DECISION MODEL AND COST-EFFECTIVENESS ANALYSIS OF COLORECTAL CANCER SCREENING AND SURVEILLANCE GUIDELINES FOR AVERAGE-RISK ADULTS

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Running head: Cost-effectiveness of colorectal cancer screening

Abstract

Objectives: Guidelines on colorectal cancer screening and surveillance in people at average risk and at increased risk have recently been published by the American Gastroenterological Association. The guidelines for the population at average risk were evaluated using cost-effectiveness analyses. Methods: Since colorectal cancers primarily arise from precancerous adenomas, a state transition model of disease progression from adenomatous polyps was developed. Rather than assuming that polyps turn to cancer after a fixed interval (dwell time), such transitions were modeled to occur as an exponential function of the age of the polyps. Screening strategies included periodic fecal occult blood test, flexible sigmoidoscopy, double-contrast barium enema, and colonoscopy. Screening costs were estimated using Medicare and private claims data, and clinical parameters were based on published studies. Results: Cost per life-year saved was $12,636 for flexible sigmoidoscopy every five years and $14,394 for annual fecal occult blood testing. The assumption made for polyp dwell time critically affected the attractiveness of alternative screening strategies. Conclusions: Sigmoidoscopy every five years and annual fecal blood testing were the two most cost-effective strategies, but with low compliance, occult blood testing was less cost-effective. Lowering colonoscopy costs greatly improved the cost-effectiveness of colonoscopy every ten years.

Keywords: Colonoscopy, Colorectal Neoplasms, Cost-Benefit Analysis, Mass Screening, Occult Blood

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Colorectal cancer is the second leading cause of cancer death in the United States. Together, colon and rectal cancers were estimated to account for 131,200 new cancer cases and 54,900 deaths in 1997 (2). Although a small portion of the population is at high risk of colorectal cancer because of heritable genetic disorders or as a complication of inflammatory bowel disease, most cases of colorectal cancer develop in members of the general population without clearly recognized predisposing conditions. These sporadic cases are now thought to arise through the accumulation of mutations that lead sequentially to the development of small adenomatous polyps, large adenomas, invasive carcinoma, and, in some persons, metastatic disease (4).

In 1994, the former Agency for Health Care Policy and Research (AHCPR) contracted with the American Gastroenterological Association (AGA) to develop guidelines for screening and surveillance of colorectal cancer. A panel of experts convened by AHCPR and a consortium including AGA, the American Society for Gastrointestinal Endoscopy, the American College of Colon and Rectal Surgery, the American College of Gastroenterology, and the Society of American Gastrointestinal Endoscopic Surgeons developed a set of recommendations that were published under AGA auspices in 1997 (38). These recommendations present a choice of alternative screening strategies. This study examines these recommended colorectal cancer screening and surveillance strategies for average-risk adults by using a decision model and cost-effectiveness framework.

Approximately 30% of persons develop some type of colonic polyp by age 50 (34). Many such polyps are hyperplastic (generally small and of no clinical importance), but others are adenomatous (premalignant) and can lead to cancer unless detected and removed early in their growth phase. The effectiveness of screening average-risk persons is derived from early detection of cancer and removal of polyps, lowering the incidence of cancer and cancer-related deaths. Early detection of polyps and cancer can also reduce eventual treatment costs. However, screening everyone for colorectal cancer is expensive. Whether to screen all persons after a certain age, what types of screening methods to use, and how frequently to apply the tests are important policy questions. The choice and frequency of tests determine not only how quickly polyps and cancers are detected and treated but also how much it will cost to implement such screening and surveillance programs.

This study developed an elaborate model by which polyps may lead to colorectal cancer, compared alternative screening strategies, and conducted extensive sensitivity analyses. Past studies have concluded that screening after a certain age can be a cost-effective method of reducing morbidity and mortality from colorectal cancer (11;12;22;30;34;35). This study significantly extended earlier work in terms of the assumptions regarding polyp dwell time and post-polypectomy surveillance. While earlier studies provide comparisons of alternative screening tools, no clear consensus has emerged regarding the most appropriate screening strategies. In part, this lack of consensus reflects a lack of understanding of the colorectal cancer disease process, including the dwell times of polyps at different stages of development. Considerable uncertainly surrounds how polyps progress, and the effectiveness of the various screening options depends critically on that process. This study particularly addressed this issue using a disease model that captured the uncertainty associated with polyp dwell time. This model also built an extensive surveillance period during which screening of heightened intensity could be applied on the basis of guidelines recommended for the surveillance population.

METHODS

Screening and Surveillance Strategies

The analyses considered four principal methods of screening for colorectal cancer addressed by the AGA guidelines (fecal occult blood testing or FOBT, flexible sigmoidoscopy or FSIG, double-contrast barium enema or DCBE, and colonoscopy) (38). FOBT is widely used to screen for colorectal cancer because the method is simple and inexpensive. Polyps and cancers may bleed, and FOBT detects neoplasms by revealing blood in the stool. However, FOBT is least effective at detecting small polyps. Sigmoidoscopy and colonoscopy permit inspection of the colonic lumen, and barium enemas display the contours of the colonic mucosa. Sigmoidoscopy does not permit examination beyond the left (descending) side of the colon, whereas colonoscopy offers the potential of surveying the entire colon. Colonoscopy can be used both as a screening and as a surveillance procedure and is often selected to follow other screening tests when polyps or cancer are suspected. Removal of polyps (polypectomy) can

also be carried out in the course of colonoscopy, so this procedure can provide definitive therapy for premalignant polyps as well as diagnostic information.

Only average-risk persons were included in this analysis. This group included those aged 50 and older without predisposing factors, who account for approximately 75% of colorectal cancer incidence (38). Based on screening tests and intervals recommended by Winawer et al. (38), we evaluated eight screening strategies (annual FOBT, FSIG every 3 years, FSIG every 5 years, annual FOBT and FSIG every 3 years, annual FOBT and FSIG every 5 years, DCBE every 5 years, colonoscopy every 5 years, and colonoscopy every 10 years). Screening started at age 50 and continued until age 85.

Decision Model

The disease and screening process was based on a dynamic state transition model. During each cycle, each person would occupy one of eight primary states (disease free, hyperplastic polyp, adenomatous polyp, undetected cancer, surveillance, treatment, death due to colorectal cancer or test complications, and death from other causes). The complete model had more than 60 states, depending upon polyp histology (size and stage of development); location of polyp and cancer (distal or proximal); age (5-year intervals); and cancer stage (local, regional, distant, and number of years in each stage). Each state was assigned an initial probability, representing the distribution of a hypothetical cohort. A probabilistic model of transitions based on incidence and progression of polyps and cancer, and intervention and outcome of screening tests determined the state in the subsequent cycle. During each cycle, the subject in the model cumulated cost and, by living through the cycle, gained life-years. Iterating the model until death yielded the average life expectancy and the total costs of colorectal cancer screening, diagnosis, and treatment.

The first twenty years of dwell time for adenomatous polyps were modeled extensively using 10 states of 2-year duration. Polyps could transform to cancer with higher and higher probability the longer they dwelled in the colon. This probability distribution was based on an equation derived by Whynes et al. (36) using published data on the radiographic surveillance of adenomas in the period before the availability of colonoscopy. While polyp dwell time is not known with certainty, it holds the key to

successful screening. Accordingly, alternative models of dwell time in which polyps turned to cancer after a fixed length of time (34) were explored in sensitivity analysis. Persons who were found to have polyps moved to surveillance after polyps were removed. We assigned a higher probability of developing polyps to this group (surveillance) compared to those with no prior polyps (screening). The length of time in surveillance and the frequency of tests depended on the size and type of polyp (38).

Multiple decision trees were constructed to represent transition in and out of the various primary states. Test sensitivity, which varied by polyp size, and test specificity measures determined the success or failure of screening tests. Test performance was also a function of the location of polyp (proximal or distal). When test results were positive, a follow-up colonoscopy was assumed regardless of the polyp size. Implicit in all invasive tests was the risk of complication. Three stages of colorectal cancer, depending on anatomic extent, were modeled (local, regional, and distant), conceptually paralleling carcinoma in situ and Dukes A, Dukes B and C, and Type 4, respectively. Persons with advanced stages of undiagnosed cancer were presumed to have a progressively higher likelihood of seeking medical care, better chances of detection, and higher levels of mortality. In each cancer stage, a patient could stay for as many as five years in tunnel states (31). The model also allowed individuals with undetected cancer to experience disease progression until screening or symptom-driven visits revealed the disease. The model was evaluated using DecisionMaker 7.0 software (Pratt Medical Group, Boston, Massachusetts).

Parameter Values

Estimates for the model required parameters related to incidence and progression of polyps and colorectal cancer, survival rates, risk factors and complications, compliance, test performance, and costs. For adenomatous and hyperplastic polyps, initial proabilities were estimated to be 25% and 5%, respectively (34, 38). Incidence rates for new polyps were estimated as 0.7%, 1%, and 1.5%, respectively, for the three age groups (50-65, 66-70, and 71-85 years) (34, 37). The initial probabilities of various cancer stages was based on Abrams and Reines (1). Rates for large adenomatous polyps turning to cancer depending on polyp dwell time were based on Whynes et al. (36). For small polyps, only one-tenth of those probabilities was used (38). A 2-year time period was assumed between the first two cancer stages (11, 33). The final stage of cancer developed within 1 year after the second stage. Five-

year survival rates based on Surveillance, Epidemiology, and End Results (SEER) data (26) were used for the yearly probability of dying from colorectal cancer based on the stage and number of years with cancer. Age-specific rates of death from other causes were estimated based on the above source combined with statistics published by the National Center for Health Statistics (23).

Parameter values related to screening test performance (shown in Table 1) and complications were primarily based on Winawer et al (38). It is important to note that sensitivity and specificity values could vary depending on the polyp size and between polyps and cancer. Since very little is known about compliance with colorectal cancer screening, we assumed full compliance in the base model and used a 23% compliance rate for sensitivity analyses based on a study of FOBT compliance (3).

Table 2 reports screening costs for the elderly and non-elderly U.S. population. For the elderly, a random 5% sample of all Medicare beneficiaries from 1992 through 1994 was used. For younger subjects, we used claims data from a large sample of privately insured patients (MEDSTAT, Inc.). Only outpatient (physician and hospital outpatient department) costs were used, since inpatient procedures were generally confounded with unrelated services. Flexible sigmoidoscopy and colonoscopy costs were separately estimated for simple screening procedures versus those with polypectomy/biopsy and pathology (complex). All cost estimates were adjusted to 1994 dollars using the national medical inflation rate of 4.8% (7). Cancer treatment and lifetime costs were estimated based on Fireman et al. (14). The cost of complications was based on Wagner et al. (34).

RESULTS

Base Case

Table 3 shows discounted lifetime measures of cost and effectiveness under eight alternative screening strategies. Each strategy was compared to a baseline of no screening to estimate incremental cost-effectiveness (CE) ratios. Without screening, lifetime cost of colorectal cancer was $643 per person due to diagnosis and treatment for those who happen to seek care. Annual FOBT adds an additional $1,415 in lifetime cost. This includes screening costs for everyone and follow-up diagnostic and other

costs for those with a positive FOBT. Absent screening, the model predicted that an average person would live 18.14 years beyond the age of 50 (discounted at 3%). For simplicity, the model did not assign any remaining life beyond age 85 (the end of the screening interval) since the residual life would apply to screening and non-screening strategies alike. With annual FOBT, persons reaching age 50 were predicted to live 18.24 years, a marginal gain of 0.0983 life-years. Flexible sigmoidoscopy every 5 years had the lowest cost per person ($1,713) among all screening strategies. Colonoscopy, performed every 5 years, had the highest cost per person. Among the eight strategies, flexible sigmoidoscopy every 5 years ranked lowest in terms of cost per life-year saved ($12,636). This strategy was closely followed by annual FOBT ($14,394). Sigmoidoscopy every 3 years cost $3,625 more than when offered at 5-year intervals. Colonoscopy every 5 years cost the most ($28,724).

Table 4 shows the cumulative numbers of people developing cancer and dying from it at ages 60, 70 and 85. Without cancer screening, 770 persons would develop colorectal cancer by age 60, and 5,550 (approximately 56 per 1,000) would develop colorectal cancer by age 85. Cancer incidence and death rates reduced substantially with screening. Colonoscopy every 5 years led to the lowest cancer rate at each age because of its superior effectiveness (high sensitivity and frequent screening). In contrast, annual FOBT, with its low sensitivity, was associated with the highest cancer rates. Even so, cancer rates were 18% lower by age 60 with annual FOBT relative to no screening. In general, preventive effects of screening increased cumulatively with age for those strategies that involved repeated tests. Without screening, 2,920 people (out of 100,000) would die from colorectal cancer by age 85. Any of the screening strategies lowered death rates considerably. For example, annual FOBT would lead to only 590 deaths by age 85 (80% lower than no screening). Most other strategies, with the exception of flexible sigmoidoscopy, would reduce death rates even further.

Sensitivity Analysis

Sensitivity analyses focused on key parameters of the disease process, screening performance, costs, and compliance. Particular attention was directed at polyp dwell time since much of the preventive effect of screening arose from the time lag inherent in malignant transformation of adenomatous polyps into cancer. By analogy to Wagner et al. (34), two alternative scenarios were

considered at the end of tenth year of polyp. In one scenario, precancerous polyps turned to cancer with a probability of 1.0, and in another scenario, with a probability of 0.25. As shown in the last two columns of Table 3, cost-effectiveness estimates were very sensitive to the assumption regarding polyp dwell time. Relative to the base case model with time-dependent polyp-cancer transitions, CE ratios were significantly lower for all screening options (ranging from $3,504 for 5-year flexible sigmoidoscopy to $7,048 for 5-year colonoscopy). On the contrary, CE ratios were much higher when polyps had only a 25% chance of turning to cancer at the end of the 10th year. Assuming that malignant transformation occurred abruptly at the end of the 10^{th} year of polyp dwell, sigmoidoscopy every 5 years was the most cost-effective strategy, followed by sigmoidoscopy every 3 years. Generally, strategies with less frequent screening (i.e., with longer intervals between tests) were dominant over more frequent strategies such as annual FOBT. Wagner et al. generally found strategies with a 10-year screening interval to be most cost-effective given a 10-year dwell time, and 5-year screening strategies to be most cost-effective given a 5-year dwell time (34).

Sensitivity analysis was performed on models of flexible sigmoidoscopy with reach-adjusted parameters. Since the flexible sigmoidoscope reaches only a part of the colon, the base case separately modeled proximal and distal parts of the colon and assumed a zero sensitivity when polyps were located beyond the reach of the flexible sigmoidoscope. This adjustment was done in order to avoid overestimating the effectiveness of this test. In sensitivity analysis, we developed an alternative assumption by stipulating a sensitivity of 90% for sigmoidoscopy in the distal colon and 0% for proximal. This model in essence used a 45% reach-adjusted sensitivity parameter if polyps were distributed equally between distal and proximal colons. This approach invariably overestimated the effectiveness of flexible sigmoidoscopy since the calculation ignored the fact that in repeated tests proximal polyps would continue to be undetected. Overestimation of effectiveness in the reach-adjusted model portrayed flexible sigmoidoscopy every 5 and every 3 years as the two most cost-effective strategies.

Sensitivity analysis was also performed at 23% compliance as opposed to 100% as in the base model. Flexible sigmoidoscopy at 3 and 5 years ranked as the two most cost-effective strategies. Annual FOBT was the second last preferred alternative (superior to 5-year colonoscopy) in terms of CE

ratio. With imperfect compliance, insensitive strategies such as annual FOBT lost their cost-effectiveness as the advantage conferred by repeated tests was lost.

Table 5 illustrates the impact of high and low values of selected other parameters on CE ratios. Strategies are ranked from the most cost-effective (ranked 1) to the least cost-effective (ranked 8). Using low values for sensitivity of FOBT dropped annual FOBT from second most preferred to second least preferred status. At high values of FOBT sensitivity, annual FOBT ranked as the most cost-effective strategy, followed by sigmoidoscopy every 5 years. In general, flexible sigmoidoscopy at 5-year intervals and annual FOBT continued to be the two most cost-effective strategies under a broad range of assumptions. However, poor compliance can make annual FOBT less cost-effective, and lower colonoscopy cost can make that test more cost-effective if applied every 10 years.

DISCUSSION

The study provides an economic evaluation of the colorectal cancer screening options recommended by the AGA. Under a more realistic assumption of polyp-cancer transitions as demonstrated by the base case model, most of the screening options had a CE ratio less than $20,000 in 1994 dollars. Although the definition of what is an acceptable CE ratio remains arbitrary, the median cost per life-year saved reported for 310 health care interventions was $19,000 using 1993 dollars (32). Thus, other than that for 5-year colonoscopy, CE ratios for all screening options considered in this study can be considered at or below the median. The ratios reported here also compare favorably against other mass screening or prevention alternatives. For example, mammography screening for women between the ages of 50 and 69 years reported a CE ratio of $21,400 in 1995 dollars (29). Biennial and triennial pap smear (with AutoPap-assisted rescreen) for women aged 20 to 65 years were $42,666 and $16,259, respectively, using 1996 dollars (6). Over a broad range of inputs, CE ratios reported for primary prevention of cardiovascular disease with pravastatin remained below $25,000 per life-year gained (9).

Both flexible sigmoidoscopy every 5 years and annual FOBT were cost-effective under a broad range of assumptions. FOBT reduces colorectal cancer mortality (19;21) at acceptable cost (18;28;35), and annual FOBT is claimed by some researchers to be most cost-effective (11;22;30).

Flexible sigmoidoscopy and barium enema were found to be more cost-effective than some of the other screening tools by other researchers (5;15;34). Due to methodological differences, these results often are not comparable. For example, Wagner et al. (34) assumed that polyps turn to cancer at fixed intervals while the current study introduced time dependence by allowing polyps to transform to cancer with higher probability as they dwell longer. A shortcoming of models that assume a constant dwell time as in the Wagner et al. study is that they do not explain the empiric observation that the incidence of cancer in general and of colorectal cancer in particular increases exponentially with increasing age (10;20).

The results obtained here should be useful to clinicians, policy-makers, and payers in choosing among screening methods and in considering payment for colorectal cancer screening in view of the cost and effectiveness associated with each alternative strategy. However, many key assumptions represent a best guess based on the available literature. This is partly because of the lack of definitive clinical studies on the kinetics of malignant transformation of adenomatous polyps and the growth and spread of colorectal cancer as well as on the effectiveness of various tests (24). As demonstrated by sensitivity analyses, the dynamics of polyp-cancer transition has significant effect on the magnitude of the CE ratios. A clearer understanding of the development of colorectal cancer, including the dwell time of polyps and the progress of cancers through different stages of development is central to understanding the effectiveness of various diagnostic tests. Future studies should also consider patient quality-of-life and societal impacts arising from adenomatous polyps, colorectal cancer, and screening interventions (16).

POLICY IMPLICATIONS

The cost of screening is an important issue in the development of public policy. Inherent in a successful colorectal cancer program is the role of population screening. Spurred by mounting evidence that the detection and treatment of early stage colorectal cancers and adenomatous polyps can reduce mortality, Medicare and some other payers recently authorized reimbursement for colorectal cancer screening in persons at average risk. Medicare beneficiaries may now receive coverage for annual FOBT and flexible sigmoidoscopy every four years, with DCBE considered as an alternative. Although private

insurers can be expected to provide such coverage, payers carefully weigh the relative risks, costs and effectiveness of the various test strategies. Some payers may prefer FOBT and sigmoidoscopy because these procedures have the lowest up front costs and meet the standard of care. Others with a stable patient base and secure long terms financial future may choose colonoscopy provided they can negotiate the charge down to an acceptable level (25). However, as this study illustrates, colonoscopy as an alternative is sensitive to its high cost, and its administration every 10 years can be further associated with problems of recall and compliance.

This study, particularly the cost analysis, is oriented to the United States. The economics of colorectal cancer screening is expected to be different across health care systems and across countries. Although colorectal cancer meets the World Health Organization's suitability for mass population screening (35), Canada, Australia and most European countries are still debating its adaptation (17, 27). Given favorable results based on randomozed studies, the Department of Health in the U.K. is considering FOBT for national implementation (27). Data for mammography screening for breast cancer seem no more convincing than that for colorectal cancer screening. Yet U.K. had adopted national screening programs for the former since the 1980s. An European group of experts has recently published their strong recommendation to implement FOB testing associated with follow-up colonoscopy as appropriate (13). The authors agree that an uniform approach to screening across all European countries is not possible due to diverse health systems and resource constraints.

Policy uncertainties arise from the high cost of national screening programs. The annual cost of FOB testing 52 million individuals older than 50 years of age in the U.S. has been estimated in excess of $1 billion (8). Rising costs for medical care will only increase the need for economic evaluations of large scale health care interventions. Significant resource utilization issues are involved in procurement and administration, infrastructure and training, education and awareness and ensuring patient and physician compliance. Without an overall effort, the success of mass screening will not achieve optimum results. In the final analysis, the choice among alternatives are most often based on societal resource constraints and value judgements.

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Table 1. Test Sensitivity and Specificity Values

Parameter	Value
Sensitivity of FOBT	
small polyps	0.06
large polyps	0.10
cancer	0.60
Specificity of FOBT	0.92
Sensitivity of FSIG	
small distal polyps	0.73
large distal polyps	0.97
distal cancer	0.97
Specificity of FSIG for distal polyps/cancer	0.92
Sensitivity of DCBE	
small distal polyps	0.67
large distal polyps	0.82
distal cancer	0.84
Specificity of DCBE for small polyps	0.75
Sensitivity of colonoscopy:	
small distal polyps	0.79
large distal polyps	0.85
distal cancer	0.97
Specificity of colonoscopy	1.00

Table 2. Screening Cost Values

Parameter	Age<65	Age 65+
FOBT	$11	$7
DCBE	$176	$175
Simple FSIG	$176	$94
Complex FSIG	$299	$214
Simple colonoscopy	$670	$438
Complex colonoscopy	$981	$702

Table 3. CE Estimates for Base Case and Fixed Length Models

	Base Case Model			Fixed Length (10-year) Polyp Model	
	Cost ($ per person)	Effectiveness (life-years)	Incremental cost-effectiveness (CE) ratio	CE ratio (polyp-cancer tranistion prob. = 1)	CE ratio (polyp-cancer tranistion prob. = 0.25)
Baseline (no screening)	$643	18.14	-------	-------	-------
Annual FOBT	$2,058	18.24	$14,394	$5,586	$21,350
3-year FSIG	$2,079	18.23	$16,261	$3,567	$23,045
5-year FSIG	$1,713	18.23	$12,636	$3,504	$18,848
Annual FOBT/3-year FSIG	$2,854	18.25	$20,334	$5,326	$27,751
Annual FOBT/5-year FSIG	$2,639	18.25	$18,204	$5,070	$26,412
5-year DCBE	$2,577	18.25	$17,553	$4,468	$25,024
5-year colonoscopy	$3,906	18.25	$28,724	$7,048	$38,536
10-year colonoscopy	$2,602	18.25	$17,696	$4,657	$25,474

Table 4. Cumulative Incidence and Death Rates (per 100,000) for Colorectal Cancer

	Cumulative cancer rates			Cumulative cancer deaths		
	Age			Age		
Screening procedure	60	70	85	60	70	85
Baseline (no compliance)	770	2,350	5,550	350	990	2,920
Annual FOBT	630	1,310	2,220	200	340	590
3-year FSIG	480	940	1,750	210	390	850
5-year FSIG	520	1,030	1,890	220	430	920
Annual FOBT/3-year FSIG	450	830	1,130	170	240	360
Annual FOBT/5-year FSIG	480	750	1,130	170	240	340
5-year DCBE	450	600	770	180	250	310
5-year colonoscopy	350	410	520	150	160	190
10-year colonoscopy	410	560	750	170	230	300

Table 5. Ranking of Screening Strategies Under Selected Alternatives
(1 = lowest CE ratio, 8 = highest CE ratio)

Assumptions	Annual FOBT	5-year DCBE	5-year FSIG	3-year FSIG	Annual FOBT/5-year FSIG	Annual FOBT/3-year FSIG	10-year colono-scopy	5-year colono-scopy
Baseline values	2	4	1	3	6	7	5	8
50% below base value								
FOBT sensitivity	7	3	1	2	5	6	4	8
DCBE sensitivity	2	7	1	3	5	6	4	8
Colonoscopy sensitivity	3	6	1	2	4	5	7	8
Colonoscopy cost	1	4	3	5	6	7	2	8
50% above base value								
FOBT sensitivity	1	4	2	3	6	7	5	8
DCBE sensitivity	2	4	1	3	6	7	5	8
Colonoscopy sensitivity	2	4	1	3	7	6	5	8
Colonoscopy cost	3	4	1	2	5	6	7	8