

Cost-effectiveness of Colorectal Cancer Screening

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Colorectal cancer is an important public health problem. Several screening methods have been shown to be effective in reducing colorectal cancer mortality. The objective of this review was to assess the cost-effectiveness of the different colorectal cancer screening methods and to determine the preferred method from a cost-effectiveness point of view. Five databases (MEDLINE, EMBASE, the Cost-Effectiveness Analysis Registry, the British National Health Service Economic Evaluation Database, and the lists of technology assessments of the Centers for Medicare and Medicaid Services) were searched for cost-effectiveness analyses published in English between January 1993 and December 2009. Fifty-five publications relating to 32 unique cost-effectiveness models were identified. All studies found that colorectal cancer screening was cost-effective or even cost-saving compared with no screening. However, the studies disagreed as to which screening method was most effective or had the best incremental cost-effectiveness ratio for a given willingness to pay per life-year gained. There was agreement among studies that the newly developed screening tests of stool DNA testing, computed tomographic colonography, and capsule endoscopy were not yet cost-effective compared with the established screening options.

colonography, computed tomographic; colonoscopy; colorectal neoplasms; cost-benefit analysis; mass screening; occult blood; sigmoidoscopy

Abbreviations: CTC, computed tomographic colonography; FIT, fecal immunochemical test; FOBT, fecal occult blood test; LYG, life-year gained; USPSTF, U.S. Preventive Services Task Force.

INTRODUCTION

More than 1 million people worldwide are newly diagnosed with colorectal cancer each year (1). Approximately half of these patients die of the disease, making colorectal cancer the fourth leading cause of cancer death in the world (1). Screening can prevent many of these deaths by detecting colorectal cancer in an early, more treatable stage and by detecting and removing its nonmalignant precursor lesion, the adenoma, thereby preventing colorectal cancer incidence (2, 3). Colorectal cancer screening is not only an effective tool for reducing colorectal cancer mortality but also has been estimated to do so at acceptable costs. In 2002, Pignone et al. (4) conducted a systematic review for the U.S. Preventive Services Task Force (USPSTF) showing that, compared with those for no colorectal cancer screening, the costs per life-year gained (LYG) of several colorectal cancer screening strategies were all less than \$50,000 per LYG. However, when the established colorectal cancer screening strategies were compared, no strategy was consistently found to be the most effective or to be the preferred strategy for a given willingness to pay (4).

The uncertainty about what is the most (cost-)effective test has resulted in a wide variety of screening strategies being offered worldwide. Guidelines in the United States recommend that individuals undergo screening with one of several options (5, 6), whereas the European Union recommends screening with only a guaiac fecal occult blood test (FOBT) (7). Initiatives to implement nationwide colorectal cancer screening programs are currently being developed in Canada (8) and several European countries (9). Given the large budget deficits most countries currently face, it is of great importance that resources be used efficiently and that a cost-effective option for colorectal cancer screening be chosen.

Options for colorectal cancer screening are evolving rapidly. Several screening methods that were either not under consideration or unavailable at the time of the USPSTF review have since been deemed viable options (5). Included are computed tomographic colonography (CTC) and stool DNA testing, as well as the screening option currently recommended in several countries—fecal immunochemical

testing (FIT) (10–13). Therefore, this paper aims to provide an updated review of the cost-effectiveness of colorectal cancer screening to inform policy makers and others who may be deciding which colorectal cancer screening strategy to recommend or implement. Specifically, we examined the following 3 questions:

1. How do the costs and LYGs from colorectal cancer screening with the established screening tests (i.e., guaiac FOBT, sigmoidoscopy, the combination of sigmoidoscopy and guaiac FOBT, and colonoscopy) compare with those for no screening?
2. Do the results of the cost-effectiveness analyses of the established screening options point to an optimal strategy for screening?
3. Are the newly developed screening tests FIT, stool DNA testing, CTC, and capsule endoscopy cost-effective compared with the established colorectal cancer screening tests?

MATERIALS AND METHODS

We conducted this review according to the framework for reviews of economic analyses (14). We searched MEDLINE, EMBASE, the Cost-Effectiveness Analysis Registry (<https://research.tufts-nemc.org/cear/default.aspx>), the British National Health Service Economic Evaluation Database (<http://www.crd.york.ac.uk/CMS2Web/AboutNHSEED.asp>; <http://www.crd.york.ac.uk/CMS2Web/SearchPage.asp>), and the lists of technology assessments of the Centers for Medicare and Medicaid Services (<http://www.cms.gov/medicare-coverage-database/indexes/technology-assessments-index.aspx?bc=BAAAAAAAAAAAA&>) for cost-effectiveness analyses published between January 1993 (the year the first trial of colorectal cancer screening was published) and December 2009. We used different queries matching the keywords in each database to identify the relevant cost-effectiveness analyses. Web Appendix 1 contains an overview of the search queries. (This Appendix and all other supplementary Web material mentioned in this review are posted on the *Epidemiologic Reviews* Web site (<http://epirev.oxfordjournals.org/>)). To identify studies not captured by our database searches, we manually checked the reference lists of retrieved articles.

We used similar criteria for exclusion and inclusion of articles, as in the USPSTF review (4), excluding studies that were not cost-effectiveness or cost-utility analyses; studies for which costs per (quality-adjusted) LYG could not be correctly calculated; studies that did not contain original analyses; studies that did not address at least one of our research questions; and studies performed from perspectives other than the societal perspective or payer perspective. We did include studies using non-US cost or disease estimates. When multiple publications were retrieved from the same cost-effectiveness model, we included the most comprehensive analysis and used the other papers for supplemental information.

For each included study, we extracted the life-years and costs per person for each strategy evaluated. When necessary, costs were translated to US dollars by using the exchange rate reported in the studies. If not reported, we

used historic exchange rates from July 1 (or an adjacent date, if rates for July 1 were unavailable) of the year in which cost estimates were expressed (15). Costs were updated to 2010 US dollars by using the Consumer Price Index for medical care (16). If no base year for the cost estimates was explicitly mentioned in a study, we assumed that costs were expressed in the currency of the year 2 years prior to publication.

To answer the second and third research questions (i.e., about the cost-effectiveness of screening tests), we performed an incremental cost-effectiveness analysis. Specifically, we ranked the strategies in order of increasing effectiveness. If one strategy was more costly and less effective than another strategy, it was considered to be strongly dominated. If a strategy was both less effective and provided additional years of life at a higher cost than a more effective strategy (i.e., it had a higher incremental cost-effectiveness ratio), it was considered to be weakly dominated. Incremental cost-effectiveness ratios were then recalculated for each nondominated strategy by dividing the additional cost of a specific strategy by its additional clinical benefit compared with the next less expensive strategy. The calculated incremental cost-effectiveness ratios will almost always differ from the incremental cost-effectiveness ratios reported in the studies because of the cost adjustments, and because some studies reported cost per LYG with each strategy compared with no screening.

RESULTS

Identification of cost-effectiveness analyses

The search (conducted in January 2010) retrieved a total of 641 citations. Of these, 217 were duplicates and were excluded, leaving 424 citations for further consideration. In total, 297 relevant abstracts were reviewed in detail, with 123 articles retrieved for possible inclusion in the review. Fifty-six publications relating to 32 unique colorectal cancer models were considered in this review. Web Figure 1 shows the reasons for excluding the remaining articles. Through a manual search of the reference lists of retrieved articles, we identified 2 additional studies that met our inclusion criteria (17, 18). Both concerned additional analyses with models already included in this review. This review includes 5 new studies with US-based costs and disease incidence not yet included in the USPSTF review (19–22) and 2 studies with updated estimates from previously included models (22, 23).

Study descriptions

Web Table 1 presents the characteristics of all 32 studies included in this review. Thirty studies reported costs per LYG from colorectal cancer screening, 2 reported costs per quality-adjusted LYG only (24, 25), and 2 reported costs per LYG and either costs per quality-adjusted LYG (26) or costs per disability-adjusted LYG (27). Seven studies were published in 1993–1999 (18, 25, 28–32), 13 in 2000–2004 (20, 24, 27, 33–42), and 12 in 2005–2009 (19, 21–23, 26, 43–47). Fourteen analyses evaluated colorectal cancer screening in North America (13 in the US population and one in the Canadian population). Ten studies were

conducted for European countries, 5 for Asia, and 3 for Australia. The majority of studies used a third-party payer perspective, and approximately half evaluated lifetime costs and benefits; the remainder evaluated time horizons from 10 to 50 years. Three percent and 5% were the most commonly used discount rates. Only 3 United Kingdom studies used a different discount rate (25, 26, 45). Adherence assumptions ranged from 40% to 100%, with adherence between 60% and 70% and 100% adherence most often used. Only 2 studies considered differential adherence between screening tests.

The studies differed widely in the screening strategies evaluated. US and Asian studies generally assessed many colorectal cancer screening strategies and typically evaluated annual FOBT as opposed to biennial FOBT. European and Australian studies more often included biennial FOBT. The strategies that have long been recommended in US guidelines, namely, annual and biennial unrehydrated guaiac FOBT, 5-yearly sigmoidoscopy, the combination of 5-yearly sigmoidoscopy and annual guaiac FOBT, and 10-yearly colonoscopy, were evaluated most frequently, each in at least 9 studies. Because it is impossible to examine all analyzed colorectal cancer screening strategies in this review, we focused on these established colorectal cancer screening strategies when addressing the first 2 research questions. For guaiac FOBT, we focused on Hemoccult II (Beckman Coulter, Inc., Brea, California) because this test was evaluated in large randomized trials and has therefore been evaluated most in the cost-effectiveness studies. If a study did not explicitly mention the guaiac FOBT under consideration, we assumed it was Hemoccult II.

Web Table 2 gives a more detailed overview of assumptions for the 12 models that evaluated at least the strategies of annual guaiac FOBT, 5-yearly sigmoidoscopy, and 10-yearly colonoscopy. Nine of 12 models explicitly simulate the natural history of colorectal cancer, but only 4 allow for multiple adenomas within one individual and explicitly simulate different parts of the gastrointestinal tract. Eight models assume that all colorectal cancers arise from adenomas, whereas 2 assume that 15%–30% of colorectal cancers arise without a precursor lesion.

The models differ most strongly on the dwell time, with estimates ranging from 5 to 87 years. These dwell times reflect the average time it would take an adenoma to become cancer in the absence of death. In reality, the faster-growing adenomas are mainly the ones that become cancer in a person's lifetime, so the average time a diagnosed cancer has been present is shorter than this average, particularly in the models with long adenoma dwell times. Many of the included studies acknowledge that dwell time is the most uncertain parameter in their model. The difference in dwell time seems to arise from the modeling philosophy followed when estimating adenoma dwell time. Short adenoma dwell times were from models that directly input a dwell time (distribution) based on assumption or expert opinion, whereas the longer adenoma dwell times resulted from models that did not directly input dwell time but rather simulated probabilities of transitioning through a series of health states. The values of these transition probabilities were obtained by

calibrating the models to data on adenoma prevalence in autopsy studies and polyp growth rates in observational studies.

With respect to test characteristics, the models are in agreement regarding endoscopy sensitivity. However, sensitivity of guaiac FOBT for cancer varies from 25% to 60% between the models. These estimates all pertain to the Hemoccult II test, but differences in rehydration of the test between the models may explain some of the difference in assumed characteristics. Whether guaiac FOBT screening was based on unrehydrated or rehydrated analysis was often not reported in the studies.

As a result of the described differences in model assumptions, the colorectal cancer mortality reduction is also strikingly different from model to model. The mortality reduction from annual guaiac FOBT varies from 18% to 80%, that from 5-yearly sigmoidoscopy from 23% to 68%, that from 10-yearly colonoscopy from 39% to 90%, and that from the combination of annual guaiac FOBT and 5-yearly sigmoidoscopy from 71% to 88%. There is even greater variety in test costs between the models. Translated to 2009 US dollars, guaiac FOBT costs \$1 in one model compared with \$59 in another, sigmoidoscopy \$43 compared with \$622, and colonoscopy \$80 compared with \$1,570. Even when looking at US-based studies only, test costs still vary from \$5 to \$59 for guaiac FOBT, \$149 to \$622 for sigmoidoscopy, and \$533 to \$1,570 for colonoscopy. Although we adjusted for the year of the study by updating all cost estimates to 2009 dollars, doing so does not fully account for differences by year (or for differences by setting) because nominal Medicare reimbursement rates for screening procedures have not increased over time while costs in other settings have.

Question 1: Costs and LYGs of established screening strategies compared with no screening

The estimated effectiveness of screening, measured in discounted LYGs compared with no screening, differed considerably between the studies (Table 1). For example, the LYGs with annual FOBT ranged from 0.006 in the study that found the smallest effectiveness to 0.160 in the study that found the greatest effectiveness, an almost 30-fold difference. Part of this difference can be explained by differences in study design: the first study looked at costs and effects on the level of a population cohort (including individuals from 0 to 100 years of age), whereas the latter study looked at a cohort of only those aged 50 years. Because costs and effects of screening are accumulated mostly in the population aged 50–75 years, dividing the costs over a total population cohort results in significantly lower per-person costs and effects than when dividing over the number of persons aged 50 years only. However, differences in study design were insufficient to explain most of the differences in costs and effectiveness between studies. For example, 2 studies evaluated annual FOBT screening in a US cohort of persons aged 50 years followed for life, assuming 100% adherence with screening (37, 41). The LYGs with this strategy varied from 0.019 to 0.100 across models, a more than 5-fold difference.

Table 1. Discounted Life-years Gained, Costs, and Costs per Life-year Gained of Established Screening Strategies for Colorectal Cancer Compared With no Screening

Study: First Author, Year (Reference No.) ^a	Annual gFOBT			Biennial gFOBT			Flexible Sigmoidoscopy Every 5 Years			Flexible Sigmoidoscopy Every 5 Years + Annual gFOBT			Colonoscopy Every 10 Years		
	LYG	Cost	Cost/LYG	LYG	Cost	Cost/LYG	LYG	Cost	Cost/LYG	LYG	Cost	Cost/LYG	LYG	Cost	Cost/LYG
Flanagan, 2003 (34)	0.025	328	13,100	0.016	185	11,600									
Frazier, 2000 (35)	0.042	825	19,600				0.039	751	19,500	0.059	1,523	26,000	0.048	1,514	31,700
Gyrd-Hansen, 1998 (28)	0.006	36	6,400	0.004	20	5,300									
Hassan, 2007 (44)													0.036	-10	CS
Helm, 2000 (36)				0.014	72	4,000									
Khandker, 2000 (37)	0.100	2,519	25,600				0.090	1,904	22,500	0.110	3,553	32,400	0.110	3,487	31,500
Lejeune, 2004 (38)				0.029	126	4,400									
Leshno, 2003 (39)	0.160	-158	CS							0.182	-324	CS	0.180	-26	CS
Macafee, 2008 (45)				0.009	30	3,400									
O'Leary, 2004 (40)													0.021	2,883	9,800
Pickhardt, 2007 (19)													0.046	495	10,700
Shimbo, 1994 (32)	0.013	750	56,300												
Song, 2004 (20)	0.056	508	9,100				0.048	940	19,600	0.063	1,347	21,500	0.062	1,330	21,500
Sonnenberg, 2000 (41)	0.019	285	15,100				0.036	2,059	56,600				0.080	1,355	17,000
Steele, 2004 (42)	0.008	94	11,700				0.012	132	11,400				0.019	515	26,800
Stone, 2004 (27)				0.001	23	15,500									
Tappenden, 2007 (26)				0.026	147	5,700									
Tsoi, 2008 (46)	0.094	651	7,000				0.110	989	9,000				0.159	1,281	8,100
Vijan, 2007 (23)	0.029	202	6,800				0.031	948	30,100	0.050	1,138	22,800	0.053	544	10,200
Wagner, 1995 (18)	0.059	1,086	18,500				0.036	705	19,700	0.067	1,461	21,700	0.059	1,028	17,300
Whynes, 1998 (25)				0.017	76	4,600									
Wu, 2006 (47)	0.025	-27	CS				0.014	35	2,500				0.025	-2	CS
Zauber (MISCAN), 2009 (22)	0.066	-88	CS				0.077	102	1,300	0.085	133	1,600	0.087	205	2,400
Zauber (SimCRC), 2009 (22)	0.060	-305	CS				0.069	-231	CS	0.087	-315	CS	0.094	-207	CS
Zauber (CRC-SPIN), 2009 (22)	0.064	-471	CS				0.080	-375	CS	0.095	-413	CS	0.106	-403	CS

Abbreviations: Cost, net costs (in US dollars) of the screening strategy compared with no screening; CS, cost-saving; gFOBT, guaiac fecal occult blood test with Hemoccult II (Beckman Coulter, Inc., Brea, California); LYG, life-year gained compared with no screening.

^a The paper by Zauber et al. (22) contained analyses from 3 independently developed colorectal cancer models: MISCAN, SimCRC, and CRC-SPIN.

Web Table 2 indicates several reasons for this difference. First, the sensitivity of guaiac FOBT was assumed to be 40% in the Sonnenberg et al. study (with 0.019 LYG) compared with 60% in the Khandker et al. study (with 0.100 LYG), a 1.5-fold difference. Furthermore, Khandker et al. assume an additional 10% sensitivity for adenomas with each test use; in the Sonnenberg et al. study, no sensitivity for adenomas is reported. With a 10% sensitivity for adenomas each year, an adenoma has a more than 65% probability of being detected after 10 consecutive guaiac FOBTs, assuming conditional independence of repeat testing (which all models seem to assume). This additional 65% probability of detection of an adenoma can be expected to give substantial extra LYGs with screening compared with no extra benefit from adenoma detection in the Sonnenberg et al. model.

Despite these differences, all studies consistently found that colorectal cancer screening was cost-effective compared with no screening for each of the established screening strategies (Table 1): for all models, the costs per LYG of the established screening strategies were less than \$60,000, and only 2 were more than \$50,000. Six models found one or more colorectal cancer screening strategies to be cost-saving. Biennial guaiac FOBT was the only strategy not found to be cost-saving. However, none of the models that found one or more screening strategies to be cost-saving evaluated biennial guaiac FOBT. If they had, biennial guaiac FOBT would have likely been found cost-saving as well. The costs per LYG of each screening strategy differed widely between the studies. Compared with those for no screening, costs per LYG for annual guaiac FOBT varied from cost-saving to more than \$56,000, for biennial guaiac FOBT from \$3,400 to \$16,000, for 5-yearly sigmoidoscopy from cost-saving to \$57,000, for the combination of 5-yearly sigmoidoscopy and annual guaiac FOBT from cost-saving to \$26,000, and for colonoscopy from cost-saving to \$34,000.

No distinctive pattern was found between the cost-effectiveness ratios in US studies compared with non-US studies. The range of cost-effectiveness ratios from US studies was so wide that it included the ranges reported in studies outside the United States. For example, the cost per LYG of annual FOBT compared with no screening ranged in US studies from cost-saving to almost \$26,000, whereas the same ratio in the European studies ranged from \$6,400 to almost \$12,000.

Although the previous review for the USPSTF already concluded that colorectal cancer screening was highly cost-effective (4), the cost-effectiveness of colorectal cancer screening seems to have further improved over time. The cost-effectiveness ratios in the US studies published after the review for USPSTF (19, 20, 22, 23) were generally lower (i.e., more favorable) compared with those reported in the review (18, 35, 37, 41, 48). For example, the cost per LYG of colonoscopy screening compared with no screening ranged from \$13,000 to \$32,000 in the older studies versus cost-saving to \$19,000 in the newer studies. Similar findings were observed for the other strategies. One study explicitly reappraised the cost-effectiveness of colorectal cancer screening over time in light of the rising colorectal cancer treatment costs (49). This study showed that the costs per

LYG of colorectal cancer screening had indeed decreased over time as a result of an increase in treatment costs; guaiac FOBT and FIT changed from being highly cost-effective compared with no screening in the past to being cost-saving in the present.

Question 2: Do cost-effectiveness analyses point to an optimal strategy for screening?

Eight models evaluated all 4 screening strategies that have been recommended in the United States since 1997: annual guaiac FOBT, 5-yearly sigmoidoscopy, a combination of 5-yearly sigmoidoscopy and annual guaiac FOBT, and 10-yearly colonoscopy (Table 2). The models differed with respect to which strategy was most effective in terms of discounted LYGs: 5 found 10-yearly colonoscopy to be most effective (22, 23, 37) and 3 the combination of sigmoidoscopy and FOBT (18, 20, 35).

When the 3 models that found the combination strategy most effective are compared with the 5 that found colonoscopy most effective, an important difference in assumptions for adenoma sensitivity of guaiac FOBT is evident (Web Table 2). The former studies all assume a sensitivity for small adenomas of 8%–10%, whereas the latter studies assume sensitivities for small adenomas of 2%–6%. Although this difference in sensitivity may seem minor, a 5% sensitivity for small adenomas leads to less than 40% of adenomas being detected after 10 consecutive FOBTs compared with more than 65% with 10% sensitivity (again assuming conditional independence of repeat testing). Of the studies that found colonoscopy to be the most effective test, the Khandker et al. study (Web Table 2) had the highest sensitivity for small adenomas with guaiac FOBT (6%). In this study, the LYGs with the combination of flexible sigmoidoscopy and guaiac FOBT are almost identical to those for colonoscopy, supporting our argument that the sensitivity of guaiac FOBT for adenomas is an important determinant of the relative effectiveness of colonoscopy versus the combination of flexible sigmoidoscopy and guaiac FOBT.

At the commonly used willingness-to-pay threshold of \$50,000 per LYG, colonoscopy was the preferred method of screening in 4 of the 8 analyses, the combination strategy of annual guaiac FOBT and sigmoidoscopy in 2, and annual FOBT and sigmoidoscopy alone in 1 each. Besides the differences in effectiveness between the tests described before, the test costs are important drivers of these differences in optimal strategies. For example, endoscopy costs in the study by Song et al. (Web Table 2) are considerably higher compared with the costs of FOBT, whereas the additional benefit of endoscopy over FOBT is negative (sigmoidoscopy) to small (10% additional mortality reduction for colonoscopy), explaining why FOBT was found to be the optimal strategy. In the Khandker et al. study, we observe the opposite, with sigmoidoscopy costs being quite low compared with those of FOBT or colonoscopy, explaining why that strategy is the optimal one.

An additional 5 studies also evaluated all these strategies with the exception of the combination of sigmoidoscopy and FOBT (Table 3). When only the remaining 3 strategies of annual guaiac FOBT, 5-yearly sigmoidoscopy, and

Table 2. Preferred Strategy From Incremental Cost-effectiveness Analysis (US Dollars) at Different Thresholds of Willingness-to-Pay for a Life-year Gained for the 7 Models That Evaluated the 4 US Colorectal Cancer Screening Strategies Recommended Since 1997

Study: First Author, Year (Reference No.) ^a	Willingness-to-Pay for a LYG			
	\$10,000/LYG	\$20,000/LYG	\$50,000/LYG	\$100,000/LYG
Frazier, 2000 (35)	No screening	FSIG	FSIG + gFOBT	FSIG + gFOBT
Khandker, 2000 (37)	No screening	No screening	FSIG	COL
Song, 2004 (20)	gFOBT	gFOBT	gFOBT	gFOBT
Vijan, 2007 (23)	gFOBT	COL	COL	COL
Wagner, 1995 (18)	No screening	COL	COL	FSIG + gFOBT
Zauber (MISCAN), 2009 (22)	gFOBT	FSIG + gFOBT	FSIG + gFOBT	COL
Zauber (SimCRC), 2009 (22)	COL	COL	COL	COL
Zauber (CRC-SPIN), 2009 (22)	COL	COL	COL	COL

Abbreviations: COL, 10-yearly colonoscopy; FSIG, 5-yearly flexible sigmoidoscopy; gFOBT, annual guaiac fecal occult blood test with Hemoccult II (Beckman Coulter, Inc., Brea, California); LYG, life-year gained.

^a The paper by Zauber et al. (22) contained analyses from 3 independently developed colorectal cancer models: MISCAN, SimCRC, and CRC-SPIN.

10-yearly colonoscopy were considered, all 12 studies found colonoscopy to be the most effective. Furthermore, 8 of the 12 studies found colonoscopy to be the preferred method if \$50,000 per LYG was willing to be paid. FOBT and sigmoidoscopy were found to be the preferred strategy in 2 studies each.

Question 3: Cost-effectiveness of newly developed screening tests compared with established tests

Since the review for the USPSTF was published in 2002 (4), FIT, stool DNA testing, and CTC have been deemed acceptable options for colorectal cancer screening,

at least by some societies (5). Capsule endoscopy is not mentioned in any of the average-risk colorectal cancer screening guidelines.

Seven studies have evaluated FIT screening (Table 4) (22, 32, 33, 43, 49). Three evaluated a hypothetical “average” FIT, whereas the remaining studies all evaluated a different FIT. Sensitivity for cancer and specificity were comparable between studies. Four studies found FIT to be cost-saving compared with no screening, and all showed acceptable costs per LYG compared with no screening. Approximately half of the studies found FIT to be a dominant screening strategy, providing more life-years for lower costs than the comparator strategies. The other half found that FIT was

Table 3. Preferred Strategy From Incremental Cost-effectiveness Analysis (US Dollars) at Different Thresholds of Willingness-to-Pay for a Life-year Gained for the 7 Models That Evaluated Annual Fecal Occult Blood Testing, 5-Yearly Sigmoidoscopy, and 10-Yearly Colonoscopy

Study: First Author, Year (Reference No.) ^a	Willingness-to-Pay for a LYG			
	\$10,000/LYG	\$20,000/LYG	\$50,000/LYG	\$100,000/LYG
Frazier, 2000 (35)	No screening	FSIG	gFOBT	gFOBT
Khandker, 2000 (37)	No screening	No screening	FSIG	COL
Song, 2004 (20)	gFOBT	gFOBT	gFOBT	gFOBT
Sonnenberg, 2000 (41)	No screening	COL	COL	COL
Steele, 2004 (42)	No screening	FSIG	FSIG	COL
Tsoi, 2008 (46)	COL	COL	COL	COL
Vijan, 2007 (23)	gFOBT	COL	COL	COL
Wagner, 1995 (18)	No screening	COL	COL	COL
Wu, 2006 (47)	gFOBT	gFOBT	COL	COL
Zauber (MISCAN), 2009 (22)	gFOBT	COL	COL	COL
Zauber (SimCRC), 2009 (22)	COL	COL	COL	COL
Zauber (CRC-SPIN), 2009 (22)	COL	COL	COL	COL

Abbreviations: COL, 10-yearly colonoscopy; FSIG, 5-yearly flexible sigmoidoscopy; gFOBT, annual guaiac fecal occult blood test with Hemoccult II (Beckman Coulter, Inc., Brea, California); LYG, life-year gained.

^a The paper by Zauber et al. (22) contained analyses from 3 independently developed colorectal cancer models: MISCAN, SimCRC, and CRC-SPIN.

Table 4. (Incremental) Cost-effectiveness of Newly Developed Colorectal Cancer Screening Strategies Compared With no Screening and With Established Tests

Strategy and Study: First Author, Year (Reference No.) ^a		Study Details		Comparator Strategies	CER ^b	ICER ^{b,c}
FIT		Test Used ^d	Sensitivity for Cancer, Specificity	Test Costs ^b		
Berchi, 2004 (33)		Magstream	82, 96	12	gFOBT	3,900
Chen, 2007 (43)		OC-SENSOR	64.6–84.6, 77.1–97.1	3	No screening	CS Dominant
Parekh, 2008 (49)		Insure FIT	76, 91	25	gFOBT, COL, stool DNA test	CS Dominant
Shimbo, 1994 (32)		Reversed passive hemagglutination assay	48.1–84.3, 99	13	gFOBT	25,900 Dominant
Zauber, 2009 (MISCAN) (22)		Mix of tests	70, 95	24	gFOBT, SENSA, COL, FSIG, CTC, FSIG + gFOBT	800 Dominated by SENSA
Zauber, 2009 (SimCRC) (22)		Mix of tests	70, 95	24	gFOBT, SENSA, COL, FSIG, CTC, FSIG + gFOBT	CS Dominated by SENSA
Zauber, 2009 (CRC-SPIN) (22)		Mix of tests	70, 95	24	gFOBT, SENSA, COL, FSIG, CTC, FSIG + gFOBT	CS Dominated by SENSA
Stool DNA		Test Used ^d	Sensitivity for Cancer, Specificity	Test Costs ^b		
Leshno, 2003 (39)		PreGen-Plus	91, 90	86	gFOBT, COL, FSIG + gFOBT	600 Dominated by COL and FSIG + gFOBT
Parekh, 2008 (49)		PreGen-Plus	65, 95	879	gFOBT, COL, FIT	17,500–23,700 Dominated by all tests
Wu, 2006 (47)		PreGen-Plus	52, 94	53	gFOBT, FSIG, COL	9,300–11,900 Dominated by all tests
Zauber (MISCAN), 2007 (52)		PreGen-Plus	70, 96	375	gFOBT, SENSA, COL, FSIG, FIT, FSIG + gFOBT	12,200–23,900 Dominated by all tests
Zauber (SimCRC), 2007 (52)		PreGen-Plus	70, 96	375	gFOBT, SENSA, COL, FSIG, FIT, FSIG + gFOBT	10,800–31,800 Dominated by all tests
CTC		Follow-up Interval	Sensitivity for Cancer, Specificity	Test Costs ^b		
Hassan, 2007 (44)		10 years, all findings	95, 86	97	FSIG, COL	CS Dominant vs. FSIG, ICER COL vs. CTC: 14,600
Ladabaum, 2004 (53)		10 years, all findings	95, 85	1,037	COL	36,300 Dominated by COL
Pickhardt, 2007 (19)		10 years, findings 6+ mm	95, 86	555	FSIG, COL	5,100 Dominant vs. FSIG, ICER COL vs. CTC: 74,200
Sonnenberg, 2000 (54)		10 years, all findings	80, 95	741	COL	17,800 Dominated by COL

Vijan, 2007 (23)	5 years, all findings	91, 91	707	gFOBT, COL, FSIG, FSIG + gFOBT	10,300–21,800	197,200
Zauber, 2009 (MISCAN) (22)	5 years, findings 6+ mm	84–92, 80–88	522	gFOBT, SENSAs, COL, FSIG, FIT, FSIG + gFOBT	9,500–10,200	Dominated by COL, FSIG + gFOBT
Zauber, 2009 (SimCRC) (22)	5 years, findings 6+ mm	84–92, 80–88	522	gFOBT, SENSAs, COL, FSIG, FIT, FSIG + gFOBT	3,600–4,200	Dominated by COL, FSIG + gFOBT
Zauber, 2009 (CRC-SPIN) (22)	5 years, findings 6+ mm	84–92, 80–88	522	gFOBT, SENSAs, COL, FSIG, FIT, FSIG + gFOBT	1,900–2,100	Dominated by COL, FSIG + gFOBT

Abbreviations: CER, cost-effectiveness ratio compared with no screening; COL, colonoscopy; CS, cost-saving; CTC, computed tomographic colonography; FIT, fecal immunochemical test; FSIG, flexible sigmoidoscopy; gFOBT, guaiac fecal occult blood test with Hemoccult II (Beckman Coulter, Inc., Brea, California); ICER, incremental cost-effectiveness ratio; SENSAs, guaiac fecal occult blood test with Hemoccult SENSAs (Beckman Coulter).

^a The paper by Zauber et al. (22) contained analyses from 3 independently developed colorectal cancer models: MISCAN, SimCRC, and CRC-SPIN.

^b Values are expressed as 2010 US dollars.

^c Dominant indicates that the test of interest (i.e., FIT, stool DNA, or CTC) was more effective and less costly than the comparator strategies. Dominated indicates that the test of interest was less effective and more costly than the reported comparator strategies.

^d Insure FIT, Enterix Inc., Edison, New Jersey; Magstream, Fujirebio Inc., Tokyo, Japan; OC-SENSOR, Eiken Chemical Co. Ltd., Tokyo, Japan; PreGen-Plus, EXACT Sciences Corporation, Madison, Wisconsin.

dominated by a guaiac-based FOBT, namely, Hemoccult SENSAs (Beckman Coulter). This comparator strategy was not included in the former analyses, showing the dominance of FIT. This finding seems to indicate that FIT screening is not cost-effective compared with Hemoccult SENSAs. However, the dominance of Hemoccult SENSAs is based on US cost estimates for FIT and guaiac FOBT, where the rates of reimbursement for guaiac FOBT are very low at \$4.50 compared with \$22 for FIT. In other parts of the world, the unit costs of guaiac FOBT and FIT are closer (32, 33, 50). A more detailed cost-effectiveness analysis of FIT by one of the models that found FIT to be dominated shows that, at a cost of \$17.25 per test, FIT would be a cost-effective alternative to Hemoccult SENSAs (at a per-test cost of \$4.50) (51).

Stool DNA testing was evaluated in 5 analyses (Table 4) (39, 47, 49, 52). All studies evaluated the PreGen-Plus (EXACT Sciences Corporation, Madison, Wisconsin), although the different sensitivities and specificities between the studies indicate that different versions of the test have been evaluated. The costs per LYG compared with no screening varied from \$600 to almost \$32,000. All 5 models concluded that, with performance characteristics and test costs as of 2009, stool DNA testing is dominated by the established screening options and is therefore not cost-effective.

CTC was evaluated in 8 models (19, 22, 23, 44, 53, 54). Half evaluated 5-yearly CTC and the other half 10-yearly CTC. In 4 studies, a follow-up colonoscopy was assumed to be performed for individuals with any finding at CTC; in the other 4 studies, a follow-up colonoscopy was assumed to be performed for only those individuals with findings 6 mm or larger at CTC. CTC was deemed cost-effective compared with no screening, with costs per LYG varying from cost-saving to \$36,300. However, CTC was not found to be cost-effective in 5 of the analyses because it was dominated by the established screening strategies. At a willingness-to-pay threshold of \$50,000 per LYG, CTC would be the recommended strategy in only one of the analyses (19).

To date, the cost-effectiveness of capsule endoscopy has been evaluated in only one known study (55). This study showed that 10-yearly screening with capsule endoscopy costs \$31,300 per LYG compared with no screening. However, 10-yearly screening with colonoscopy was both more effective and less costly than capsule endoscopy, and capsule endoscopy was therefore dominated. Only if capsule endoscopy was able to increase screening participation by 30% would capsule endoscopy be a cost-effective alternative for colorectal cancer screening.

DISCUSSION

This review confirms the findings of the earlier USPSTF review (4)—that colorectal cancer screening is cost-effective compared with no screening, irrespective of the screening modality used. Moreover, it shows that there is a tendency toward more favorable costs per LYG with colorectal cancer screening in more recent years. However, as in the previous review, no single strategy is consistently found to be the most effective or to be preferred for a given willingness to pay per LYG.

Web Table 2 indicates several reasons for the disparate findings between studies. Despite recommendations from the Panel on Cost-Effectiveness in Health and Medicine (56), this table shows that included studies still differ widely with respect to perspective, population, time horizon, and discount rate. These differences potentially explain the differences in model results. However, even 2 models evaluating the same strategy of annual FOBT, both from a third-party-payer perspective, looking at a cohort aged 50 years followed for a lifetime, discounting costs and results at 3%, arrived at very different results (37, 41).

A closer look at these studies (Web Table 2 Continued) reveals that the costs for FOBT are 2–3 times higher in the first study than in the second, while FOBT sensitivity is 60% and 40%, respectively. These differences alone may explain a large portion of the observed differences, and we have not yet considered differences in modeling of the natural history of disease. Comparing the natural history assumptions between the models proves difficult. The Sonnenberg et al. study reports an adenoma incidence of 1% per year but does not report on progression parameters from adenoma to cancer or on progression from early to late cancer. The models differ with respect to how the effectiveness of screening is modeled: in the Sonnenberg et al. model, benefit of screening is an explicit model parameter of 18% for early detection and 75% for adenoma removal; in the Khandker et al. model, the screening benefit is the result of the improved stage distribution with screening and prevention of colorectal cancer with removal of adenomas. Thus, even when considering just 2 models, it proves impossible to determine exactly which model parameters are responsible for the disparity in model outcomes. For more models, it would become only more difficult.

The model differences in adenoma dwell time and unit test costs are most striking. The former difference seems to occur from disparities in modeling philosophy between studies, where short adenoma dwell times are based on assumption or expert opinion and long adenoma dwell times were calibrated to observed adenoma prevalence and polyp growth rates. Although the calibrated dwell times have a more empirical basis, these estimates often do not allow for heterogeneity in adenoma dwell times, implying a very long adenoma duration for all adenomas. The fact that there was only very little attenuation of the protective effect of sigmoidoscopy screening even 12 years after having the test (57) indicates that an adenoma dwell time of 12 years or less is unlikely and that adenoma dwell times are indeed long for most adenomas.

In an attempt to reconcile differences between models and determine what causes model differences, the Institute of Medicine (58) and the National Cancer Institute's Cancer Intervention and Surveillance Modeling Network (59) have offered platforms for modelers to cooperate with each other and standardize selective model inputs such as costs and test characteristics of their models. These exercises showed that with standardization of these model inputs, the model outcomes become more similar. Although the models continue to differ on the absolute costs and benefits of colorectal screening, the relative costs and effects of one screening strategy compared with another become similar (58, 60).

Although no more than 2 of 5 models could agree on the preferred colorectal cancer screening strategy at a willingness-to-pay threshold of \$50,000 with original model assumptions in the Institute of Medicine workshop, all 5 models recommended the same screening strategy with standardized model assumptions (58). However, these standardized assumptions were not evidence based, so no conclusions concerning the optimal colorectal cancer screening strategy can be reached based on these results.

A joint analysis of CTC screening by the 3 colorectal cancer models in the Cancer Intervention and Surveillance Modeling Network group found disparate estimates for costs per LYGs of all screening strategies. However, all 3 models were consistent in their estimated costs per LYG of CTC screening relative to the other tests (22). In addition, the models reached similar conclusions concerning what level of test costs would make CTC screening cost-effective.

The fact that different models reach similar conclusions when model inputs are standardized indicates uncertainty regarding what the values of these inputs should be. The differences between models (or model inputs, such as costs) may very well reflect the fact that they were developed for different settings, for example, different countries or payer settings. If cost-effectiveness studies publish sufficient model outcomes, local decision makers should be able to judge at least the face value of the models and translate the outcomes to their own specific setting in which they operate.

An example of such an outcomes table has recently been suggested (61). Cost-effectiveness of a colorectal cancer screening test is only one of the factors influencing the decision to implement a colorectal cancer screening program. An outcomes table would provide decision makers with additional factors such as the number of colonoscopies required and the number of harms, such as the number of false-positive test results and overdiagnosed cases (i.e., detection of cases that would not have been detected without screening). Furthermore, with sufficient details, policy makers could apply local costs to the model outputs on tests and colorectal cancer diagnoses and estimate cost-effectiveness of colorectal cancer screening in their particular setting. However, since no single colorectal cancer screening strategy emerges as the most cost-effective, it is likely that the cost-effectiveness of all established colorectal cancer screening strategies is comparable and that other factors such as patient acceptability, screening compliance, capital versus operational costing, and colonoscopy and human resources required will determine the final verdict with respect to which colorectal cancer screening program to implement.

Differences in local preferences for colorectal cancer screening are already reflected in the different colorectal cancer screening policies in place throughout the world. In Australia and Japan, colorectal cancer screening programs are based on FIT testing. The European Union recommends only guaiac FOBT screening and none of the other tests because the effectiveness of these tests was not yet established by randomized controlled trials at the time of recommendation. Despite this recommendation, the colorectal cancer screening strategies currently being implemented in Europe differ widely between countries. Of 17 countries

with colorectal cancer screening, 10 have adopted only FOBT, 6 use both FOBT and endoscopy, and only 1 uses colonoscopy (9). In the United States, all established screening strategies, and in some guidelines even the newly developed screening strategies of stool DNA and CTC, are recommended for the general population (5, 6). The FOBT and endoscopic tests are currently reimbursed by Medicare and most other health care insurers (62), so US individuals can choose their preferred screening strategy.

Availability of (high-quality) resources for colonoscopy and population preferences are expected to be the most important determinants of the final decision on which colorectal cancer screening program to implement. Even without a (colonoscopy) screening program, several countries already have a waiting list for colonoscopy, with waiting times of more than 6 months reported (63–65). Implementing a guaiac FOBT screening pilot has been shown to increase colonoscopy activity by 21%–31% (66). Screening programs with FIT or colonoscopy will only further increase the demand for colonoscopy. However, even when sufficient colonoscopy capacity is available, some countries may still opt out of implementing an invasive colonoscopy screening program, despite colonoscopy being the most accurate test. Some countries might prefer to offer a 2-step approach, with a less accurate, but also less invasive strategy—for example, FOBT—to stratify the population before offering invasive colonoscopies to only those at higher risk (i.e., with a positive result on the noninvasive test). Population preferences are important to consider when offering screening because, in the end, any screening test can be effective and thus cost-effective only if the population adheres to it.

The modeling of population adherence is an important limitation of all of the included cost-effectiveness analyses. Thirty of 32 models assumed the same adherence for all screening tests. The 2 cost-effectiveness analyses that looked at differential adherence among screening tests both assumed a higher adherence for FOBT compared with endoscopy (40, 47). This assumption is supported by recent results from a randomized controlled trial in the Netherlands that showed a 61.5% initial uptake with FIT, a 49.5% uptake with guaiac FOBT, and only a 32.4% uptake with sigmoidoscopy (67). However, these results are for initial adherence only. FOBT is generally repeated every other year, whereas the recommended interval for endoscopy screening is 5–10 years. To be effective, high adherence with repeat FOBT is necessary. Experience with mammography screening has shown that, with frequent testing, adherence may decline over time (68). It is possible that a similar pattern may occur for FOBT.

Even in a country such as the United States, where individuals can generally choose the colorectal cancer screening test they prefer, adherence to colorectal cancer screening is far from perfect, with an estimated 50% of the population having had an FOBT within the past year and/or endoscopy within the past 10 years (69). This lack of adherence is one of the reasons that new tests such as FIT, stool DNA, CTC, and capsule endoscopy are being developed.

The included studies clearly show that, from a cost-effectiveness point of view, only FIT may currently be ready

for widespread implementation in the general population. There are many caveats regarding this conclusion. First, there is no such thing as a FIT test. Instead, several FITs are currently available, each with its own performance characteristics and costs (70). Cost-effectiveness analyses generally evaluate just one of the available FITs or a hypothetical FIT, with test characteristics that average those available in the literature. In this review, we simply paired the studies evaluating FIT together without considering which FIT was evaluated. Similar problems occur with stool DNA testing, with several versions of the test being available and new ones being developed (71–73).

CTC performance characteristics will highly depend on the scan used as well as the expertise of the radiologist. However, even when considering the same machine and radiologist, several other aspects drastically influence the cost-effectiveness of CTC, such as the criterion for referral for a follow-up colonoscopy, the screening interval, and the cost setting (e.g., public vs. private insurer). Again, it was beyond the scope of this review to extensively examine the details concerning these settings between studies, but these factors will influence the study results considerably. Reassuringly, irrespective of the referral threshold or screening interval considered, CTC was shown not to be cost-effective compared with colonoscopy in the majority of studies.

Despite not being cost-effective compared with the established tests, a situation exists where implementation of the newly developed colorectal cancer screening tests can still be considered. If the tests would entice a previously unscreened segment of the population to adhere to screening, the no-screening strategy would be the relevant comparator for these people. Since the costs per LYG of these new tests are favorable compared with no screening, the new tests could, in that case, be recommended. Although there is some evidence that patients prefer CTC or stool DNA testing over the established screening strategies, no evidence currently shows that any of the newly developed tests increase colorectal cancer screening uptake among subjects unwilling to perform any of the established tests.

In conclusion, this review shows that colorectal cancer screening is cost-effective compared with no screening, but no screening method can be identified as the most effective or is the preferred strategy for a given willingness to pay per LYG. This finding indicates that the cost-effectiveness of the established colorectal cancer screening tests is likely to be comparable and that factors other than cost-effectiveness, such as population preferences and colonoscopy resources, might be more important in the decision about which colorectal cancer screening program to introduce. The newly developed screening tests of stool DNA testing, CTC, and capsule endoscopy are not yet cost-effective compared with the established screening options.

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