The Cost-Effectiveness of Colorectal Cancer Screening in Average-Risk Adults

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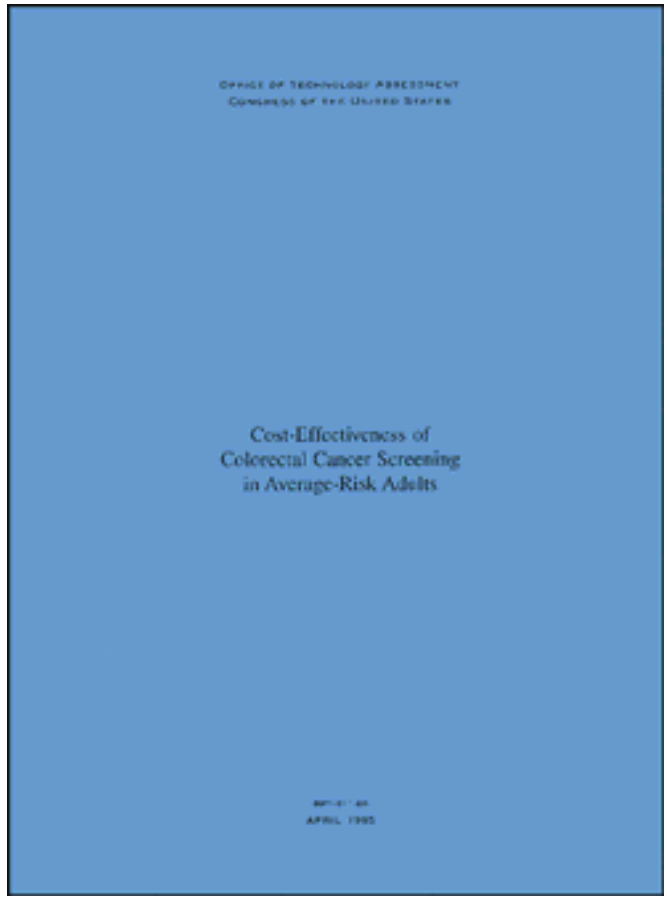

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Project Staff

Clyde J. Behney
Assistant Director, OTA

Sean R. Tunis
Health Program Director

JUDITH L. WAGNER
Study Director

Alex Ching
Research Assistant

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Martin Brown
National Cancer Institute
Bethesda, MD

Bruce Fireman
Kaiser Foundation Health Plan
Oakland, CA

Kevin Hayes
Physician Payment Review Commission
Washington, DC

Joseph Selby
Kaiser Foundation Health Plan
Oakland, CA

Irene Tekawa
Kaiser Foundation Health Plan
Oakland, CA

INTRODUCTION

This OTA Background paper presents an analysis of the cost-effectiveness of colorectal cancer (CRC) screening in average-risk adults beginning at age 50. It examines the relative cost-effectiveness of competing CRC screening technologies and schedules. This paper draws on an earlier study of CRC screening in the elderly (OTA, 1990; Wagner et al., 1991). That study was limited to screening strategies that start at age 65. The earlier OTA study had other limitations as well. First, it examined screening strategies involving only the fecal occult blood test (FOBT) and flexible sigmoidoscopy (FSIG). It did not examine the cost-effectiveness of screening with full colonoscopy (CSCPY) or with double contrast barium enema (DCBE), both of which have been advocated by some as reasonable alternative CRC screening technologies. The current paper examines all four potential screening technologies.

Second, the earlier OTA study, which was undertaken at the request of Congress to support a Yes/No Medicare coverage decision, utilized conservative assumptions. That is, the values of uncertain parameters were chosen to bias the results against finding screening to be cost-effective. Despite this conservative bias, the OTA study showed that colorectal cancer screening in the elderly is at least as cost-effective as biannual screening mammography in Medicare beneficiaries (OTA, 1991). New evidence now exists to support claims for effectiveness of CRC screening (Selby, 1992; Mandel et al. 1993,) and to provide greater confidence about the "correct" values of certain important parameters of OTA's analysis. In this paper, we make assumptions about key parameters that represent the best available evidence about their true values and examine the effects of uncertainty through sensitivity analyses.

OTA'S CRC SCREENING MODEL

OTA's expanded CRC screening model is a natural-history-based model that traces the health status and health care costs of a population from age 50, when a specific screening

strategy begins, through age 85, when screening stops. Improvements in mortality from early detection and prevention of cancer are translated into added years of life lived in the population compared with a no-screening scenario. The model estimates the incremental costs of screening, diagnostic followup of positive screening tests, and periodic surveillance of patients found through screening to have a polyp, as well as the potential savings from treating cancer in earlier stages or from preventing CRC altogether. The OTA model also accounts for the extra costs and lost years of life resulting from detection and treatment of some cancers that would have remained silent throughout a person's life in the absence of the screening program.

The cost-effectiveness of a particular screening strategy (one or more screening technologies applied at scheduled intervals throughout an individual's lifetime) is defined as the net present value of the incremental health care costs associated with the strategy divided by the net present value of the added years of life gained as a result of the strategy.[1]

All models of disease processes or health interventions are to some extent abstractions from reality and therefore present a rough map of what can be expected from the implementation of a program. The OTA model has three important restrictions:

. The analysis does not address possible radiation hazards associated with the DCBE procedure.

. CRC is assumed to have two stages -- early and late. These stages correspond to Dukes A&B and Dukes C&D respectively. We opted for a simplified model because of data limitations. A more detailed model would improve the predicted cost-effectiveness of screening strategies, because survival improvements between more refined disease categories would be included. The importance of this limitation in affecting the qualitative results is probably minor, however, because most colorectal cancers destined to progress appear to move quickly from earlier to later stages.

[1]Costs and effects occurring in future years (after age 50) are discounted to their present value in the year of program initiation (when the population is age 50) at an annual rate of 5 percent. The discount rate takes account of the time preferences associated with costs and benefits. (Receiving medical benefits earlier is preferred to receiving them later, while bearing costs later is preferred to bearing them today.)

. The impact of imperfect compliance with screening, diagnostic followup or surveillance regimens cannot be investigated in great detail. Once an individual embarks on a screening schedule, the model assumes he or she sticks with it for the duration of the 35-year program. Adherence to diagnostic followup of any positive screening test is assumed to be perfect. A patient may refuse to comply with surveillance, but OTA assumes that if the patient complies with the first surveillance examination, he or she will continue for the duration of the surveillance period. Any patient who refuses to comply with surveillance is lost to the program altogether (i.e., no rescreening).

Finally, as a map of the true effects of a screening program, the model is limited by the current state of knowledge about the natural history of colorectal cancer, including the adenoma/carcinoma sequence. The model is based on the assumption that a given proportion of cancers begin as adenomatous polyps, and that adenomas remain detectable (with a given sensitivity) by available screening technologies for a given length of time. The evidence to support specific values for these assumptions is sparse. This paper analyzes the impact of changing the values of these key assumptions on the estimated cost-effectiveness of alternative strategies.

SCREENING STRATEGIES EXAMINED

In this paper OTA examines the following strategies for screening average risk adults for CRC beginning at age 50:

1. Annual FOBT;
2. FSIG every 3, 5 or 10 years;
3. DCBE every 3, 5 or 10 years;
4. CSCPY every 3, 5, or 10 years;
5. FSIG every 5 years and FOBT every year;
6. DCBE every 5 years and FOBT every year.

ASSUMPTIONS

For every screening strategy, OTA assumes that an individual with a positive screening test would be subjected to diagnostic workup by CSCPY, except for screening CSCPY, which would involve a polypectomy as part of the same procedure. We also assume that the surveillance schedule or those found to have an adenomatous polyp on screening would be every 4 years.[2]

Table 1 contains a summary of the specific assumptions about parameter values used in this analysis and the range of reasonable values for particularly uncertain parameters. The evidence for many of these assumptions is reviewed in OTA's previous report (OTA, 1990). Several assumptions merit further comment.

Sensitivity of FOBT for Polyps and Cancer (Table 1, no. 1 & 2)

OTA reviewed the evidence in 1990 on the sensitivity and specificity of FOBT for colorectal cancer and polyps (OTA, 1990). That review placed estimates of FOBT sensitivity for CRC at roughly 25-60 percent and for adenomatous polyps at 3-25 percent. The higher sensitivities for CRC were typically in studies of symptomatic individuals referred to a clinic for evaluation or in patients with proven CRC. These studies are biased in favor of high sensitivity. Only a few studies examined FOBT sensitivity in screening or asymptotic populations, and these found FOBT sensitivity for cancer in the 25 percent range. Most of the studies reporting FOBT sensitivity were based on the unrehydrated Hemoccult II (t.m.) test. Recent results from the Minnesota FOBT clinical trial suggest a higher overall FOBT sensitivity in a screening population when the slides are dehydrated before analysis, with a corresponding decline in test

[2] The surveillance schedule can be varied in the model, but any changes in the schedule affect only the costs of the program, not its medical benefits. All people with polyps removed as a result of screening are assumed to live out their life expectancy at the time of first polyp removal regardless of the surveillance schedule. Thus, the model assigns the maximum possible benefits to surveillance regardless of its frequency.

Table 1
Summary of Assumptions

	Parameter	Base Case Value	Range	Source
	Sensitivity/Specificity of Screening and Diagnosis			
1.	Sensitivity of FOBT for Polyps	10%		Table *C-1* (p. 42) in OTA, 1990; see text
2.	Sensitivity of FOBT for Cancer	40%	40-85%	Table C-1 (p. 42) in OTA, 1990; see text
3.	Sensitivity of CSCPY for polyps/ca	90%		see text
4	~~Sensitivity of DCBE for polyps~~/Ca	70%	60%-80%	Table 2 in this paper.
5.	Sensitivity of FSIG for polyps/ca	90%	85%-95%	see text
6.	Reach of FSIG	50%	**35%-70%**	see text
7.	Specificity of FOBT	90%	**90%-98%**	Table C-1 (p. 42) in OTA, 1990
8.	Specificity of CSCPY	100%		see text
9.	Specificity of FSIG	98%		see text
10.	Specificity of DCBE	98%		see text
	Natural History of Polyp/Cancer Sequence			
11.	Prevalence of polyps at age 50	30%		Table 4 in OTA, 1990; see text
12.	Annual polyp incidence rate	age-specific: 50-65: 1.33% per yr. 66-70: 2% per year 70+ : 1% per year		see text
13.	Percent of cancers originating as polyps	70%	56%-90%	OTA, 1990; see text
14.	Annual cancer incidence with no screening	age-specific		SEER data (see OTA, 1990)
15.	Percent of cancers detected in early stages with no screening	40%		SEER data (see OTA, 1990)
16.	Dwelling time of cancer in early stages	2 years		OTA, 1990
17.	Percent of total dwelling time in early stages before clinical detection (0-100%)	100%		
18.	Dwelling time of cancer in late stages before detection	2 years		OTA, 1990
19.	Five-year all cause survival for early cancer	age-specific		SEER data (see OTA, 1990)
20.	Five-year all cause survival for late cancer	age-specific		SEER data (see OTA, 1990)
	For polyps destined *to be clinically* detected *as* cancers in *absence of screening:*			
21.	precancerous polyp dwelling time detectable as FSIG, DCBE, CSCPY	*5* years	*1-20* yrs	see text
22.	precancerous polyp dwelling time detectable by FOBT	*5* years	*1-20* yrs	see text
	Complications and Unintended Consequences			
23.	Rate of perforation of colon in CSPCY	0.1%		OTA, 1990
24.	Death rate from perforated colon	0.02%		OTA, 1990
35.	Surgical mortality rate from colonic resection	4%		OTA, 1990; see text
26.	Prevalence of lifetime-latent cancers at age 50	0.2%		OTA, 1990: see text
27.	Annual incidence of lifetime-latent cancers	age-specific: 50-65: 0.02% 65-85: 0.05%		see text
28.	Rate of perforation from DCBE, FSIG	0		see text.

	costs			
29.	Unit cost of screening FOBT	$10		see Table 3
30.	Unit cost of screening FSIG	$80	+100%	see Table 3
31.	Unit cost of screening DCBE	$131	+100%	see Table 3
32.	Unit Cost of screening CSCPY	$285	+100%	see Table 3
33.	Unit cost of diagnostic CSCPY	$285	+100%	see Table 3
34.	Unit Cost of diagnostic CSCPY with polypectomy	$434	+100%	see Table 3
35.	Unit cost of surveillance CSCPY	$285	+100%	see Table 3
36.	Unit cost of tissue pathology for polyps and lesions	$64	+100%	see Table 3
36.	Lifetime cost of treating early cancer	**$35,000**		see text
37.	Lifetime cost of treating late cancer	**$45,000**		see text
38.	Lifetime cost of treating perforated colon	$35,000		see text
39.	Discount Rate	5% per year		

specificity. Mandel and colleagues reported FOBT sensitivity for cancer (detected within one year of the screening FOBT) at 92.8 percent, with specificity of 90.4 percent, compared with a test sensitivity for CRC of 81 percent and specificity of 98 percent with unrehydrated slides.

The very high sensitivity for cancer in the Minnesota trial -- higher than almost all estimates of sensitivity in the pre-1990 studies including those in symptomatic or confirmed cases -- may be partly an artifact of the research environment of the trial. Not only would the procedures followed by both patients and providers be more carefully controlled than in a real-world setting, but the likely prevalence of more advanced cancers at the beginning of the trial could produce a sensitivity that is higher than what would occur in a population screened first at age 50.

As a base case, OTA assumes that not all FOBT slides would be dehydrated. We assume that the sensitivity of FOBT for cancer would be 40 percent. However, we estimate the effect of increasing the sensitivity of FOBT to 85 percent on the absolute and relative cost-effectiveness of FOBT.

Because most polyps, especially small ones, probably do not bleed, a low sensitivity of FOBT for polyps is to be expected. Although the Minnesota trial did not report on the sensitivity of FOBT for polyps, it appears to be low, since the rate of new cancer incidence in the population did not fall during the course of the trial. This conclusion is consistent with the pre 1990 studies, which found a low sensitivity for polyps, especially small ones, in screening populations (OTA, 1990). Screening studies in high risk workers in the U.S. revealed a sensitivity of Hemoccult II for polyps in the rectosigmoid of 3-5 percent (Bang et al., 1986; Demers et al., 1985). Slides were not dehydrated in these studies, however. OTA therefore assumed that FOBT would detect 10 percent of all polyps.[3]

[3] In the OTA model, sensitivity and the time that cancers spend in the precancerous adenomatous polyp stage before transforming into cancers interact to determine the number of cancers prevented and the cost of preventing those cancers. The

Sensitivity of Colonoscopy for Polyps and Cancer (Table 1, no. 3)

Recent studies have documented the high but imperfect sensitivity of CSCPY in detecting adenomatous polyps and cancer (Hixon, 1990; Cutler et al., abstract). Small polyps, those less than 1 cm in diameter, appear to have a false negative rate up to 15 percent in non-screening populations. Whether the sensitivity of CSCPY in a screening context would be higher or lower than that observed in recent studies is unknown. On the one hand, colonoscopists may be less suspicious and therefore miss more lesions in a screening examination. On the other hand, if high-volume screening CSCPY programs were initiated, the sensitivity of the test could increase. OTA assumed that the sensitivity of CSCPY for polyps and cancer would be 90 percent in all examinations, including screening, diagnostic followup and surveillance.

Sensitivity of DCBE for Polyps and Cancer (4)

We searched the literature for studies of the sensitivity of DCBE. Table 2 summarizes the methods and findings of 22 such studies. None were conducted in asymptomatic screening populations, and most studies suffered from serious biases. Often, DCBE sensitivity was estimated at least in part from referrals after a positive DCBE. (See, for example, Steine et al., 1993; Thoeni and Petras, 1982; Ott et al., 1989; Ott et al., 1985; de Roos et al., 1985). When the universe of cases against which the sensitivity of the DCBE is tested is built from referrals based on the same DCBE, sensitivity is bound to be overstated. People with false negative DCBEs not referred for further evaluation are inappropriately excluded from the universe of cases in these studies. Not surprisingly, these studies uniformly showed high sensitivity of DCBE, in the range of 85-95 percent. Other investigators retrospectively reviewed prior newly diagnosed cancer

sensitivity of FOBT for polyps may be high for a brief period as polyps grow and bleed more frequently, but much lower when polyps are newer and smaller. The length of the precancerous dwelling time of adenomatous polyps is a model parameter of great uncertainty. In this paper, two dwelling times are assumed --5 years and 10 years. These may both be high as estimates of the time that most polyps are detectable by FOBT. The joint assumption of 10 percent FOBT sensitivity for polyps and a 5-year polyp dwell time means that every polyp destined to become cancer will bleed enough to be detectable by FOBT 10% of the time for 5 years.

Table 2
Summary of Studies of DCBE Sensitivity

Author(s)	Time and Place	No. of confirmed cases	Definition of Universe of Cases	Sensitivity	Study Design Biases (+) = toward overestimate of sensitivity (-) = toward underestimate of sensitivity
Anderson et al., 1991	New Zealand, 1981-1984	89	CRC cases diagnosed by CSCPY and pathologically confirmed within 3 years of BE	CRC: 70.8	• not screening population + • negative DCBEs not all confirmed (cases with delay > 3 yrs not included in universe) + • interval cases defined as false negative -
Beggs and Thomas, 1983	England, 1976-1980	90	All histologically proven colon cancers (not including rectum) seen at hospital with a BE prior to diagnosis	CA. 96.6	not screening pop a • false negative BE findings not referred to clinic+
Bolin et al., 1988	Sweden, 1971-1983	708	patients treated with CRC who had undergone 1 or more BE examinations before treatment.	CA. 90	• not screening population+ • false negative BE findings not referred to clinic+
Brady et al., 1994	Canada, 1990	161	colorectal cancers treated in 1990 with BE and CSCPY within three years prior to treatment	8[illegible]	• not screening population+ • false negative BE findings not referred to clinic+
Brewster et al., 1994	Scotland	294	patients referred to clinic for DCBE with abnormalities confirmed either by DCBE or FSIG performed on same day	rectal polyps: 11/38 sigmoid polyps: 17/47 recto-sigmoid CA: 100%	• not screening population+ • censured follow-up period: some double false negatives not counted+
deRoos, et al., 1985		49	consecutive patients undergoing DCBE with ultimate positive diagnosis confirmed by CSCPY, surgery, autopsy, or SCBE	Polyps and CRC: 90.9	- not screening p..p..a... • false negative DCBEs not referred for DCBE+
Durdey et al., 1987	England 1985-86	43	Consecutive patients presenting to surgical clinic with symptoms of colonic disease and referred for a barium enema after a negative FSIG with a final diagnosis of cancer or polyp	adenomatous polyp 27 CA: 0	..o. s..ee g p p a • FSIG may have screened out larger polyps +
Evers et al., 1981	USA 1976-1978	90	retrospective review of hospital records of patients with pathological diagnosis of rectal carcinoma	rectal CA. 91	- not s..ee....g p..p..a... • clinically detected cancers with potential late stage distribution and large size +
Fork, 1983	Sweden 1976-1980	99 CA 127 polyps	All CRC cases identified through 3- to 4-year followup period in a series of 2590 consecutive patients referred for DCBE May 1976-January 1977. Virtually all CRC cases would be treated at the same hospital as the DCBE. All benign polyps identified in 31 CRC cases	CA. 94 Polyps: <5 mm: 5 >=5 mm: 89	• not screening population+ • negative DCBEs not all confirmed + • interval cases defined as false negative - • all DCBEs read by at least 3 radiologists+

Hogan et al., 1977	USA	50	prospective study of patients referred to clinic for polyps found on routine BE. Prospective study of CSCPY and DCBE in these patients. True positive identified as lesions found either on DCBE or CSCPY	< 5 mm: 6; 5-9 mm: 52 > 1 cm: 82	• false negative SCBE findings not referred to clinic+
Jensen et al., n.d. (abstract)	Sweden	N.G.	patients referred for followup of positive screening FOBT. Cases of polyps or cancer identified through followup CSCPY or clinical detection in 2-yr followup period	CRC&polyps>1 cm: 72	• not screening population ◦ negative DCBEs not all confirmed (cases with delay > 2 yrs not included in universe) • interval cases defined as false negative -
Jensen et al, BJS, 1986	Sweden	99	Rectosigmoid lesions found in patients referred for followup due to positive screening FOBT. Lesions found by FOBT, FSIG or CSCPY. DCBE interpreters did not know results of FSIG	Adenomas: all: 71 > 1 cm: 66 CRC: 60	• did everyone get FSIG or CSCPY? If no, +
Jensen et al., 1990	Sweden 1982-88	509	Colorectal lesions found in patients referred to clinic after a positive FOBT screening examination with colorectal lesions found on diagnostic examination or in followup ranging from 1 to 5 years	adenomas: 74 CA: 61	• negative DCBEs not all confirmed + • interval cases defined as false negative -
Johnson et al., 1983	USA 1976-81	1084	all pathologically proven colon cancers in which a BE had been performed at Mayo Clinic.	colon cancer: 95.5 rectal cancer: 86.4	• not screening population+ • false negative BE findings not referred to clinic+ • DCBEs were double-read+ • Selection between DCBE or SCBE was made by referring physicians?
Kelvin et al., 1981	USA 1977-1979	195	All primary CRC cases diagnosed in study period having a DCBE wihtin a 3-year period prior to diagnosis	CA: 94	• not screening population + • clinically detected cancers with potential late stage distribution and large size +
Ott et al., 1989	USA	78	Chart review of consecutive patients having a DCBE and 1 or more polypoid lesions diagnosed by CSCPY	polyps >= 5 mm: 91%	• not screening population+ ◦ false negative DCBEs may not have been referred for CSCPY+
Ott, Chen, et al., 1985	USA	85	chart review of consecutive patients having a DCBE and 1 or more colonic polyps diagnosed endoscopically	polyps: 5-9mm: 88 10-19 mm: 97 >=20 mm: 95	• not screening population+ • false negative DCBEs may not have been referred for CSCPY+

Saito, 1989		193	Polyps of rectum and sigmoid colon found either by DCBE or FSIG in 675 patients examined by both DCBE and FSIG. (DCBE immediately followed FSIG)	5 mm 38.4 6-10 mm: 71.4 >=11 mm: 87.5	ee g p p a
Steine et al.,	Norway		patients referred for a DCBE; lesions confirmed by CSCPY	all polyps: 70 >= 10 mm: 81	• not screening population+ • false negative DCBEs may not have been referred for CSCPY+
Thoeni and Petras, 1982	USA 1980-81	53	Right colon lesions detected in consecutive patients receiving DCBE followed by CSCPY within 3 weeks	right colon CA polyps: 88.2	- ee....g population+ • false negative DCBEs may not have been referred for CSCPY+
Williams, 1982	England	63	Polyps >= 7 mm found on CSCPY in 500 consecutive patients given a post-CSCPY DCBE prior to polypectomy	65	• not screening population+
Williams et al, 1974	England	11	cases selected from a population for CSCPY, most because of positive DCBE, but a few with symptoms and a normal DCBE. Selected cases were those with polyps demonstrated on the DCBE. Sensitivity based on synchronous polyps identified on CSCPY	polyps: < 5 mm: 73 6-10 mm: 87 >10 mm: 98	• not screening population+ • false negative DCBEs may not have been referred for CSCPY+ • selected cases limited only o hose already positive with DCBE+

Key: DCBE: double contrast Barium Enema; FSIG: flexible fiberoptic sigmoidoscopy (60 cm); CSCPY: colonoscopy; SCBE: single-contrast barium enema; CA: cancer; CRC: colorectal cancer.
Source: Office of Technology Assessment, 1995; based on sources on reference list.

cases with a prior DCBE. (See, for example, Anderson et al., 1991; Beggs and Thomas; Bolin et al., Brady et al., 1994). These studies, too, found high sensitivity of DCBE, but they are also likely to be biased upward, because the cases with prior DCBE probably contain more true positives than in cases not receiving a DCBE. Perhaps more important, the sensitivity in these studies is for cancer only, since most polyps, even large ones, are asymptomatic.

A better study design is to prospectively follow a group of patients referred for DCBE and assess the true disease state in each with a procedure or process independent of the DCBE. The studies taking this route (Jensen et al., 1986, 1990; Williams, 1982; Brewster, 1994) routinely found DCBE sensitivity to be in the 65-75 percent range. OTA assumed the sensitivity of DCBE in a screening program would be 70 percent but as with colonoscopy, the sensitivity in a screening context could vary in either direction.

Sensitivity of FSIG for Polyps and Cancer (5)

In the early study, OTA used a sensitivity of 92 percent for FSIG based on evidence from a comparative study in England (Williams, 1982), In this paper, we assume the sensitivity of FSIG would be the same as for CSCPY, or 90 percent of those within reach of the sigmoidoscope.

Reach of FSIG (6)

The earlier OTA study contained a detailed analysis of the proportion of polyps and cancers that could be visualized by the 60 cm FSIG (OTA, 1990). In that study, we conservatively estimated that 35 percent of all polyps lie within the reach of the FSIG. In this paper, OTA more realistically assumes that FSIG can reach 50 percent of colorectal polyps and cancer.

Specificity of FOBT (7)

The Minnesota FOBT trial reported a specificity of 90 percent in dehydrated slides and 98 percent in non-rehydrated slides (Mandel et al., 1993). OTA assumed that FOBT slides would be dehydrated and therefore assumed FOBT specificity at 90 percent.

Specificity of CSCPY, DCBE and FSIG (8,9, 10)

We assume that the false positive rate for polyps and cancer with CSCPY is zero (since polypectomy coincides with the screening procedure), but FSIG and DCBE would identify lesions not found on followup colonoscopy about 2 percent of the time.

Prevalence and Incidence of Polyps (10, 11)

OTA's 1990 report summarized the available evidence on the prevalence of polyps of all kinds from autopsy and colonoscopy studies. At 65, the prevalence reported in studies varies from about 40 to 60 percent (OTA, 1990). Recent studies based on screening colonoscopies have found polyps in 30-60 percent of people around age 65 (Lieberman and Smith, 1991; Rex et al., 1991; DiSario et al., 1991). The prevalence at age 50 for adenomas ranges from 11 to 28 percent in these studies. OTA assumes that 30 percent of screenees will have polyps of some kind (including both adenomas and hyperplastic polyps) at age 50, and 50 percent will have polyps at age 65. The incidence between age 50 and 65 is assumed to be a constant rate calibrated with the two prevalence rates. After age 65, polyp incidence rates are assumed to rise slightly and then decline after age 70 to about 1 percent per year.

Percent of Cancers Originating as Polyps (13)

There is widespread consensus that the vast majority of colorectal cancers originate as adenomatous polyps. In the 1990 OTA study, we conservatively assumed that 57 percent of all

cancers start as polyps. (Our assumption was based on a study that gave a realistic lower bound on the proportion.) Recent studies support the notion that cancers rarely arise de novo (Atkin et al., NEJM; Winawer et al., NEJM, 93; Toribara et al., 1995). Consequently, in this paper we assume that 70 percent of all cancers arise from adenomatous polyps. This new assumption is also probably conservative.

Precancerous Dwelling Time as Adenomatous Polyp (21, 22)

Perhaps the most uncertain aspect of CRC epidemiology is the distribution of times that adenomas spend in the precancerous state.[4] Because the natural history of adenomas is virtually always interrupted at the time they are found, studies following large numbers of small adenomas over time to record their growth and transformation to cancer do not exist. A few studies that followed patients who refused treatment have recorded a long transition period. Three years after polypectomy, investigators in the National Polyp Study found only five cancers in over 2000 patients, but almost 30 percent of all study subject had new adenomatous polyps (Winawer et al., 1993; Zauber, Anne, p.c., March 1995). Thus, a few cancers may grow rapidly, but it appears that the vast majority develop over a long period of time.

OTA's model assumes a fixed polyp dwelling time, but it is possible to approximate a distribution of dwelling times by computing weighted combinations of results under different dwelling time assumptions. To show the impact of this highly uncertain variable on the absolute and relative cost-effectiveness of the alternative screening strategies, we assumed two dwelling times --5 years and 10 years.

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[4] From the modeling perspective, the length of time spent as a polyp includes only the period during which it is detectable by the screening technology at the sensitivity assumed in the model. Thus, dwelling time is probably not independent of sensitivity of the test. OTA's model differentiates between dwelling time for FOBT and the dwelling time for the other screening technologies that rely on direct visualization of the tumor.

Perforation Rates with CSCPY, DCBE, and FSIG (23, 28)

The risk of perforating the colon with colonoscopy is based on a review of the evidence conducted by OTA in 1990 (OTA, 1990). Although there is a small risk of colon perforation with DCBE, it is on the order of 1 in 10,000 (Stevenson, 1989 -ACR review). In this analysis we assume the perforation risk for DCBE and FSIG is effectively zero. Including the costs and mortality impacts of events this infrequent would have minimal impact on the analysis.

Procedure Costs (29-35)

We searched for data on which to base reasonable costs of the screening and diagnostic procedures used in the model. These include the cost of FOBT, FSIG, DCBE, diagnostic CSCPY, CSCPY with polypectomy, and tissue pathology for removed polyps.

Medicare reimburses $4 to physicians who distribute and process the results of FOBTs (p.c., Kevin Hayes, PPRC, April 10, 1995). An estimate of the per-person costs to an HMO of FOBT, including purchasing, distributing and processing returned FOBTs was approximately $9.00 (Myers et al., 1993). Private insurers typically reimburse physicians at higher rates. We use $10 as a base case estimate of the cost of FOBT.

Table 3 shows the 1995 Medicare fee schedule levels for the other technologies associated with screening and detection of colorectal polyps and cancer. The Medicare fee schedule amounts shown in the table are the fee levels approved by Medicare for each procedure performed in a physician's office. If a procedure such as colonoscopy is performed in a hospital outpatient facility, the total allowed amount depends on the cost patterns of each particular facility. In addition, geographic adjustments are made to the fee schedule amount to account for differences in labor market costs among areas. If more procedures are performed in high-fee areas, the Medicare fee schedule would underestimate the average amounts allowed by Medicare even for services offered in physicians' offices. Thus, the Medicare fee schedule amount may

Table 3
Medicare Fee Schedule for Colorectal Cancer Screening and Diagnostic Technologies, 1995*

CPT Code	Description	Average Fee
45330	Sigmoidoscopy, diagnostic	$79.96
45378	Diagnostic Colonoscopy	$284.54
45385	Colonoscopy,lesion removal	$434.08
74280	Contrast x-ray exam of colon	$130.85
88305	Tissue Exam by pathologist	$64.39

Key: N= update factor and conversion factor for non-surgical services applies to this co
A = implies currently reimbursable under Medicare

source: Federal Register, vol. 59, no. 235, 12/8/94 p. 63434ff

* Fees paid for procedures performed in physician's office including professional, technical and malpractice components. Fees vary geographically based on geographic adjusters. Amounts paid for procedures performed in outpatient hospital and ambulatory surgery centers differ from those above based on institutional costs.

represent a lower bound on the actual fees received by providers when they perform a procedure on Medicare beneficiaries.

Private health plans reimburse providers higher amounts for these services than does Medicare, although we did not have access to national average reimbursement rates for privately insured individuals. According to researchers at Kaiser Health Plan in Oakland, California, the 50th percentile of private reimbursement in Oakland is $148 for FSIG, $834 for diagnostic colonoscopy and $1048 for colonoscopy with polypectomy (p.c., B. Fireman, Kaiser Health Plan, Oakland, CA, October, 1994).,

Health maintenance organizations may have costs that are closer to the Medicare rates. Group Health Cooperative of Puget Sound, for example, reported a mean cost of all kinds of colonoscopy taken together of $273 in 1993 (p.c., Stephen Taplin, GHCPS, June 16, 1993). This cost-accounting estimate includes physician and technical costs. Myers and colleagues recently reported that US HEALTHCARE, a mid-Atlantic region HMO, paid $315 for colonoscopy (type unspecified) in 1993 and $234 for barium enema x-ray and FSIG together (Myers et al., 1993). Kaiser Oakland reported a much higher cost based. Diagnostic CSPCY was estimated to cost $575 in Kaiser in 1994 (p.c., B. Fireman, Kaiser Health Plan, Oakland, CA, October, 1994).

In this paper OTA assumes in the base case procedure costs equal to the 1995 Medicare fee schedule. The implication for cost-effectiveness of doubling the procedure costs is explored in a series of sensitivity analyses.

Cancer Treatment Costs (36-38)

The lifetime costs (discounted at 5 percent per year) of treating colorectal cancer in the Kaiser Foundation Health Plan were estimated recently in a study sponsored by the National Cancer Institute (Fireman et al., 1994). The researchers estimated the cost of treating early

cancer at approximately $35,000 and of treating late cancer at $45,000. Another study of the three-year (undiscounted) costs of treating colorectal cancer in a mid-Atlantic region HMO estimated the stage-specific costs as follows: Dukes A: $21,825; Dukes B: $23,000; Dukes C: $33,674; and Dukes D: $37,814 (Myers et al., 1993). Because these estimates were truncated three years after diagnosis, they underestimate the full costs of CRC treatment. They are roughly consistent with the Kaiser estimates, however. In this paper we use the Kaiser estimates of the cost of cancer care.

RESULTS

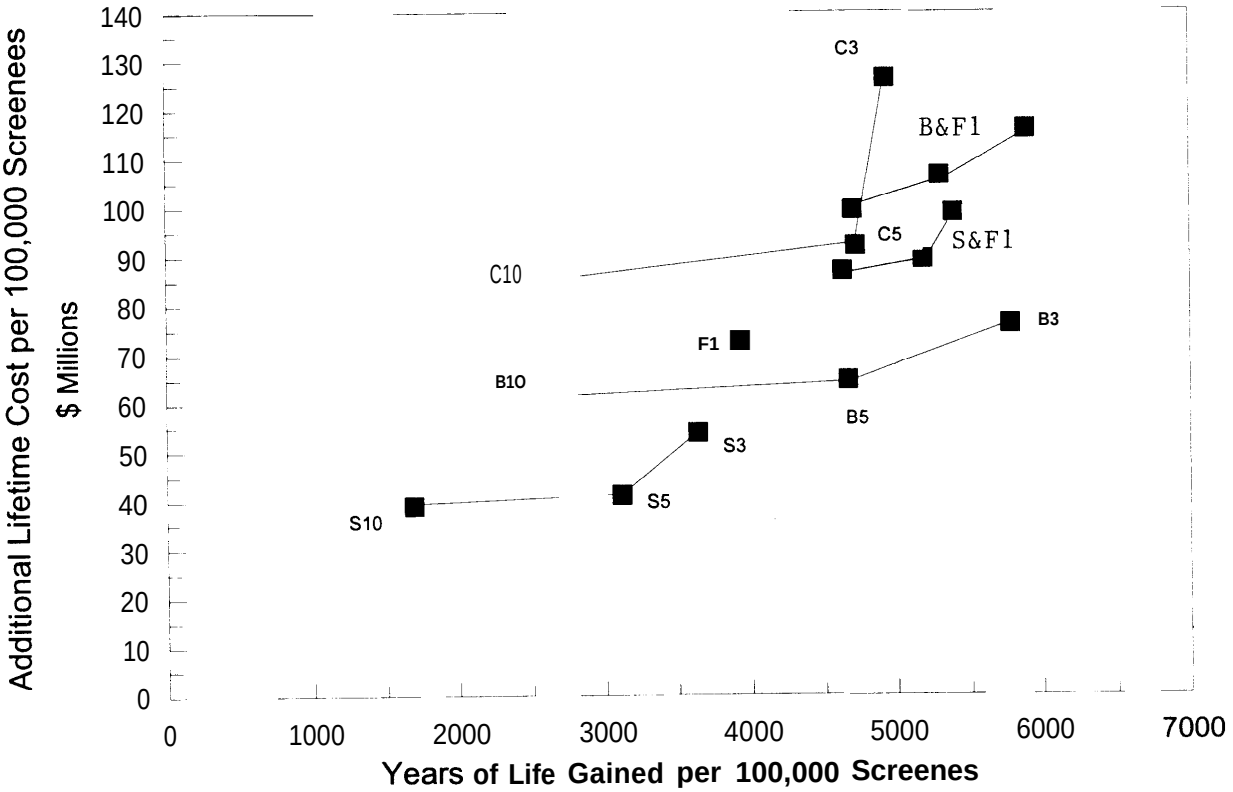
Base Case

Figures 1A and 1B show the base case results for each screening strategy under study for polyp dwell times of 5 and 10 years respectively.[5] Any strategy lying above and to the left of another strategy on these charts is dominated by the other strategy because it is both more costly and less effective than the other strategy. Regardless of whether the polyp dwell time is short or long, FSIG or DCBE strategies dominate all others, including those involving CSCPY and FOBT (alone or in combination with another technology). If the polyp dwell time is 5 years, a DCBE every 5 years is roughly equal in cost-effectiveness to FSIG every 5 years. (The cost-effectiveness ratio for DCBE is $13,844 per added year of life and for FSIG is $13,216 per added year of life.) Although they are comparable in terms of the cost per added year of life, DCBE is both more costly overall and more effective in preventing cancers and finding them early. Thus, the economic issue in selecting among the two screening technologies is one of affordability, not of relative efficiency.

[5] Detailed tables showing the cost-effectiveness ratios are presented in an appendix to his paper.

Figure 1A

Effects and Costs of CRC Screening
5-Year Polyp Dwell Time



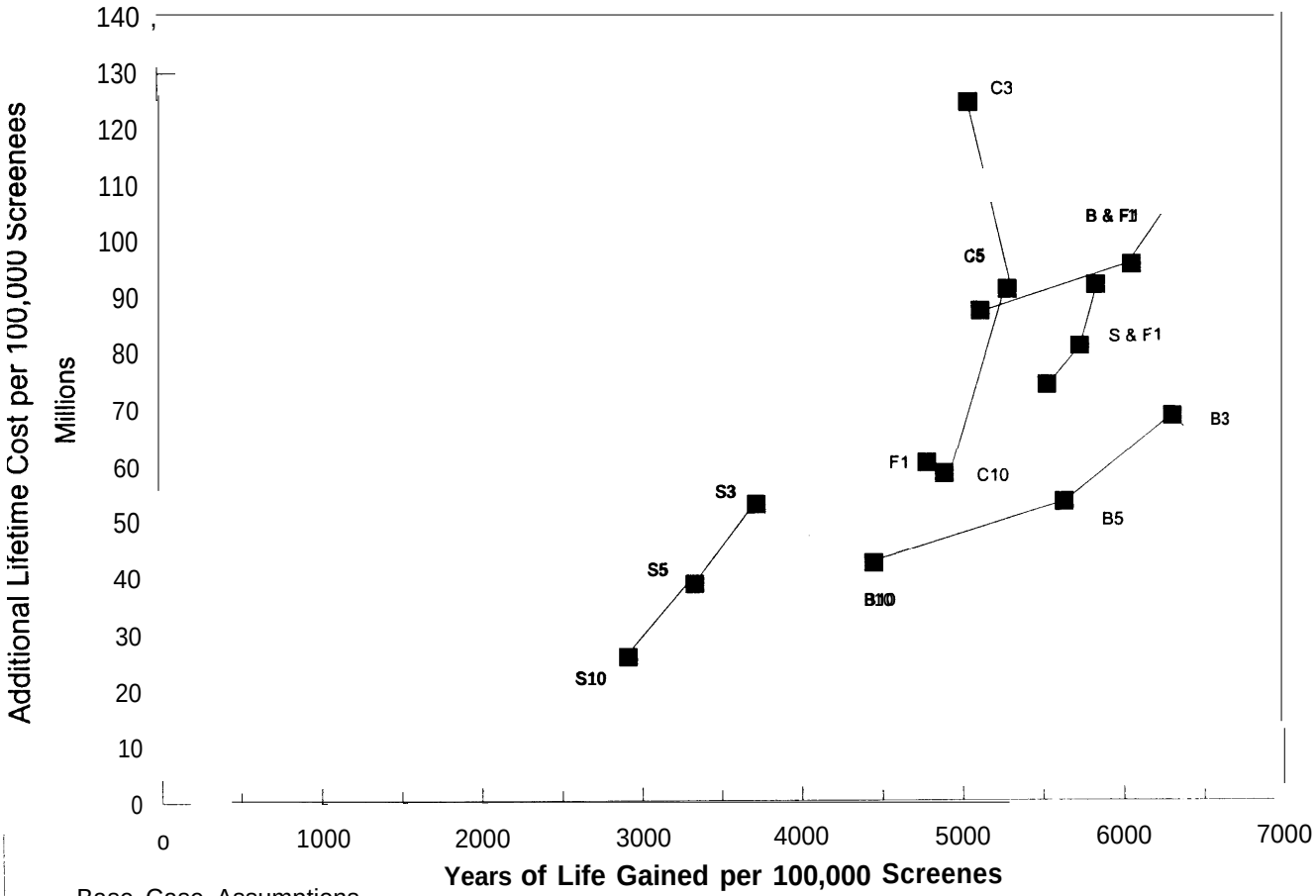
Base Case Assumptions
Source: OTA, 1995

Key: S# = FSIG every # years;
B# = DCBE every # years
C# = CSCPY every # years;
F# = FOBT every # years;
S & F1 = combination strategies of FSIG (various intervals) and FOBT
B $ F1 = combination strategies of DCBE (various intervals) and FOBT

Figure 1-B

Effects and Costs of CRC Screening

10-Year Polyp Dwell Time



Base Case Assumptions
Source: OTA, 1995

Key: Sx = **flexible sigmoidoscopy every x years; Bx = double contrast barium enema every x years; Cx = screening colonoscopy every x years; Fx = fecal occult blood test every x years; B & F1 are strategies combining double contrast barium enema and annual fecal occult blood; S & F1 are strategies combining flexible sigmoidoscopy and annual fecal occult blood test.**

If the vast majority of cancers arising from polyps progress through the polyp phase very slowly, then infrequent screening schedules are more cost-effective than more frequent intervals. If the vast majority of colorectal cancers remain as precancerous adenomas for 10 years or more, the cost-effectiveness of a 10-year schedule for either DCBE or FSIG would be in the neighborhood of $9,000 per added year of life regardless of the technology applied.

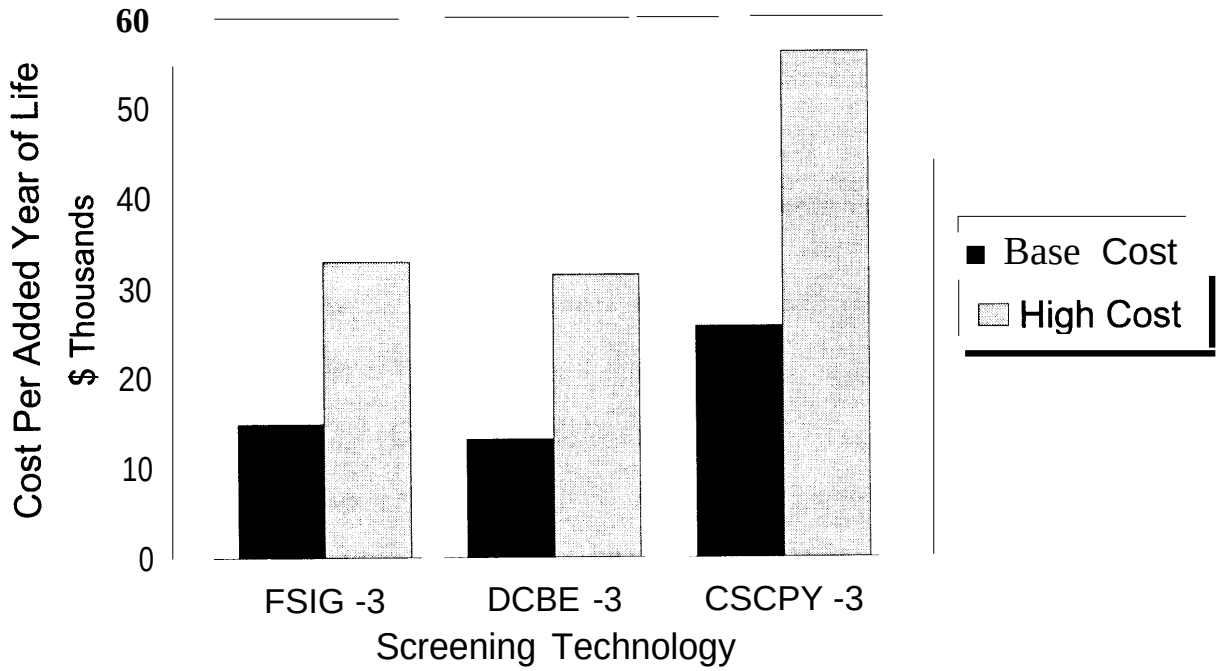
Strategies involving CSCPY as a screening technology do not perform well compared with DCBE. Under the 5-year polyp dwell time scenario, CSCPY every 5 years saves more lives than does DCBE every 5 years, but a 3-year DCBE schedule delivers more health benefits at a lower cost than does a 5-year CSCPY schedule. In the case of a slower polyp dwelling time, more frequent CSCPY schedules cost both dollars and years of life, largely because of the risks of the procedure.

Sensitivity Analysis

Figures 2, 3, and 4 show the impact of doubling the cost of every screening and diagnostic procedure simultaneously. The cost per added year of life increases substantially for all screening strategies. Two observations are very important, however. The relative balance among the alternative screening technologies does not change: what was relatively costly before remains so under the higher cost assumptions. Perhaps more important, the cost-effectiveness ratio remains under $40,000 per added year of life for every screening technology except CSCPY. Thus, if we were wrong by a factor of two in estimating the costs of screening and diagnostic tests, periodic colorectal cancer screening is still a cost-effective intervention when compared with commonly used benchmarks.

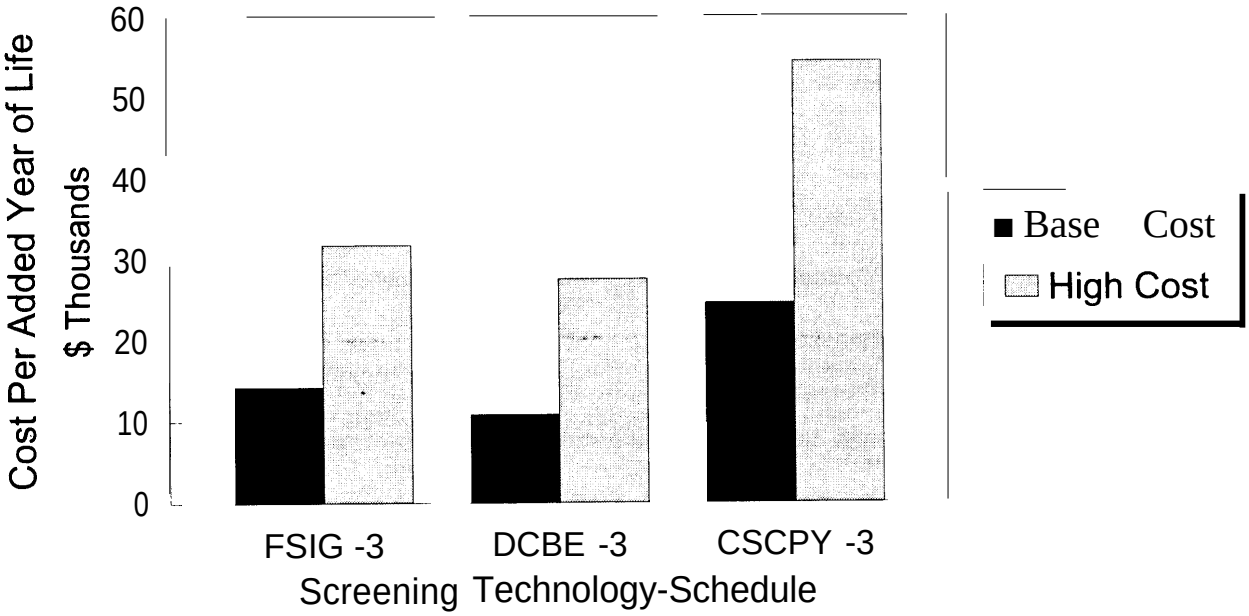
Figure 5 shows how the cost-effectiveness ratio varies with changes in the assumed sensitivity of FOBT. In the Minnesota trial, FOBT sensitivity for cancer was found to be 92 percent with dehydrated slides (Mandel et al., 1993). Assuming a higher sensitivity for cancer

Figure 2A: Sensitivity of Results to Screening Procedure Cost
Five Year Polyp Dwell Time



Source: Office of Technology Assessment, 1995

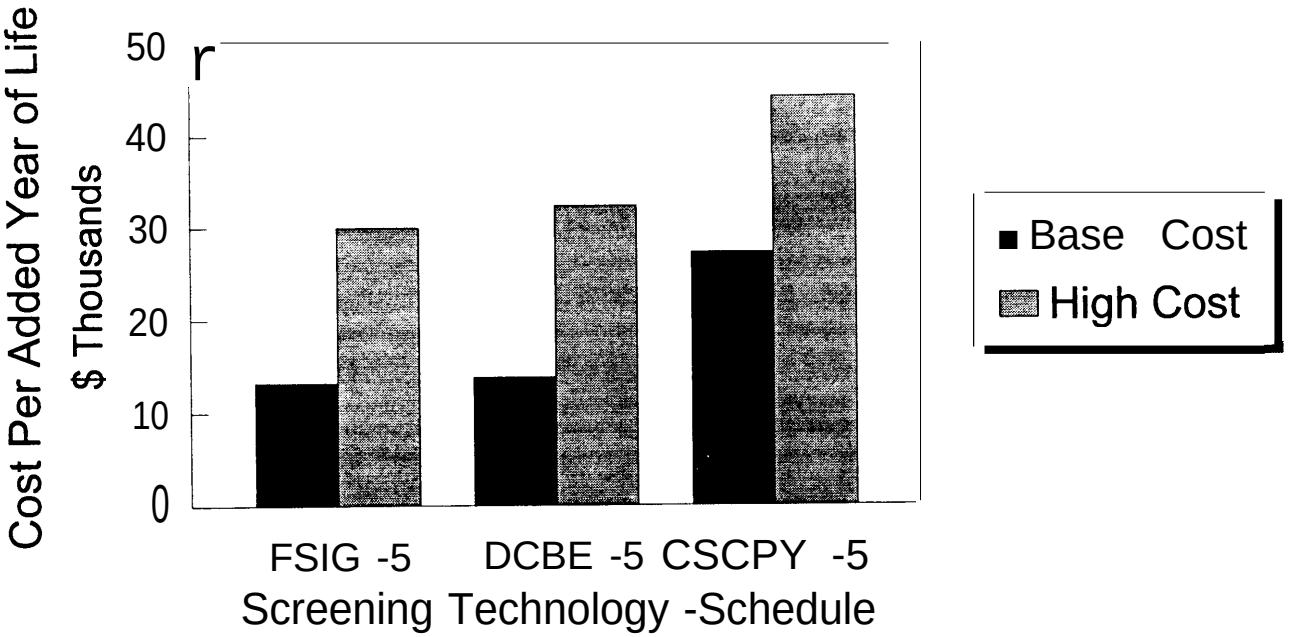
Figure 2B: Sensitivity of Results to Screening Procedure cost
Ten Year Polyp Dwell Time



Source: Office of Technology Assessment, 1995

Figure 3A: Sensitivity to Procedure costs

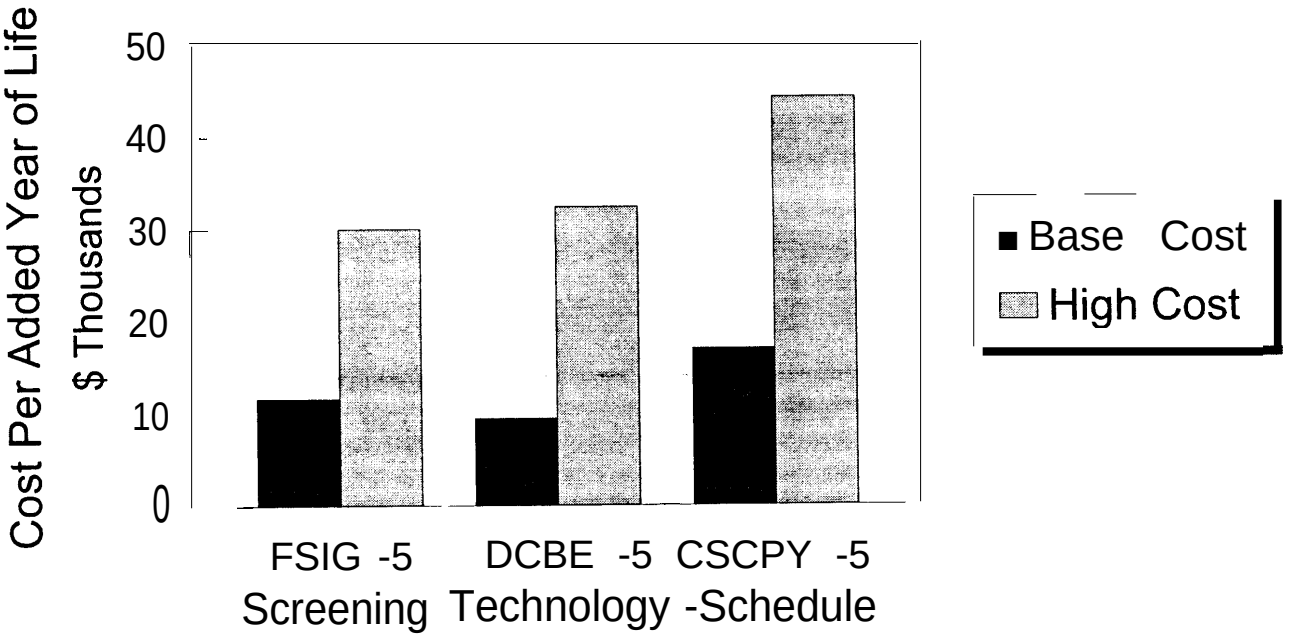
Five Year Polyp Dwell Time



Office of Technology Assessment, 1995

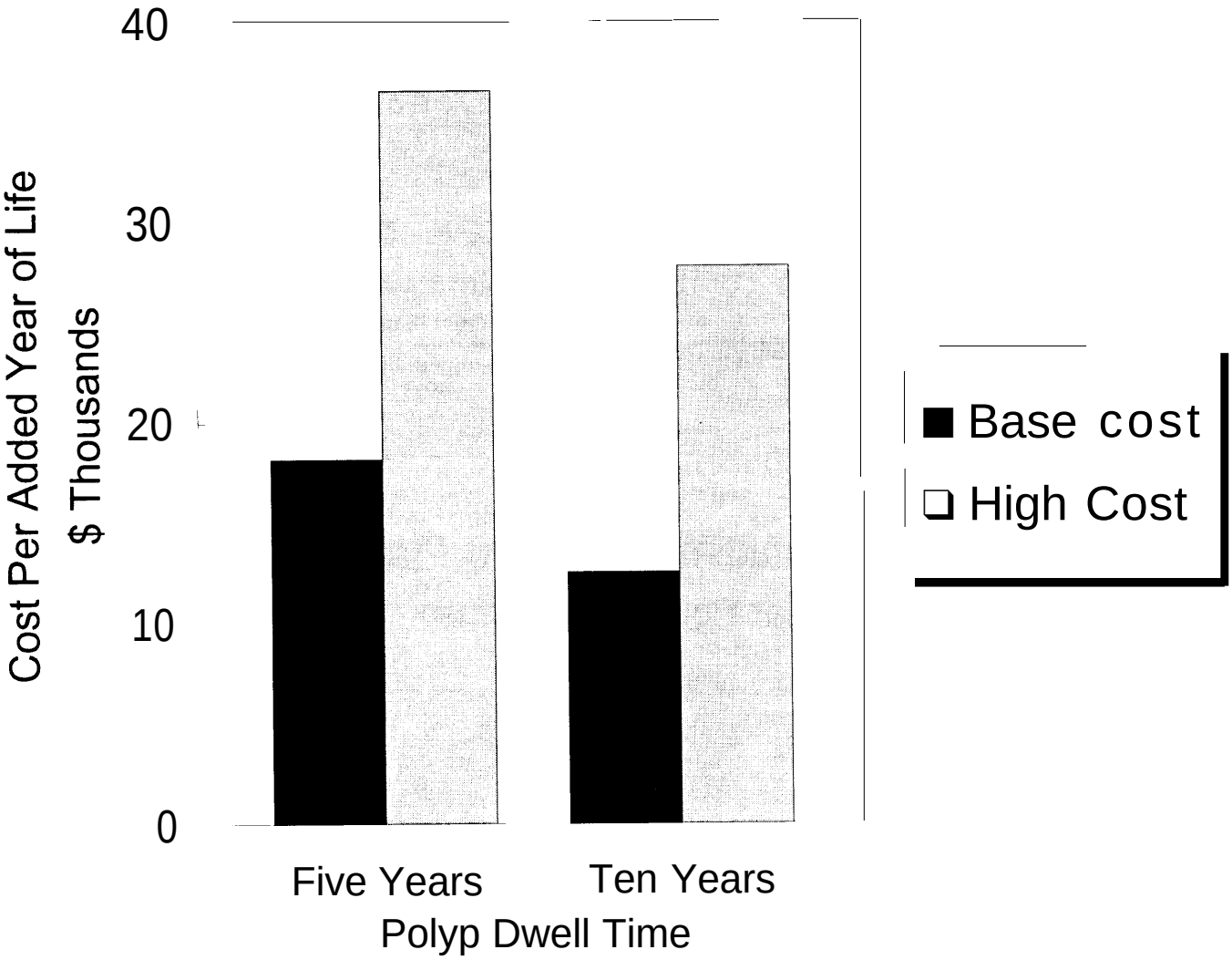
Figure 3B: Sensitivity to Procedure Costs

Ten Year Polyp Dwell Time



Office of Technology Assessment, 1995

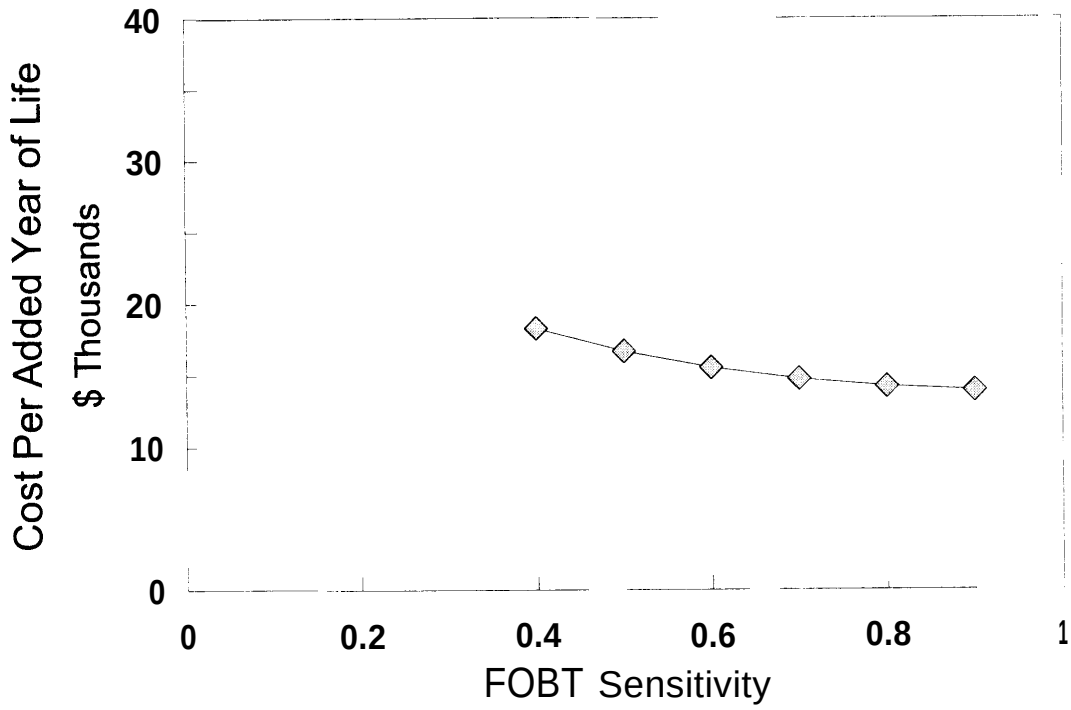
Figure 4: Cost-Effectiveness of Annual FOBT



Source: Office of Technology Assessment

Figure 5: Cost-Effectiveness of Annual FOBT

Five Year Polyp Dwell Time



Assumes FOBT specificity= .90

Source: OTA, 1995

does not markedly change the cost-effectiveness ratio for annual FOBT. This result reflects the fact that the cost saving from finding a cancer earlier ($10,000) is dwarfed by the cost saving from preventing a cancer altogether ($35,000-$45,000).[6]

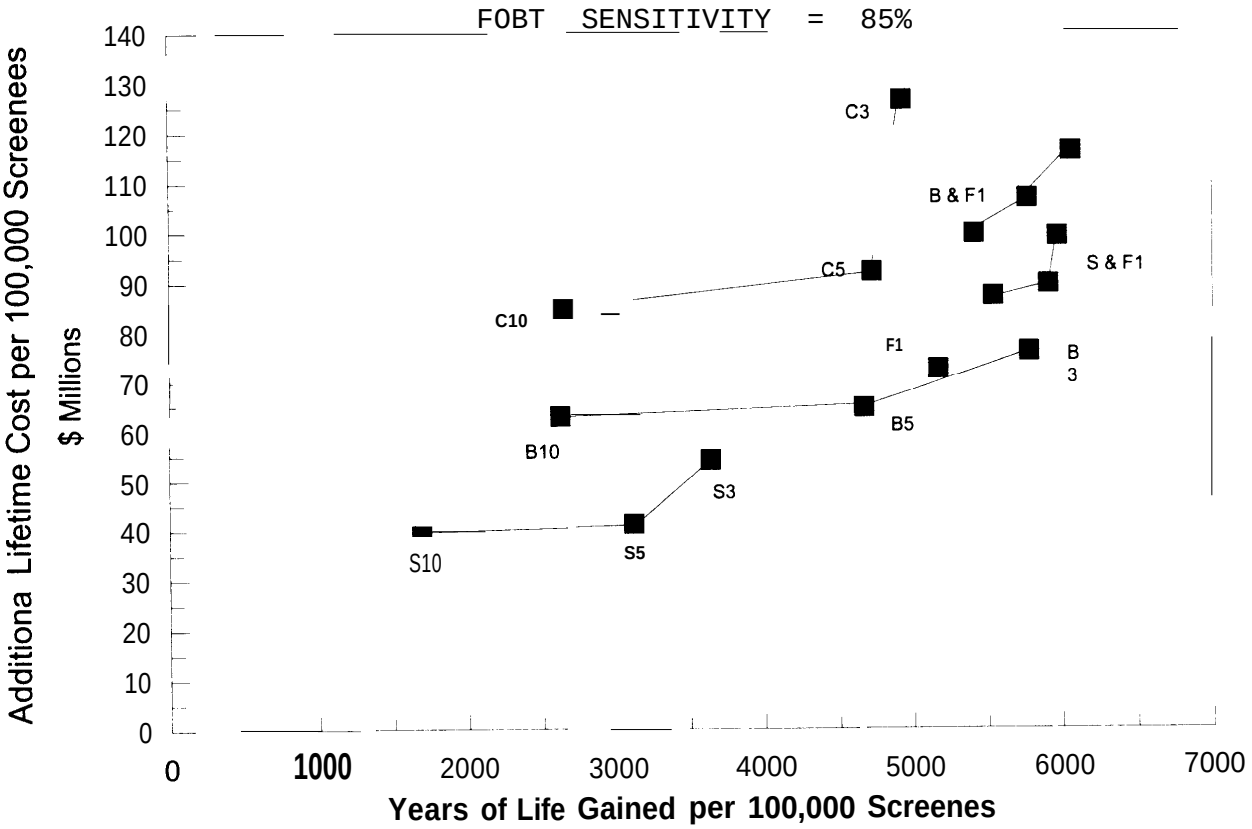
Assuming a higher FOBTsensitivity (i.e., 85 percent) does change the performance of FOBT relative to that of other screening technologies. Figures 6A and 6B show the placement of the different screening strategies when FOBT sensitivity is assumed to be 85 percent. Annual FOBT is no longer dominated by other screening technologies but is on the efficient trade-off frontier along with FSIG and DCBE. Combination strategies (i.e., those combining annual FOBT with periodic FSIG or with periodic DCBE) still remain costly, however, with little gained over frequent DCBE. If most cancers come from polyps, and if polyps move to cancer quite slowly (as assumed in Figure 6B), then little is gained by adding a test with a low sensitivity for polyps to tests that detect cancers and polyps.

The test sensitivity of DCBE is uncertain, especially in a screening context. We examined the effect on costs and years of life lived of assuming a DCBE sensitivity of 50 percent rather than 70 percent, holding all other assumptions to the base case. Table 4 contains the results of that analysis. While the years of life saved decrease by roughly 20-30 percent depending on the screening schedule, the costs of the program do not change very much. Hence, the cost-effectiveness ratio stays well under $40,000. If the true sensitivity of DCBE is only 50 percent, however, FSIG would be slightly more cost-effective. For example, under a 10-year polyp dwell time scenario, the FSIG every 5 years adds 3,334 years of life to a cohort of 100,000 screenees at a discounted net lifetime cost of $38.7 million, compared with 4,561 added years of

[6]In examining the effect of higher sensitivity, we did not change the specificity of FOBT, because the base case value (90%) corresponds to that found in the Minnesota trial with dehydrated slides. A higher specificity of FOBT would reduce the cost per year of life added for the strategies involving lower sensitivity.

Figure 6A: Effects and costs of CRC Screening

5-Year Polyp Dwell Time



FOBT Sensitivity = 85%

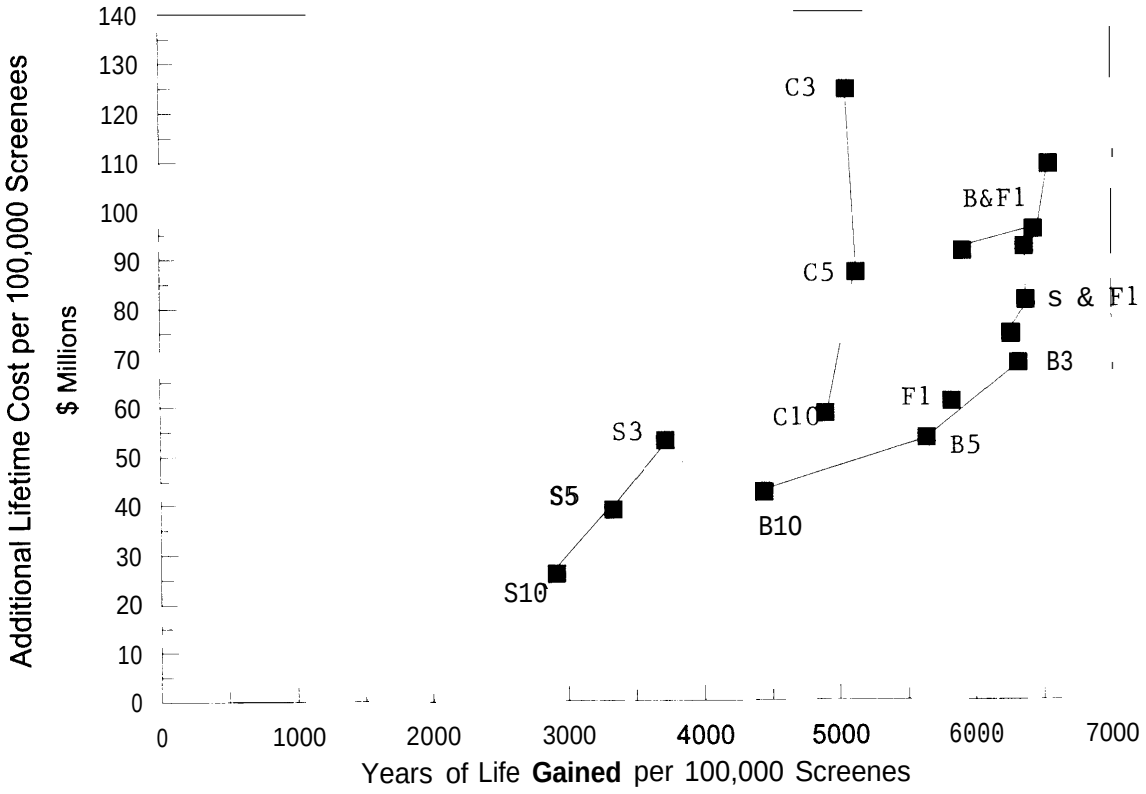
Source: OTA, 1995

KEY: S# = FSIG every # years;
B# = DCBE every # years;
C# = CSCPY every # years
F# = FOBT every # years;
S & F1 = combination strategies of FSIG (various intervals) and FOBT;
B & F1 = combination strategies of DCBE (various intervals) and FOBT.

Figure 6B: Effects and Costs of CRC Screening

10-Year Polyp Dwell Time

FOBT SENSITIVITY = 85%



Base Case Assumptions
Source: OTA, 1995

Key: S# = FSIG every # years
B# = DCBE every # years;
C# = CSCPY every # years;
F# = FOBT every # years;
S & F1 = combination strategies of FSIG (various intervals) and FOBT;
B & F1 = combination strategies of DCBE (various intervals) and FOBT.

Table 4 : Effect of Lower Sensitivity on the Cost-Effectiveness of DCBE

	Years of Life Saved*		Total Lifetime Costs* ($ Millions)		Cost Per Added Year of Life*	
Polyp Dwell Time = 5 years						
DCBE Sensitivity	0.7	0.5	0.7	0.5	0.7	0.5
DCBE Schedule						
DCBE = 3	5,777	4,582	$75.8	$81.8	$13,129	$17,858
DCBE = 5	4,669	3,363	64.6	69.2	13,844	20,571
DCBE = 10	2,630	1,842	63.1	57.9	23,998	31,421
Polyp Dwell Time = 10 Years						
DCBE Sensitivity	0.7	0.5	0.7	0.5	0.7	0.5
DCBE Schedule						
DCBE = 3	6,312	5,554	$68.5	$69.7	$10,848	$12,557
DCBE = 5	5,641	4,561	53.3	55.6	9,450	12,197
DCBE = 10	4,450	3,192	42.5	43.1	9,541	13,495

*All Effects and Costs are discounted to present value at 5% per year.
Source, OTA, 995.

life gained and net cost of $55.6 million for a DCBE every 5 years. The cost-effectiveness ratio for FSIG is $11,622, compared with $12,197 for DCBE.[7]

CONCLUSIONS

All of the screening strategies reviewed by OTA offer health benefits at a "price" that is well below the benchmark value -- roughly $40,000 per added year of life -- commonly applied to preventive technologies. Only screening CSCPY is more costly, and then only under high-cost assumptions.

A lifetime schedule of colorectal cancer screening beginning at age 50 requires a net lifetime investment whose present value is roughly $400 to $1300 per person entering the screening program, depending on both the polyp dwell time and the specific screening strategy adopted. Strategies involving either FSIG or DCBE alone require a lifetime investment whose present value is between $400 and $700 per person screened. For that investment, the population would reap gains in life expectancy on the order of roughly 1 week to 1 month per person screened. Although this gain in statistical life expectancy appears small, in the real world, the benefits would be concentrated in the roughly 6 percent of 50-year-old Americans who, in the absence of screening, are destined to suffer from colorectal cancer at some time in their life.

Thus, if OTA's model is a reasonable approximation of the natural history of CRC and the accuracy and costs of the screening interventions, the implications for CRC screening guidelines are clear: CRC screening in average-risk adults beginning at age 50 is a relatively good investment for society.

[7] Detailed results for every strategy are included as an appendix to this paper.

Much more difficult is the choice among alternative screening strategies. OTA's analysis suggests that strategies involving either FSIG or DCBE (but not both) are comparable with one another and are more cost-effective than other strategies. Whether the screening interval should be long or short is unclear, however, because much depends on the distribution of speeds with which polyps destined to become cancer progress through the precancerous polyp stage. FOBT may also be competitive with these two strategies if it does deliver a sensitivity equal to that seen in the Minnesota FOBT clinical trial.

This analysis did not address the acceptability of the alternative technologies to the individuals who would undergo screening. All of the screening tests are uncomfortable or unpleasant to one degree or another, and people's attitudes about the acceptability of different tests surely vary. Public policy makers should consider the practical implications of limiting the screening technologies offered to the public both for the rational organization of screening programs and for rates of participation.

Finally, the accuracy or safety of some CRC screening technologies may vary widely with the details of program organization or operator competence. OTA's analysis does not consider the costs of promoting quality assurance in CRC screening. These issues need to be addressed both by policy makers and program developers if CRC screening is to deliver the major health benefits so clearly indicated by recent clinical evidence and by OTA's cost-effectiveness analysis.

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Table Appendix A-1
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RESULTS FOR BASE CASE ANALYSIS: (FIGURE 1-A)
Five Year Polyp Dwell time
Per 100,000 Screenes

	Years of Life Saved discounted	Total Discounted C discounted	Cost per Year of Lif discounted
FSIG -3	3,637	54,000,860	14,849
FSIG -5	3,116	41,184,639	13,216
FSIG-10	1,690	39,136,926	23,160
FSIG10/FOBT1	4,642	86,929,372	18,727
FSIG5/FOBT	5,182	89,236,309	17,222
FSIG3/FOBt	5,386	98,703,444	18,326
DCBE -3	5,777	75,841,959	13,129
DCBE -5	4,669	64,643,862	13,844
DCBE-10	2,630	63,113,305	23,998
DCBE5/fobt	5,300	106,349,982	20,067
DCBE10/fobt	4,709	99,347,323	21,096
DCBE3/FOBt	5,883	115,757,634	19,678
FOBT - 1	3,968	72,080,548	18,166
CSCPY -3	4,931	126,387,557	25,632
CSCPY-5	4,728	92,016,472	19,464
CSCPY-10	2,646	84,720,803	32,013

Appendix Table A-2

RESULTS FOR BASE CASE ANALYSIS: (FIGURE 1[3]
Ten Year Polyp Dwell Time
Per 100,000 Screenees

	Years of Life Saved discounted	Total Discounted Co discounted	Cost per Year of Life discounted
FSIG -3	3,721	52,936,451	14,226
FSIG -5	3,334	38,744,480	11,622
FSIG-10	2,916	25,794,441	8,846
FSIG10/FOBT1	5,536	73,943,319	13,358
FSIG5/FOBT	5,743	80 936,550	14,094
FSIG3/FOBt	5,844	91,741,566	15,697
DCBE -3	6,312	68,479,282	10,848
DCBE -5	5,641	53,309,463	9,450
DCBE-10	4,450	42,459,954	9,541
DCBE5/fobt	6,066	95,321,427	15,713
DCBE10/fobt	5,299	91,011,124	17,177
DCBE3/FOBt	6,379	108,507,731	17,010
FOBT - 1	4,792	60,171,093	12,557
CSCPY -3	5,061	124,299,908	24,560
CSCPY-5	5,129	87,177,047	16,996
CSCPY-10	4,898	58,271,024	11,897

Appendix Table A-3
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RESULTS FOR ANALYSIS with FOBT SENSITIVITY = 85% (Figure 6A)
Five Year Polyp Dwell time
Per 100,000 Screenees

	Years of Life Saved discounted	Total Discounted C discounted	Cost per Year of Life discounted
FSIG -3	3,637	54,000,	14,849
FSIG -5	3,116	41,184,639	13,216
FSIG-10	1,690	39,136,926	23,160
FSIG10/FOBT1	5,540	87,237,461	15,747
FSIG5/FOBT	5,907		15,163
FSIG3/FOBT	5,968	99,1	16,605
DCBE -3	5,777	75,841,959	13,129
DCBE -5	4,669	64,64	13,844
DCBE-10	2,630	63,113,305	23,998
DCBE5/fobt	5,770	106,559 006	18,469
DCBE10/fobt	5,414	99,587,324	18,395
DCBE3/FOBt	6,063	116,067,899	19,144
FOBT - 1	5,170	72,391,502	14,002
CSCPY -3	4,931	26,387,557	25,632
CSCPY-5	4,728	92,016,472	19,464
CSCPY- 0	2,646	84,720,803	32,013

Appendix Table A-4

RESULTS FOR ANALYSIS with FOBT SENSITIVITY = 85% (Figure 6
Ten Year Polyp Dwell Time
Per 100,000 Screenees

	Years of Life Saved discounted	Total Discounted Co discounted	Cost per Year of Life discounted
FSIG -3	3,721	52,936,451	14,226
FSIG -5	3,334	38,744,480	11,622
FSIG-10	2,916	25,794,441	8,846
FSIG10/FOBT1	6,264	74,415,648	11,880
FSIG5/FOBT	6,370	81,358,575	12,773
FSIG3/FOBt	6,361	92,202,172	14,494
DCBE -3	6,312	68,479,282	10,848
DCBE -5	5,641	53,309,463	9,450
DCBE-10	4,450	42,459,954	9,541
DCBE5/fobt	6,428	95,658,721	14,882
DCBE10/fobt	5,915	91,351,550	15,443
DCBE3/FOBt	6,538	108,903,224	16,656
FOBT - 1	5,824	60,171,093	12,557
CSCPY -3	5,061	124,299,908	24,560
CSCPY-5	5,129	87,177,047	16,996
CSCPY-10	4,898	58,271,024	11,897