# Cost-effectiveness Analyses of Colorectal Cancer Screening: A Systematic Review for the U.S. Preventive Services Task Force

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## Epidemiology

Colorectal cancer (CRC) is the second leading cause of cancer mortality in the United States, with over 57,000 deaths expected in 2001.[1] Evidence from several studies suggests that screening for, detecting, and removing colorectal cancers and pre-cancerous adenomatous polyps can reduce CRC incidence and CRC-related mortality.[2] Questions remain, however, about which method or methods of screening should be employed, how frequently screening should be performed, and at what ages screening should begin and end. In addition, health care policy makers wish to know not only whether screening is effective but also whether it is cost-effective. Existing clinical trials of colorectal cancer screening have not directly compared different screening approaches and have not tested different starting and stopping ages. In the absence of such data, cost-effectiveness analyses using simulation models may provide the best information for answering such questions.[3]

To help inform the U.S. Preventive Services Task Force's (USPSTF) deliberation on recommendations regarding screening for colorectal cancer, we examined 3 questions:

(1) What is the cost-effectiveness of colorectal cancer screening by any method compared to no screening? (2) Can we use incremental cost-effectiveness data to determine the relative effectiveness and cost-effectiveness of different screening options and thus determine if there is a preferred strategy for screening? (3) What is the incremental cost-effectiveness of continuing screening to age 85 compared with stopping screening at age 70, 75, or 80? What is the incremental cost-effectiveness of starting screening at age 40 or 45 compared with age 50?

## Methods

The principles and rationale for our approach to conducting systematic reviews of cost-effectiveness studies have been described previously.[4] We searched the MEDLINE database and the British National Health Service Economic Evaluation Database (NHS EED) (available at: http://agatha.york.ac.uk/nhsdhp.htm) between January 1993 and September

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2001. (See Appendix A for search details.) We chose 1993 as a starting point because it was the year in which the first trial establishing strong evidence for the effectiveness of colorectal cancer screening was published.[5] To identify studies not captured by our database searches and studies that are ongoing or unpublished, we manually searched the reference lists of retrieved articles and contacted selected authors and experts in the field.

Two investigators reviewed titles and abstracts of publications identified by our literature searches. Using information in the abstracts, we excluded studies that were not cost-effectiveness or cost-utility analyses, including other types of economic evaluations that did not quantify the health outcomes achieved for a given cost; studies that reported only cost per patient screened, cost per cancer detected, or costs per death prevented; studies that did not contain original analyses; articles that did not address at least 1 of our 3 questions of interest; studies performed from perspectives other than the societal perspective or the perspective of public third-party payers; and studies that used cost or disease incidence estimates from outside the United States. When we encountered multiple publications reporting results from the same cost-effectiveness model, we included the most comprehensive analysis and used other papers for supplemental information.

When the decision about whether to include a study could not be made by reading the title or abstract, we evaluated the full article. Disagreements regarding study inclusion were resolved by consensus of the authors.

All authors reviewed each included article. Reviews focused on the assumptions of each study regarding the epidemiology and natural history of colorectal cancer; estimates of parameters related to the effectiveness of screening, including test accuracy, adherence rates, and complication rates; estimates of the costs of screening, diagnosis, and treatment; the proportion of cancers and cancer deaths prevented by screening; and the effect of varying key variables (sensitivity analyses).

For each study, we used available data to tabulate outcomes of life-years gained and costs per person for each of the major strategies under consideration: fecal occult blood testing (FOBT) annually; sigmoidoscopy every 5 years; combination of annual FOBT and sigmoidoscopy every 5 years; double-contrast barium enema (DCBE) every 5 years; and colonoscopy (every 10 years, at ages 55 and 65, or once-lifetime). The evaluated strategies were arrayed in order of effectiveness. Costs were updated to U.S. dollars in 2000 using the Consumer Price Index for medical care.

If 1 strategy was more costly and less effective than another strategy, it was considered strongly dominated. If a strategy was both less effective and had a higher cost-effectiveness ratio than another strategy, it was considered weakly dominated. Incremental cost-effectiveness ratios were then calculated for all non-dominated strategies, using the formula: (costs strategy 2 - costs strategy 1) / (life-years gained with strategy 2 - life-years gained with strategy 1).

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# Results

## Identification of Cost-effectiveness Analyses

Our initial searches identified 180 potentially relevant studies. On initial review of titles and abstracts, we excluded 159 articles that were clearly not related to our topic of interest. Of the 21 full articles retrieved and reviewed by the investigators, 6 met inclusion criteria. The reasons for exclusion of the remaining articles are given in Appendix B.

Through supplemental searches, we identified 2 additional studies that met our inclusion criteria. One was identified through manual searching of the

**Table 1. Study characteristics**

| Author | Wagner[6] | Frazier[10] | Khandker[9] | Sonnenberg[13] | Vijan[11] | Loeve[12] | Ness[8] |
|---|---|---|---|---|---|---|---|
| **Journal** | **Rozen book** | **JAMA** | **IJHTA** | **Ann Intern Med** | **Am J Med** | **JNCI** | **Am J Gastro** |
| Year | 1996 | 2000 | 2000 | 2000 | 2001 | 2000 | 2000 |
| Model Type | ? | Markov | Dynamic state transition | Markov | Markov | Microsimulation Model | Discrete-event stimulation Cost-utility analysis |
| Perspective | Societal | Societal | Unknown (appears societal) | Third party payer | Third party payer | ? | ? |
| Age Range for Screening | 50-85 | 50-85 | 50-85 | 50 - death | 50-85 | 50-75 | Single screening |
| Time Horizon | Lifetime | Lifetime | 35 years | Lifetime | Lifetime | Lifetime | Lifetime |
| **Key Biologic Assumptions** | | | | | | | |
| % Cancers from Adenomas | 70% | 100% | 100% | 100% | 75% | 100% | 100% |
| Polyp Dwell Time (Years) | 10 | NR | Variable | NR | 10 years | 20 years | 2 populations: one with mean of 26 years, other with mean of 52 years |
| Cancer Sojourn Time from Early to Late (Late to Symptoms) | 2 years (2 years) | NR | 5 years | NR | 2 years in localized, 1 year in regional | 5.3 years | 5.55 years |
| **Additional Features** | | | | | | | |
| Relevant Intervention(s) Considered | FOBT q1<br>FS q5<br>FOBT q1 + FS q5<br>BE q5<br>COL q10 | FOBT q1<br>FS q5<br>FOBT q1 + FS q5<br>BE q5<br>COL q10 | FOBT q1<br>FS q5<br>FOBT + FS, q1 + q5<br>BE q5<br>COL q10 | FOBT q1<br>FS q5<br>COL q10 | FOBT q1<br>FS q5<br>FOBT q1 + FS q5<br>COL @ ages 50 and 60 | FS every 5 years between ages 50-75 | Single COL ages 45-50, 50-54, 55-59, or 60-64 |

*Continued on page M–76*

**Table 1. Study characteristics *(continued)***

| Author | Wagner[6] | Frazier[10] | Khandker[9] | Sonnenberg[13] | Vijan[11] | Loeve[12] | Ness[8] |
|---|---|---|---|---|---|---|---|
| Discount Rate (%) | 5% | 3% | 3% | 3% | 3% | 3% | 3% |
| Was Adherence Modeled? | No | Yes | Yes (2 scenarios) | Yes | Yes | No | No |
| How Were Benefits Measured? | Costs per life-year saved; SEER data based on stage at diagnosis used to determine effect of treatment | Costs per life-year saved; SEER data based on stage at diagnos is used to determine effect of treatment | Costs per life-year saved; SEER data based on stage at diagnosis used to determine effect of treatment | Costs per life-year saved; most benefit from prevention; early detection reduces mortality by 18% | Costs per life-year saved; SEER data based on stage at diagnosis used to determine effect of treatment | Net costs per person and life-years gained per 1,000 persons | Cos per QALYs saved |
| **Adverse Effects** | | | | | | | |
| Source of Harms Data | Systematic review | 2 articles | Unclear | 2 articles | 2 articles | Non-systematic reviews | Multiple studies |
| Perforation Rate for COL (with Polypectomy) | 0.07 (NR) | NR | 0.85% * | 0.2% (0.38%) | 1/1000 | 0.2% (NR) | 0.1% (NR) |
| Bleeding Rate for COL (with Polypectomy) | NR | NR | NR | 0.15% (2.0%) | NR | NR | NR (0.3%) |
| Mortality Rate for COL per 100,000 exams (range), n | 5 (NR) | 5 (0.5-50) | 23.6 (12-35) | 10 (NR) | 7.5 (0-30) | NR | 20 (NR) |
| **Costs** | | | | | | | |
| Types of Costs Included | Direct | Direct | Direct | Direct | Direct | Direct | Direct |
| Sources for Cost Information | Medicare reimbursement data | Data from large HMO | Medicare and survey of private payers | Medicare cost data from 1998 | Data from Medicare and Kaiser Permanente | Estimates based on published literature | Medicare rates and previous studies |
| Cost of COL (with Polypectomy) | $285 ($434) | $1012 ($1519) | $438 - $670 ($702 - $981) | $695 ($1003) | $550 ($765) | $300 ($400) | $303 ($530) |

*Continued on page M–77*

**Table 1. Study characteristics *(continued)***

| Costs | Wagner[6] | Frazier[10] | Khandker[9] | Sonnenberg[13] | Vijan[11] | Loeve[12] | Ness[8] |
|---|---|---|---|---|---|---|---|
| Cost of FOBT | $10 | $38 | $7.50 - $10 | $3.50 | $17 | NA | NA |
| Cost of SIG | $80 | $279 | $94-$175 | $400 | $225 | $100 | NA |
| Cost of Care for Perforation (for Bleeding) | $35,000 | NR | $28,200 | $13,000 ($4360) | $20,000 | $30,000 | NR |
| Cost of Cancer Care | Early: $35,000<br>Late: $45,000 | Local: $22,000<br>Regional: $43,900<br>Distant: $58,300 | Local: $49,587<br>Regional: $79,857<br>Distant: $60,180 | $45,228 | Local: $60,000<br>Regional: $82,800<br>Distant: $73,000 | Initial $25,000 over 6 months | Initial<br>Local: $16,051<br>Regional: $1,944<br>Distant: $21,093 |
| | | | | | | Ongoing $2,200/year | Ongoing<br>Local: $425/year<br>Regional: $1,944/year<br>Distant: $21,209 |
| | | | | | | Terminal: $16,000 over 6 months | Terminal: $16,722 |
| Measured in U.S. Dollars From What Year? | 1995 | 1998 | 1994 | 2000 | 1999 | 1993 | 1998 |
| **Relevant Intermediate Outcomes** | | | | | | | |
| Sensitivity of a Single Test for Cancer (Detection of Large Polyps) | FOBT: 40-60% (10%) | FOBT: 33% (10%)<br>FS: 95%<br>BE: 70% (50%)<br>COL: 95% | FOBT: 60% (10%)<br>FS:NR<br>BE: 84% (82%)<br>COL: 97% (85%) | FOBT: 40% (NR) | FOBT: 30% local; 50% regional (5%) | COL: 95% (95%) | COL: 95% (85%) |
| % Polyps and Cancers Reachable by SIG | 50% | Variable | 70% | 45% | 55% | ? | NA |

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**Table 1. Study characteristics *(continued)***

| Relevant Intermediate Outcomes | Wagner[6] | Frazier[10] | Khandker[9] | Sonnenberg[13] | Vijan[11] | Loeve[12] | Ness[8] |
|---|---|---|---|---|---|---|---|
| % Mortality Reduction from Screening | FOBT: 28%<br>FS: NR<br>FOBT + FS: NR<br>BE: NR<br>COL: NR | FOBT: 55%<br>FS: 40%<br>FOBT + FS: 71%<br>BE: 47%<br>COL: 64% | FOBT: 80%<br>FS: 69%<br>FOBT + FS: 88%<br>BE: 89%<br>COL: 90% | FOBT: 18%<br>FS: 34%<br>FOBT + FS: NR<br>BE: NR<br>COL: 90% | FOBT: 52%<br>FS: 44%<br>FOBT + FS: 70%<br>BE: NR<br>COL: 75% | 55% | Men: 68%<br>Women: 65% |
| % Cancers Prevented During Course of Program | NR | FOBT: 39%<br>FS: 37%<br>FOBT + FS: 60<br>BE: 38%<br>COL: 58% | FOBT: 60%<br>FS: 66%<br>FOBT + FS: 80%<br>BE: 86%<br>COL: 86% | FOBT: 16%<br>FS: 34%<br>FOBT + FS: NR<br>BE: NR<br>COL: 75% | FOBT: 60%<br>FS: 66%<br>FOBT + FS: 70%<br>BE: 86%<br>COL: 86% | 47% | Men: 64%<br>Women: 61% |
| Important Variables in Sensitivity Analysis | Polyp dwell time | Mortality from COL | Polyp dwell time<br>Adherence<br>COL cost | Adherence | Adherence | Dwelling time distribution mean dwelling time | NR |

**Note:** AHCPR indicates Agency for Health Care Policy and Research; BE, barium enema; COL, colonoscopy; CRC, colorectal cancer; FOBT, fecal occult blood test; FS, flexible sigmoidoscopy; NA, not available; NR, not reported; QALY, quality adjusted life year; SEER, Surveillance, Epidemiology, and End Results; Asterisk (*), any complication.

reference lists of retrieved articles.[6] The other was identified through contact with experts that was subsequently published and indexed in MEDLINE.[7] Because the book chapter by Wagner et al[6] was the most comprehensive description of the model developed by the Office of Technology Assessment, we used it rather than the more recent analysis by Glick et al.[7]

## Study Descriptions

The basic features of the included analyses are shown in Table 1. All but 1 were cost-effectiveness analyses, with benefits expressed in days of life or life-years gained and costs expressed in U.S. dollars. One study presented results in cost per quality adjusted life-year gained.[8] Each study considered 1 or more alternative means of screening in addition to the option of no screening. The perspective of the analyses was either societal or that of a third party payer. All studies considered direct costs, including the costs of screening, diagnostic tests, and treatment; no studies considered patient-time costs associated with attendance for screening, diagnostic, or surveillance procedures or for treatment of cancer.

In general, each model used data on the incidence of colorectal neoplasms (adenomatous polyps and cancers) to simulate disease natural history in a cohort of average-risk adults, typically between the ages of 50 and 85. These neoplasms were subject to detection and removal by the different screening strategies as they progressed from adenomas to early-stage cancer and then late-stage cancer. Survival after detection was generally considered to be stage-related. The costs and complications of screening and treatment were modeled with various degrees of precision. Benefits and costs were discounted at 3% or 5% in the base case analyses. Uncertainty about the variables used to build the models was examined in sensitivity analyses. Most sensitivity analyses were 1-way, although some studies examined the effect of setting several variables to the most pessimistic levels. Factors that caused cost-effectiveness ratios to vary more than 2-fold in sensitivity analyses included polyp dwell time, the proportion of cancers arising from adenomas, adherence rates, and the cost and adverse effects of colonoscopy.

The effectiveness of screening in preventing colorectal cancers and cancer deaths also varied considerably. Khandker's analysis was the most optimistic: most strategies prevented more than 60% of cancer incidence and 80% of colorectal cancer deaths.[9] Frazier and colleagues' analysis produced the smallest reductions[10]; Vijan and colleagues found incidence reductions similar to Khandker and colleagues and mortality reductions similar to Frazier and colleagues.[11] The analyses by Loeve and colleagues and Ness and associates were intermediate.[8,12] Sonnenberg and colleagues' model produced the lowest estimates of efficacy for FOBT and for sigmoidoscopy, but their estimate for the efficacy of colonoscopy was among the highest.[13]

### Question # 1: What Is the Cost-effectiveness of Screening for Colorectal Cancer With Any Method Compared With No Screening?

All studies found that screening for colorectal cancer by any of the included screening strategies reduced colorectal cancer mortality for adults older than age 50 at average risk of colorectal cancer. Table 2 shows cost-effectiveness ratios for the analyses that examined 2 or more of the most commonly evaluated strategies: FOBT annually (FOBT q1), flexible sigmoidoscopy every 5 years (FS q5), a combination of FOBT and sigmoidoscopy (FOBT q1 + FS q5), barium enema every 5 years (BE q5), and colonoscopy screening every 10 years (COL q10), each compared with no screening. Most strategies had average cost-effectiveness ratios in base-case analyses between $10,000 and $25,000 per year of life saved. Among the studies examining single methods of screening, the analysis by Loeve and colleagues found sigmoidoscopy to be cost saving when relatively optimistic cost parameters were used and the time range for the analysis was extended beyond 35 years. Ness and associates found that screening adults with colonoscopy between ages 50 and 54 had a cost-effectiveness ratio less than $10,000 per life-year saved.[8,12]

Although the results of the different studies are relatively consistent, it is possible that base-case assumptions about the effectiveness or costs of

**Table 2: Cost-effectiveness ratios in dollars per life-year saved, compared with no screening**

| Study | Wagner[6] | Frazier[10] | Khandker[9] | Sonnenberg[13] | Vijan[11] |
|---|---|---|---|---|---|
| FOBT q1 | 11,725 | 17,805 | 13,656 | 10,463 | 5,691 |
| FS q5 | 12,477 | 15,630 | 12,804 | 39,359 | 19,068 |
| FOBT q 1 + FS q5 | 13,792 | 22,518 | 18,693 | | 17,942 |
| DCBE q5 | 11,168 | 21,712 | 25,624 | | |
| COL q10 | 10,933 | 21,889 | 22,012 | 11,840 | 9,038 |

**Note:** All costs are updated to year 2000 U.S. dollars
COL q10 indicates colonoscopy every 10 years; DCBE q5, double contrast barium enema every 5 years; FOBT q1, annual fecal occult blood test; FS q5, flexible sigmoidoscopy every 5 years

screening for colorectal cancer were overly optimistic. Alternative sensitivity analyses that assumed "worst-case" scenarios about the biologic behavior of neoplasms and effectiveness of treatment generally produced cost-effectiveness ratios below $100,000 per life-year saved.

### Question #2: Can We Use Incremental Cost-effectiveness Data to Determine the Relative Effectiveness and Cost-effectiveness of Different Screening Options and Thus Determine If There Is a Preferred Strategy For Screening?

Five studies we identified examined multiple screening strategies (annual FOBT, sigmoidoscopy every 5 years, DCBE every 5 years, colonoscopy every 10 years, and the combination of annual FOBT and sigmoidoscopy every 5 years) and reached heterogeneous conclusions about their effectiveness and incremental cost-effectiveness. (See Table 3 and Appendix C.)

In terms of the most effective strategy, defined as the greatest average number of life-years gained, the analyses by Wagner et al, Frazier et al, and Vijan et al found the combination of annual FOBT and sigmoidoscopy every 5 years to be most effective.[6,10,11] Khandker et al and Sonnenberg et al found colonoscopy every 10 years to be the most effective, although Sonnenberg et al did not consider the combination of FOBT and sigmoidoscopy.[9,13] Of note, 4 of 5 multiple strategy analyses found FOBT alone more effective than sigmoidoscopy alone for reduction of colorectal cancer mortality.[6,9-11]

The most "cost-effective" strategy depends on the cost threshold beyond which one no longer wishes to "pay" for additional years of life saved. Assuming one does not wish to pay more than $20,000 per life-year saved, the 5 studies reached heterogeneous conclusions about the best strategy. At least 1 analysis found annual FOBT, sigmoidoscopy every 5 years, or colonoscopy every 10 years to be the optimal method of screening. As one's willingness to pay to save more life-years increases, either colonoscopy every 10 years, or the combination of annual FOBT and sigmoidoscopy every 5 years, becomes favored.

## Factors That Affect Cost-effectiveness Results

Several important variables differed across the 5 multiple strategy analyses and may explain some of the variability in incremental cost-effectiveness ratios (See Table 1). However, we could not identify a single variable as being solely responsible for the heterogeneity in outcomes we detected.

Assumptions about the biologic behavior of colorectal cancers are important factors in the ability of the model to accurately simulate real life. Assumptions about the proportion of cancers arising from adenomas is particularly important, because screening strategies that work mostly by preventing cancers through the removal of polyps, like screening

**Table 3: Preferred strategy at different levels of "acceptable" costs per life-year saved**

| Studies | Most effective strategy* | Preferred strategy if willing to pay†: | | | |
|---|---|---|---|---|---|
| | | Less than $20,000 per life-year saved | $20-30,000 per life-year saved | $30-50,000 per life-year saved | $50-100,000 per life-year saved |
| Wagner et al 1996[6] (alternative)‡ | FOBT + FS | COL q10 | COL q10 | FOBT + FS | FOBT + FS |
| Frazier et al 2000[10] | FOBT + FS | FOBT q1 | FOBT q1 | FOBT + FS | FOBT + FS |
| Khandker et al 2000[9] | COL q10 | FS q5 | FS q5 | FOBT q1 | COL q10 |
| Sonnenberg et al 2000[13] | COL q10 | COL q10 | COL q10 | COL q10 | COL q10 |
| Vijan et al 2001[11] | FOBT + FS | FOBT q1 | FOBT q1 | COL 55/65§ | COL 55/65 |

* Most effective strategy = largest number of life-years saved among 5 main strategies
† All costs in year 2000 dollars
‡ Using sensitivity of DCBE = 50% rather than 70% used in base-case
§ Colonoscopy at ages 55 and 65 only. All costs in year 2000 US dollars

**Note:** COL q10 indicates colonoscopy every 10 years; DCBE q5, double contrast barium enema every 5 years; FOBT + FS, annual FOBT and FS every 5 years; FOBT q1, annual fecal occult blood test; FS q5, flexible sigmoidoscopy every 5 years.

colonoscopy, appear most effective when it is assumed that all cancers arise from detectable adenomas.[10,11]

Similarly, the length of the pre-cancerous and early cancer detectable phases (dwell time) affects the relative rank of screening strategies. If the dwell time is long, strategies that apply a highly accurate test at a less frequent interval (eg, screening colonoscopy every 10 years) will appear to perform well compared with a more frequent but less accurate test, such as annual FOBT.

Screening adherence is another important factor. No analysis was completely successful in simulating actual patterns of adherence. In all the models, the adherence level was changed for all tests equally, an assumption that may not be correct (ie, adherence may be different for FOBT than for colonoscopy). This assumption of equal adherence among methods again favors the more accurate but more onerous screening methods, such as colonoscopy, particularly when adherence is assumed to be low.

Most of the analyses assumed that survival was based on the stage at diagnosis and estimated stage-specific survival from the National Center of Health Statistics and Surveillance Epidemiology and End Results Survey (SEER).[14] Notably, Sonnenberg et al made the very conservative assumption that cancers detected early by screening would have a mortality rate only 18% lower than those detected clinically.[13] This assumption makes FOBT appear much less effective than a method that relies more on detection and removal of polyps, such as colonoscopy.

Modeling of adverse effects also influences the cost-effectiveness of different strategies. The adverse effects of colorectal cancer screening are mainly those associated with complications of colonoscopy

(whether initially for screening or as part of the "diagnostic cascade" following another positive screening test), which include perforation, bleeding, or, rarely, death. Studies that fail to model all adverse consequences of colonoscopy will overestimate cost-effectiveness and will favor screening colonoscopy over strategies that employ fewer colonoscopic exams.

All studies included only the direct costs of screening. No study examined the cost of patient time missed from work for screening and treatment. The effect of considering such costs on the relative cost-effectiveness of each method is unclear. Colonoscopy would have higher patient costs per test but would be required less frequently than other methods. Overall, the cost per life-year saved would likely go up for all methods.

Another important factor is the way in which each analysis models post-polypectomy surveillance for new adenomas and cancer. Studies differed with respect to the interval for repeating colonoscopy after detection and removal of a clinically significant adenomatous polyp. Wagner et al assumed that all patients with adenomatous polyps would undergo surveillance colonoscopy every 4 years and that none of these patients would develop additional polyps or cancers and would die from other causes.[6] Frazier et al assumed that all patients with a "high-risk polyp" (greater than 1 cm in size or having villous histology) would undergo surveillance colonoscopy every 3 years until age 85 or death.[10] Khandker et al used a more complicated model in which, after an initial polyp over 1 cm in size was detected, an initial surveillance colonoscopy was performed at 3 years and subsequent follow-up studies were performed every 5 years if polyps were detected on the previous exam.[9] In that study, it appears that if a colonoscopy was negative, regular screening was re-initiated, but the documentation was unclear on this point. Sonnenberg et al modeled surveillance colonoscopy 3 years after polyp detection, but allowed screening to be suspended for 10 years after negative results on a colonoscopy.[13] Vijan et al also modeled initial surveillance colonoscopy 3 years after detection of a large adenoma (greater than 1 cm) and lengthened the interval for future surveillance exams to every 5 years after a negative exam. More aggressive programs with more frequent examinations can increase effectiveness in preventing future cancers, but will increase complications and costs.[11]

### Question #3: What is the Incremental Cost-effectiveness of Continuing Screening to Age 85 Compared With Stopping Screening at Age 70, 75, or 80? What is the Incremental Cost-effectiveness of Starting Screening at Age 40 or 45 Compared With Age 50?

With respect to the age at which screening should be initiated, Ness et al examined different ages at which to perform one-time screening colonoscopy and found that, for women, screening between ages 45 and 49 was dominated by 1-time screening between ages 50 and 54. For men, screening at 45 to 49 years of age, compared with screening from 50 to 54, was associated with costs of $69,000 per quality adjusted life-year gained.8 An older study by Eddy found that starting annual FOBT at age 40 added less than 1 day of average life expectancy and increased costs per person screened almost 2-fold, compared with starting at age 50.[15]

We found no studies that examined the incremental cost-effectiveness of different stopping ages, although a study by Rich and Black used life table analyses to suggest that by age 75, 68% of the potential mortality reduction from initiating FOBT screening at age 50 had been achieved. If screening were continued to age 80, 83% of the potential mortality reduction would be achieved.[16]

## Discussion

Our systematic review identified 7 high quality cost-effectiveness analyses, 5 examining multiple colorectal cancer screening strategies and 2 examining single strategies. Compared with no screening, all 7 analyses found that any of the common screening strategies for adults ages 50 and older will reduce colorectal cancer mortality. The cost per life-year saved for colorectal cancer screening ($10,000- $25,000 for most strategies compared with no screening) compares favorably

with other commonly endorsed preventive health care interventions, such as screening mammography for women older than age 50 or treatment of moderate hypertension.

Whether 1 method for colorectal cancer screening is superior to other methods is not clear from these analyses. Many observers have interpreted recent studies[17-19] documenting the relative greater single-test accuracy of colonoscopy, compared with sigmoidoscopy, FOBT, or DCBE, for detecting colorectal cancer or adenomas as evidence proving that colonoscopy should be the screening method of choice for colorectal cancer.[20] The 5 multiple strategy analyses we identified, however, did not uniformly find that colonoscopic screening was the most effective or cost-effective strategy. The most effective strategy tended to be either colonoscopy every 10 years or the combination of annual FOBT and sigmoidoscopy every 5 years. The most "cost-effective" strategy identified depended on the level of incremental cost-effectiveness considered to be worthwhile, and was not conclusive.

The differences in effectiveness, and hence cost-effectiveness, among the models are related to different assumptions each model makes about the biologic behavior of colon cancer, the effectiveness and adverse effects associated with each strategy, and the likelihood that patients will actually complete the tests required for any given strategy. Because the limited available empiric data cannot tell us which set of assumptions is most accurate, at present we cannot definitively state the single most effective or cost-effective strategy for screening. We can say with confidence, however, that any of the methods are effective compared with no screening for adults aged 50 and older.

Other reviewers have recently examined the literature on the cost-effectiveness of colorectal cancer screening. Brown and Knopf[21] reviewed cost-effectiveness analyses completed by 1998, identifying 4 studies for inclusion.[6,12,15,22] As with our analysis, they concluded that screening by any of several methods was cost-effective compared with no screening but that the available evidence could not determine the most effective strategy. McMahon et al recently published a re-analysis of 4 previous cost-effectiveness analyses.[23] They included the studies by Eddy15 and Wagner et al[6] that were examined by Brown and Knopf, and they also included the re-analysis of the Wagner et al model by Glick et al.[7] They recalculated incremental cost-effectiveness ratios for the different methods considered, and concluded that DCBE every 3 years or the combination of DCBE every 5 years plus FOBT annually were the most effective strategies. However, these conclusions were limited by the overly optimistic estimates (compared with data from the best subsequent empirical study[19] of DCBE sensitivity and specificity) used in the 4 analyses that McMahon and colleagues included.

We did not find sufficient evidence about starting and stopping ages for screening to provide useful information for making recommendations. The analyses by Ness et al[8] and Eddy[15] suggest that the benefits of starting screening at age 40 or 45 were small and costly compared with starting at age 50, but further analyses with a range of tests are required. The cost-effectiveness of different stopping ages for screening also was not well examined, and may differ substantially depending on the health of the patient being considered for screening.[24]

Some potential limitations should be considered in interpreting our results. All but 1 of our analyses examined cost per life-year gained and did not account for differences in quality of life associated with undergoing screening, surveillance, or treatment for cancer. Differences in model structure, data inputs for key variables, and regimens evaluated limited our ability to draw definitive conclusions about the most effective and cost-effective tests. It is difficult to determine from the data presented in each report whether differences in the results obtained relate mainly to differences in the variables used or in the model structures. We only considered strategies that employed 1 kind of test (or a pair of tests) and repeated them at some regular interval. More complex strategies, including ones that screen younger people with 1 test and then switch to a different test at older ages, have not been evaluated. Uncertainty about estimates of different variables was addressed in each study by 1-way sensitivity analyses or by testing a set of "optimistic" or "pessimistic" assumptions, but only 1 of the

studies provided probabilistic ranges for its results. Finally, our findings apply only to screening patients at average risk for colorectal cancer; screening higher-risk patients may be even more cost-effective.

Some modelers attempted to validate their models by comparing their results with the results from empiric screening trials.[6,10,11] It would be valuable to have the creators of the different models participate in a validation exercise to compare intermediate and long-term model outcomes using 1 common set of variables for a common set of strategies. In this manner, we could confirm that the relative ranking of strategies is similar and not dependent on model structure and assumptions. Nonetheless, the consistent finding that any form of screening is superior to no screening supports the general conclusion that any of the commonly considered strategies are reasonable alternatives.

This review of cost-effectiveness studies has important implications for future research and policy making. It supports the consensus view among major policy-making bodies that colorectal cancer screening in some form is warranted for average risk adults older than age 50. It also shows that current evidence is insufficient to determine the most effective or cost-effective strategy for screening or to determine optimal starting and stopping ages for screening. Because no single method of screening is clearly superior to others, patient preferences can play an important role in deciding about how screening should be performed.[25] Finally, our findings suggest that further research about the natural history of colorectal cancer, the effect of screening, surveillance and treatment on quality of life, the real-world incidence of complications from screening, and longitudinal data about adherence with different screening strategies in unselected populations could help clarify some of the uncertainty about relative test performance.

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# Appendix A

## Search Strategy

We exploded medical subject headings "colorectal neoplasms" and "mass screening." We used different strategies in each database to identify cost-effectiveness analyses. For our MEDLINE search, we added the exploded medical subject heading "costs and cost analysis." In the NHS EED, we limited the search to "economic evaluations."

# Appendix B

**Excluded articles**

| Author, Year | Primary reason for exclusion |
|---|---|
| Daniels and McKee, 1995[26] | Non-comparable outcome (cost per case detected) |
| Delco and Sonnenberg, 1999[27] | Non-comparable outcome (cost per case prevented) |
| Faivre et al, 1998[28] | No cost effectiveness analysis (review article) |
| Glick et al, 1998[7] | Same model used in another included study |
| Gyrd-Hansen et al, 1998[29] | Costs, incidence and prevalence estimates not comparable to U.S. |
| Kronborg and Wahrendorf, 1994[30] | No cost effectiveness analysis (review article) |
| Lieberman, 1995[31] | Non-comparable outcome (cost per death prevented) |
| Neilson and Whynes, 1995[32] | No cost effectiveness analysis (description of model only) |
| Norum, 1998[33] | Costs, incidence and prevalence estimates not comparable to U.S. data |
| Salkeld et al, 1996[34] | Costs, incidence and prevalence estimates not comparable to U.S. data |
| Shimbo et al, 1994[35] | Costs, incidence and prevalence estimates not comparable to U.S. data |
| Sonnenberg et al, 1999[36] | Did not evaluate commonly used test |
| Sorrentino et al, 1999[37] | Non-comparable outcome (cost per death prevented) |
| Whynes et al, 1998[38]<br>Whynes et al, 1999[39] | Costs, incidence and prevalence estimates not comparable to U.S. |

# Appendix C

**Calculated Incremental Cost-effectiveness Ratios from Five Major Cost-effectiveness Analyses (all costs updated to year 2000 U.S. dollars using the Consumer Price Index for medical care)**

**1a. Wagner et al 1996[6] Base-case**

| Strategy | Effectiveness (days of life gained) | Cost per person | Incremental C-E ratios | Calculated relative to |
|---|---|---|---|---|
| No screening | — | — | — | — |
| FS q5 | 13.07 | $447 | Weakly dominated | — |
| FOBT q1 | 21.46 | $689 | Strongly dominated | — |
| COL q10 | 21.64 | $652 | $10,997 | No screening |
| DCBE q5 | 21.97 | $672 | $22,121 | COL q10 |
| FOBT + FS q5 | 24.53 | $927 | $36,357 | DCBE q5 |

**1b. Wagner et al 1996[6] with 50% sensitivity for DCBE**

| Strategy | Effectiveness (days of life gained) | Cost per person | Incremental C-E ratios | Calculated relative to |
|---|---|---|---|---|
| No screening | — | — | — | — |
| FS q5 | 13.07 | $447 | Weakly dominated | — |
| DCBE q5 | 17.81 | $703 | Strongly dominated | — |
| FOBT q1 | 21.46 | $689 | Strongly dominated | — |
| COL q10 | 21.64 | $652 | $10,997 | No screening |
| FOBT + FS q5 | 24.53 | $927 | $34,732 | COL q10 |

**2. Frazier et al 2000[10]**

| Strategy | Effectiveness (average years of) life expectancy) | Cost per person | Incremental C-E ratios | Calculated relative to |
|---|---|---|---|---|
| No screening | 17.3481 | $1,134 | — | — |
| FS q5 years | 17.3806 | $1,550 | $12,804 | — |
| DCBE q5 years | 17.3826 | $2,018 | Strongly dominated | — |
| FOBT q1 | 17.3901 | $1,708 | $16,568 | FS q10 |
| COL q10 | 17.3959 | $2,186 | Strongly dominated | — |
| FOBT + FS q5 | 17.4041 | $2,181 | $33,786 | FOBT q1 |

**3. Khandker et al 2000[9]**

| Strategy | Effectiveness (average years of) life expectancy) | Cost per person | Incremental C-E ratios | Calculated relative to |
|---|---|---|---|---|
| No screening | 18.1392 | $794 | — | — |
| FS q5 | 18.2250 | $2,119 | $15,442 | No screening |
| FOBT q1 | 18.2375 | $2,546 | $34,160 | FS q5 |
| DCBE q5 | 18.2494 | $3,188 | $53,950 | FOBT q1 |
| FOBT + FS | 18.2499 | $3,264 | Strongly dominated | — |
| COL q10 | 18.2499 | $3,219 | $62,000 | DCBE q5 |

**4. Sonnenberg et al 2000[13]**

| Strategy | Effectiveness (days of life gained) | Cost per person | Incremental C-E ratios | Calculated relative to |
|---|---|---|---|---|
| No screening | 0 | $1,471 | — | — |
| FOBT q1 | 6.92 | $1,670 | $10,496 | No screening |
| FS q5 | 13.27 | $2,902 | Strongly dominated | — |
| COL q10 | 29.02 | $2,413 | $12,271 | FOBT q1 |

**5. Vijan et al 2001[11] incremental CE ratios**

| Strategy | Effectiveness (average years of) life expectancy) | Cost per person | Incremental C-E ratios | Calculated relative to |
|---|---|---|---|---|
| No screening | 17.1230 | $1,357 | — | — |
| FS q5 | 17.1572 | $2,010 | Strongly dominated | — |
| FOBT q1 | 17.1682 | $1,614 | $5,686 | No screening |
| COL 55 and 65 | 17.1745 | $1,822 | $33,016 | FOBT q1 |
| FOBT + FS q5 | 17.1797 | $2,374 | $106,153 | COL 55 and 65 |

**Note:** COL q10 indicates colonoscopy every 10 years; COL 55 and 65, colonoscopy at ages 55 and 65 only; DCBE q5, double contrast barium enema every 5 years; FOBT + FS q5, annual fecal occult blood test and flexible sigmoidoscopy every 5 years; FOBT q1, annual fecal occult blood test; FS q5, flexible sigmoidoscopy every 5 years.

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