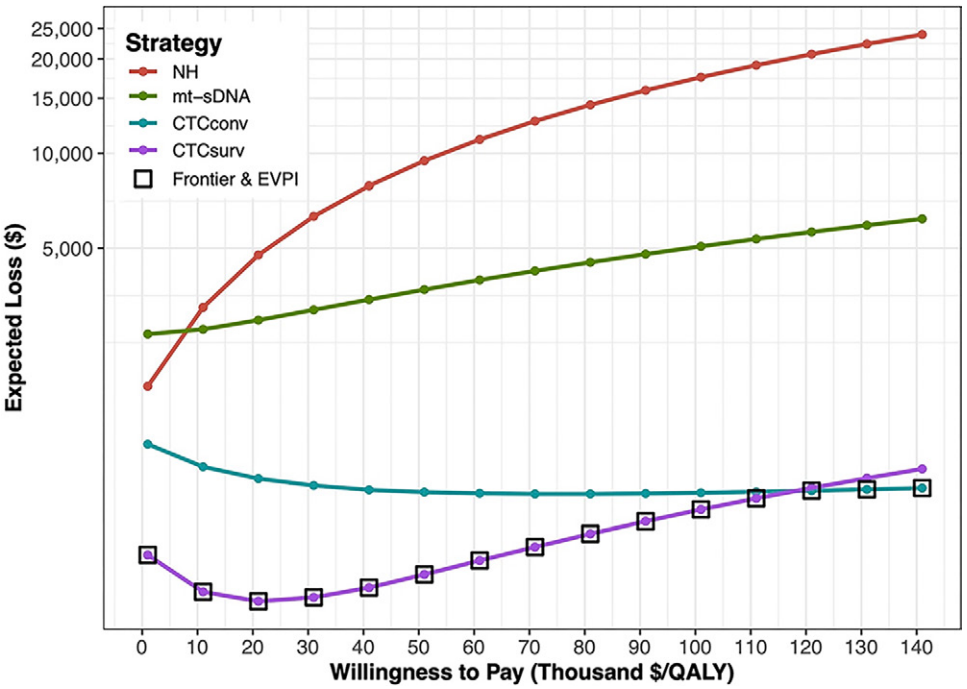

Figure 5: Graph shows expected loss curves across a broad range of willingness-to-pay thresholds. The expected loss in U.S. dollars for each screening strategy of the cost-effectiveness analysis is shown, as well as the optimal strategy inside the open squares (ie, the frontier), that is, the strategy with the lowest expected loss. The scale of the y-axis is logarithmic. Surveillance CT colonography (CTCsurv), with 3-year CT colonography (CTC) surveillance for 6-mm polyps and 10-mm threshold for colonoscopy referral, represents the optimal colorectal cancer screening strategy for a broad range of willingness-to-pay up to $121 000 per quality-adjusted life year (QALY) gained, above which conventional CTC (CTCconv), CTC with a 6-mm threshold for colonoscopy referral, was the optimal strategy. EVPI = expected value of perfect information, mt-sDNA = triennial multitarget stool DNA, NH = no screening.

This is a pivotal moment for CTC screening in the United States. Although the recent Centers for Medicare and Medicaid Services national coverage determination specifically relates to the Medicare population aged 65 years and older, this development also provides an important symbolic "blessing" for CTC screening in general, perhaps removing any lingering misunderstanding that it somehow remained "investigational." CTC can now join OC and mt-sDNA as a legitimate frontline screening option. In particular, CTC may represent a highly favorable screening strategy for younger patients (eg, aged 45–49 years). Importantly, the early-age onset of CRC (ie, younger than 50 years) is estimated to continue to substantially increase, especially if those aged 45–49 years remain largely unscreened (3,4). CTC screening may provide an intermediate option between primary OC and mt-sDNA screening by avoiding the invasiveness of the former while still providing effective cancer prevention.

Table 3: Results of the One-way Sensitivity Analyses Examining the ICER for Screening from 45 to 75 Years of Age

Parameter and Screening Technique	Base-Case Value	Value Used in Sensitivity Analysis	Stool Tests	CTC	OC	CRC Cases	CRC Deaths	QALY	QALYg	Cost	ICER		
											No Screen	mt-sDNA	CTC_{surv}
	Sensitivity for Diminutive/Small/Large Adenoma/CRC/Specificity												
No screening						752	298	21.65		$4955			
mt-sDNA	0.17/0.42/0.92/0.90	High range: 0.186/0.46/0.94/0.886	72229		17613	287	77	21.78	0.126	$5928	$9215		
CTC_{surv}	NA/0.70/0.85/0.94/0.95	Low range: NA/0.49/0.65/0.88/0.95		59827	7762	260	73	21.78	0.128	$4129	D	D	
CTC_{conv}	NA/0.70/0.85/0.94/0.87	Low range: NA/0.49/0.65/0.88/0.89		54626	15444	230	67	21.78	0.134	$4516	D	D	$429667
	Prevalence of 6–9-mm Advanced Neoplasia (%)												
No screening	0.14	High range: 1.44				1022	405	21.58		$6640			
mt-sDNA	0.14	High range: 1.44	74081		16471	416	111	21.74	0.161	$6627	D		
CTC_{surv}	0.14	High range: 1.44		59294	8508	392	109	21.76	0.174	$4812	D	D	D
CTC_{conv}	0.14	High range: 1.44		53157	17699	248	71	21.78	0.198	$4759	D	D	D
	Natural History of 6–9-mm Adenomas Progressing to CRC within 5 years in the CTC Surveillance Paradigm (%)												
No screening						752	298	21.65		$4955			
mt-sDNA			74267		16513	310	83	21.77	0.120	$6011	$8878		
CTC_{surv}	0.52	High range: 1.04		59425	8433	268	79	21.77	0.119	$4293	D	D	
CTC_{conv}				53178	17765	190	52	21.79	0.144	$4422	D	D	$5447
	Natural History of 6–9-mm Adenomas (Growth Rate/Advanced Adenoma/Malignant Transformation within 5 years in the CTC Surveillance) (%)												
No screening						752	298	21.65		$4955			
mt-sDNA					16513	310	83	21.77	0.112	$6011	$8878		
CTC_{surv}	24.9/6/0.52	High range: 64/15/0.52		56640	12599	212	60	21.7878	0.139	4136	D	D	
CTC_{conv}				53178	17765	190	54	21.79	0.144	$4430	D	D	$60037
	Natural History of 6–9-mm Adenomas (Growth Rate/Advanced Adenoma/Malignant Transformation within 5 years in the CTC Surveillance) (%)												
No screening						752	298	21.65		$4955			
mt-sDNA					16,513	310	83	21.77	0.112	$6011	$8878		
CTC_{surv}	24.9/6/0.52	Low range: 16/3.8/0.21		60550	6908	205	56	21.79	0.144	$3731	D	D	
CTC_{conv}				53178	17765	190	54	21.79	0.144	$4430	D	D	$72800000
	Percentage of Adenoma and Advanced Neoplasia in CTC Surveillance Showing Measurable Growth (%)*												
No screening						752	298	21.65		$4955			
mt-sDNA					16513	310	83	21.77	0.120	$6011	$8878		
CTC_{surv}	40/74	High range: 55/100		57974	10810	208	58	21.79	0.141	$4002	D	D	
CTC_{conv}				53178	17765	190	54	21.79	0.144	$4430	D	D	$155004
	Percentage of Adenoma and Advanced Neoplasia in CTC Surveillance Showing Measurable Growth (%)*												
No screening						752	298	21.65		$4955			
mt-sDNA					16513	310	83	21.77	0.120	$6011	$8878		
CTC_{surv}	40/74	Low range: 33/50		59509	8523	235	64	21.78	0.136	$4002	D	D	
CTC_{conv}				53178	17765	190	54	21.79	0.144	$4430	D	D	$51478
	Screening Test Costs												
No screening						752	298	21.65		4.95E+03			
mt-sDNA	$531	$265	74267		16513	310	83	21.77	0.120	4.59E+03	D		
CTC_{surv}	$493	$236		59523	8485	223	60	21.79	0.139	2.86E+03	D	D	
CTC_{conv}	$493	$236		53178	17765	190	54	21.79	0.144	3.46E+03	D	D	$130435

(Table 3 continues)

Table 3 *(continued)*: Results of the One-way Sensitivity Analyses Examining the ICER for Screening from 45 to 75 Years of Age

Parameter and Screening Technique	Base-Case Value	Value Used in Sensitivity Analysis	Stool Tests	CTC	OC	CRC Cases	CRC Deaths	QALY	QALYg	Cost	ICER		
											No Screen	mt-sDNA	CTC_{surv}
	Screening Test Costs												
No screening						752	298	21.65		$4955			
mt-sDNA	$531	Low range: 25	74267		16513	310	83	21.77	0.120	$3322	D		
CTC_{surv}	$493	High range: 1264		59523	8485	223	60	21.79	0.139	$6969	D	$186834	
CTC_{conv}	$493	High range: 1264		53178	17765	190	54	21.79	0.144	$7213	D	$161318	$53043
	Screening Test Costs												
No screening						752	298	21.65		4.95E+03			
mt-sDNA	$530.55	Low range: 25	74267		16513	310	83	21.77	0.120	3.30E+03	D		
CTC_{surv}	$493.00	Low range: 246		59523	8485	223	60	21.79	0.139	2.90E+03	D	D	
CTC_{conv}	$493.00	Low range: 246		53178	17765	190	54	21.79	0.144	3.50E+03	D	$8292	$130435
	Screening Test Costs												
No screening						752	298	21.65		4.95E+03			
mt-sDNA	$530.55	Low range: 25	74267		16513	310	83	21.77	0.120	3.30E+03	D		
CTC_{surv}	$493.00	High range: 1232.5		59523	8485	223	0	21.79	0.139	6.96E+03	$14447	$187454	
CTC_{conv}	$493.00	High range:1232.5		53178	17765	190	54	21.79	0.144	7.19E+03	$15608	$161374	$50706
	Test Costs (Commercial/Medicare)												
No screening						752	298	21.65		$4955			
mt-sDNA	$531/$531	$531/$372	74267		16513	310	83	21.77	0.120	$5689	$6173		
CTC_{surv}	$493/$493	$493/$350		59523	8485	223	60	21.79	0.139	$3642	D	D	
CTC_{conv}	$493/$493	$493/$350		53178	17765	190	54	21.79	0.144	$4205	D	D	$112596
OC costs†	1890/1428	Low range: 945/714											
No screening						752	298	21.65		$4955			
mt-sDNA			74267		16513	310	83	21.77	0.120	3.88E+03D	D		
CTC_{surv}				59523	8485	223	60	21.79	0.139	3.59E+03	D	D	
CTC_{conv}				53178	17765	190	54	21.79	0.144	3.69E+03	D	D	$21739

Note.—CRC = colorectal cancer, CTC = CT colonography, CTC_{conv} = conventional CTC strategy, CTC_{surv} = surveillance CTC strategy, D = dominates, ICER = incremental cost-effectiveness ratio, mt-sDNA = multitarget stool DNA, NA = not applicable, OC = optical colonoscopy, QALY = quality-adjusted life year, QALYg = QALY gained.

* Under this scenario, volumetric growth assessment has a positive predictive value for adenoma and advanced neoplasia of 82% and 11%, respectively.

† OC costs with and without polypectomy.

Our CEA findings for mt-sDNA screening mirror those of prior studies. Naber et al (6) reported that "compared with nearly all other CRC screening strategies reimbursed by CMS [Centers for Medicare and Medicaid Services] it is less effective and considerably more costly, making it an inefficient screening option." Skally et al (7) reported that mt-sDNA "is currently dominated by most of the other available screening options. Cost and test performance appear to be the main influences on cost-effectiveness." Finally, Ladabaum et al (5) reported that the fecal immunochemical test and colonoscopy are more effective and less costly than mt-sDNA. Previous CEA studies focusing on CTC screening have shown that ignoring diminutive polyps improves cost-effectiveness without impacting clinical efficacy (9). Prior studies have also investigated the differential handling of small colorectal polyps (10,11), but more robust natural history data now exist to better inform Markov models (12,13). A recent CEA study investigated the impact of opportunistic CT screening, specifically for unsuspected cardiovascular disease and osteoporosis, and revealed that this approach was potentially cost-saving (49). Although we did not include any such opportunistic extracolonic assumptions in the current Markov model, this would likely further improve the overall clinical efficacy and cost savings.

Our CEA study has additional limitations. Although the simulation model was calibrated and validated using the best available data, some natural history parameters remain somewhat uncertain. Nonetheless, our simulated CRC incidence is in line with the results of previous analyses. The natural history of 6–9-mm polyps is largely derived from CTC surveillance at a single center. Nonetheless, these are unique data that were previously unavailable. The model did not account for potential changes in screening modalities, costs, or adherence rates over time, which may influence the long-term cost-effectiveness of the evaluated strategies. The analysis focused solely on the health system perspective and did not consider the broader societal costs or productivity losses associated with CRC. This CEA does not consider a primary colonoscopy strategy or other emerging technologies, such as blood tests. The model cannot account for future improvements in CRC treatment, which could affect both mortality rates and treatment costs. We also assumed perfect adherence to screening, diagnostic follow-up, and surveillance in our analysis. This implies that the model predicted the maximum achievable benefit for all screening tests. Unfortunately, there are limited data on test-specific adherence for each step in the screening process and over multiple rounds of screening, making it difficult to inform our analyses with empirical evidence.

In conclusion, CT colonography (CTC) screening dominated over both multitarget stool DNA testing and no screening in our Markov model, with benefits of cost savings and improved

clinical efficacy. A CTC strategy of surveillance for small polyps, reserving polypectomy for large polyps, provided the best overall balance of programmatic costs and clinical results. This finding reinforces our clinical CTC screening mantra of "ignoring the tiny, watching the small, and removing the large" in terms of managing diminutive (≤5 mm), small (6–9 mm), and large (≥10 mm) colorectal polyps, respectively.

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