Cost Effectiveness of Alternative Work-up Strategies in Screening for Colorectal Cancer

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ABSTRACT

To the extent that economic evaluation of medical technology is frequently antedated by its diffusion, the prospects for “nay saying” in the light of opportunity costs are limited. This study provides a prospective analysis of the cost of confirmatory testing for a program not yet introduced - use of the faecal occult blood test (FOBT) for colorectal cancer screening. Specifically, it evaluates alternative diagnostic workup strategies - based on existing data on the prevalence of cancers, adenomas and other conditions; the sensitivity and specificity of confirmatory tests (rigid sigmoidoscopy, flexible sigmoidoscopy, double-contrast barium enema and colonoscopy); risks; and net costs to Medicare. Two dominant protocols are identified among the 22 protocols examined. The average cost of one with the best diagnostic yield is conservatively estimated to be $174 per FOBT positive individual. Clearly, a cheap screening test does not equate with an inexpensive screening program.
1 Introduction

1.1 Background

Cancer of the large bowel (colon and rectum) is the most common cancer (excluding skin cancer) in Australia and has the second highest mortality rate, accounting for about 7,000 new cases and 3,750 deaths each year (Giles, Armstrong and Smith, 1987). About 1 in 25 Australians will develop colorectal cancer during their lifetime (Cowan, 1984). Large bowel cancer may occur at any age but the incidence increases progressively after age 40 (see Figure 1). Patients with colorectal cancer fall into two groups: those with surgically curable disease confined to the bowel wall (Dukes’ A and B), and those whose cancer has disseminated to regional lymph nodes and other organs (Dukes’ C and D). In this latter group surgery is only palliative, and five-year survival is less than 40-45 percent. Without any improvement in our understanding of the etiology of the disease or in the treatment of metastases, early detection in the pre-symptomatic phase is seen as providing the best hope for improving the outcome for this disease.

Screening for colorectal cancer using the faecal occult blood test (FOBT) was first advocated by Greegor (1967), based on the results of a small pilot study. Very soon thereafter, the American Cancer Society (ACS) recommended annual use of the test in individuals aged 50 and over (Lefall, 1974). Subsequent technical improvements in the original stool guaiac test which increased the method’s repeatability and validity added to enthusiasm for the test’s routine use as a secondary preventive measure, especially in the United States. The fact that the test is non-invasive and inexpensive has also favoured its adoption by physicians there. Indeed, a 1984 survey of physicians’ attitudes and practices in early cancer detection indicates that three out of four doctors test stool for occult blood among asymptomatic patients and almost nine out of ten (87 percent) say they “agree completely” with ACS guidelines for digital rectal and stool blood early detection procedures (ACS, 1985). These compliance rates are quite high, even allowing for the possible effect of courtesy bias in responses.
Recently, however, a number of reviews have indicated either a considerable degree of hesitation in recommending the test or have recommended that the test not be offered to asymptomatic individuals in any age-group until further evidence regarding its efficacy becomes available. The ambiguous status of the FOBT is reflected in the latest statement of the US Preventive Services Task Force (1989b): 'current evidence is not sufficient to suggest that clinicians who currently recommend faecal occult blood testing for their patients cease this practice. On the other hand, evidence is insufficient to recommend adoption of faecal occult blood testing where it is not currently being practiced....Trials are now underway that should assess more definitely the ability of Hemoccult testing to reduce mortality from colorectal cancer (p. 586).' Similarly, the Canadian Task Force on the Periodic Health Examination (1979) which once endorsed the use of the FOBT as a means of early detection - despite its assessment that only fair evidence existed demonstrating potential benefit of Hemoccult testing - is reported to be reviewing its recommendations. As a matter of policy the Australian Cancer Society advocates awaiting the outcome of the several randomized controlled trials now underway. It recommends that, among symptomless patients at average-risk of colorectal cancer, faecal occult blood testing be restricted to individuals over age 40 who make an informed request and who understand the investigative consequences of a positive test result (Fleming, 1985; Australian Cancer Society, 1987).

The abbreviated history of FOBT screening given above is suggestive of the first few stages of the product life-cycle curve for medical technology described by McKinlay (1979). As this model indicates, diffusion tends to precede (and all too often, preclude) the kinds of formal evaluation that are necessary to determine efficacy. Needless to say, questions of effectiveness and efficiency, which deal with the benefits realised (as opposed to anticipated) and costs, are typically (even later) afterthoughts, especially for "little ticket" items.

At least as far as Australia is concerned, the prevailing diffidence about use of the FOBT as a screening test and the need to await the results of on-going randomized trials provides an opportunity to undertake a prospective economic evaluation. The present study does not seek to examine the cost-effectiveness of colorectal cancer screening per se. Rather its more limited aim is to evaluate the cost-effectiveness of some of the algorithms that can be used in the diagnostic work-up of asymptomatic individuals with positive Hemoccult tests. Although it is true that cost-effectiveness analyses should preferably focus on final outcomes rather than intermediate ones (e.g., life-years saved rather than cases detected) and include diagnostic and treatment costs (Mooney, Russell and Weir, 1980), this seems premature in the case of colorectal cancer screening. As Evans (1984) notes, prior considerations dictate that "if the project doesn't work, efficiency is no help" (p. 264). On the other hand, if it does work, knowing something about the implied order of magnitude of confirmatory tests may act as a counterpoint to enthusiasm (rekindled) for an apparently cheap and efficacious screening test. If the FOBT is to be used to screen all persons over age 50 annually, as has sometimes been recommended, the cost and health implications of different work-up strategies are huge. As will be shown, depending on the protocol chosen, there may be sizeable differences in the magnitude of the health care expenditures involved and the net health benefits realized.
1.2 Target Conditions of Screening

In the case of colorectal cancer screening, determining the prevalence of the target condition is a far from straightforward exercise. With colorectal cancer, the very definition of the target condition is complicated by the "polyp-cancer sequence" debate. The target condition can be defined more or less conservatively as including (1) only colorectal cancer or (2) colorectal neoplasm (i.e., colorectal cancer and potentially precancerous polyps).

For screening to reduce the burden of a disease, it is necessary that there should be a recognized detectable pre-clinical condition that is known to be a precursor of the disease. Screening tests that apply only to early cancers have a more limited effect (Miller, 1986). Colorectal cancers are thought to arise from polyps or from de novo mucosal lesions (i.e., from a stage where detectable polyps have not occurred). A polyp is a circumscribed lesion that protrudes above the surface of the surrounding flat mucous membrane of the gastrointestinal tract and is visible with the naked eye (Ackroyd and Hedberg, 1985). Polyps can be classified as hyperplastic polyps or neoplastic polyps (adenomas). Of these, neoplastic polyps are the only ones regarded as having malignant potential.

The precancerous potential of a polyp varies according to tissue type, degree of dysplasia and size. Neoplastic adenomas of the large bowel can be divided by histological structure into three types: tubular (or adenomatous polyps); villous (or villous adenomas); and tubulovillous (or intermediate polyps). The distribution of polyps by histological type seems to vary from series to series but, on average, 60% to 70% of adenomas are tubular, 10% are villous and 20% to 30% are tubulovillous (Knight, Fielding and Battista, 1989). Lesions that are greater than 5-mm in size are more likely to be adenomas (Fork, Lindstrom and Ekelund, 1989). The malignant potential of adenomas increases significantly with increasing degrees of dysplasia (i.e., cytologic atypia and architectural disorganization). Dysplasia is also more severe with increasing size of tumour. Overall, size is a more important predictor of malignant transformation than is histological type. The natural history of adenomas shows a mean linear growth of 0.61-mm per month: this corresponds to an average malignancy transition time of 10 to 15 years (Morson, 1974, 1978, 1984; Muto, Bussey and Morrison, 1975).

According to unselected autopsy studies, the overall prevalence of adenomas in asymptomatic individuals over 50 years of age is upwards of 30 to 50 percent, but applicable endoscopic

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1 The view that adenomatous polyps are precursors of colorectal cancer is widely held, but not universally accepted (e.g. Bader, 1986; Frank, 1985a; Miller, 1986). We are obviously not in a position to evaluate this evidence. However, we do note parenthetically that the evidence cited in support of the adoption of a conservative approach to the definition of target conditions is indirect. The association between colorectal carcinoma and adenomatous polyps is based on (1) the similar anatomic distribution of cancers and adenomas; (2) the finding of microscopic cancers in some adenomas; (3) the earlier age of onset of polyp compared to cancer; and (4) the demonstration of cancers at the site of adenomatous polyps previously demonstrated radiologically (Neil and Bruce, 1988). The problem is that there is no guarantee that the factors that lead to the formation of polyps are the same as those that initiate or promote colorectal cancer. Many cancers arise de novo, and most adenomas are found to be benign on long-term follow-up. As Bader (1986) notes, the only data available regarding the probability of a given polyp becoming cancerous 'are statistical data relating to the percentage of malignant polyps, and there are naturally no data concerning transformation during life' (p. 445). This state of uncertainty promotes a leap of faith from association to pseudo-causality and the adoption of risk-averse management strategies. For example, Fork et al (1983) state: 'The ideal approach to treating cancer of the large bowel is prevention. Because circumstantial evidence indicates an intimate relationship between benign polyps and carcinoma of the large intestine, it seems desirable to detect and remove all polyps before they degenerate into malignant lesions' (p. 163).
surveys suggest a much lower prevalence - in the range of 10 to 20 percent in adults (Burt and Samowitz, 1988). A small prospective study by Johnson et al (reported in *Gastroenterology and Endoscopy News*, 1988) found adenomas to be present in only 24% of patients with only age-related risk.

The difficulty in setting up screening programs for cancer of the colon and rectum is the need to identify and treat the relatively high proportion of the population who have adenomatous polyps (despite the fact that, in the absence of screening, only a proportion would go on to develop the disease), often in multiple sites, and to find those who have early cancer without polyps.
2. DIAGNOSTIC PROCEDURES

2.1 Screening Test

A screening test for colorectal cancer can look for either indirect evidence of the presence of neoplasia (faecal occult blood) or direct visual evidence of precancerous or cancerous lesions (endoscopy). The analysis presented below assumes that the screening manoeuvre used is faecal occult blood testing rather than flexible sigmoidoscopy. This is not to prejudice the question of which test procedure is more cost-effective as a screening test. Obviously, this is an empirical issue.

The most popular and widely studied commercial test for faecal occult blood is the Hemoccult II (Smith-Kline Diagnostics). The test consists of a set of slides, each of which contains two windows of guaiac-impregnated paper onto which the patient smears a small amount of stool with a supplied applicator, and is completed over three consecutive days. The principle of the test depends on the presence of a phenolic compound in the guaiac resin. The stool sample contains peroxidases due to the presence of blood. When a solution of oxygen peroxides is poured over the guaiac-impregnated filter paper that has absorbed peroxidases from the stool, the phenolic compound is oxidised. Phenolic oxidation of guaiac in the presence of blood yields a blue colour. It is standard to adopt the any-test-abnormal criterion in interpreting the results of this test i.e., a single reaction among the six smears is regarded as a positive test on that patient, and further investigations are advised.

Faecal occult blood testing has attracted attention as a screening test for colorectal cancer because of its simplicity and its low (direct) cost. Its validity is based on several assumptions: (1) that early colorectal cancers and `premalignant' adenomatous polyps bleed; (2) that the bleeding occurs frequently enough for it to be detected in the course of random testing; (3) that the test is sufficiently sensitive to detect the blood loss; and (4) that the bleeding detected will tend to be due to tumours as opposed to normal blood loss or other factors (Macrae, 1985). In fact, there are unique technical problems associated with the Hemoccult test which contribute to reservations about its use as a screening test. To begin with, it is important to note that the occult blood reaction is not specific to human haemoglobin and may be affected by a variety of dietary peroxidases and catalases, including meat, uncooked fruit and vegetables, and some drugs (e.g., aspirin, iron compounds). A delay of four or more days in developing the slides may result in false-negative tests, especially if bleeding is slight. "Rehydrating" slides with water restores their sensitivity but lowers their specificity.

Because haemoglobin tends to be altered chemically and to lose its peroxidase-like activity as it passes through the gastrointestinal tract, upper gastrointestinal bleeding is less likely to yield a positive test result than lower gastrointestinal tract bleeding. Nevertheless, gastrointestinal bleeding can be due to conditions other than colorectal adenomas or cancer, such as haemorrhoids and diverticulosis. Consequently, when faecal occult blood testing is performed on asymptomatic individuals, the majority of positive reactions are falsely positive for neoplasia.

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2 A third possible screening test, digital rectal examination, is generally discounted because the examining finger, which is only 7 to 8 cm in length, has limited access to even the rectum, which is about 11 cm in length. Given the distribution of cancers in the colon and rectum (see Figure 3), it is not surprising that it has been estimated that fewer than 10% of colorectal cancers can be palpated by digital rectal examination (Schottenfeld and Winawer, 1980).
Reported studies of colorectal cancer screening fall into two groups: uncontrolled “feasibility projects”; and controlled studies. Most uncontrolled trials of screening with Hemoccult report overall positivity rates of 2% to 6% despite differences in their protocols (for a summary see Diehl, 1981, Table 2; Simon, 1985, Table 1). Across the five controlled trials now underway (Gilbertsen, Church, Grewe, et al, 1980; Gilbertsen, McHugh, Schumann, et al, 1980; Hardcastle, Armitage, Chamberlain, et al, 1986; Kewenter, Bjork, Haglind et al, 1988; Kronberg, Fenger, Sndergaard et al, 1987; Winawer, Andrews, Flehinger, et al, 1980) positive results are found for between 1% and 2.2% of individuals screened.

The positive predictive value (PPV) of a test is a function of its specificity, the prevalence of the condition in the population screened, and the sensitivity of the test. Regardless of test sensitivity and specificity, the positive predictive value is very sensitive to disease prevalence at the very low rates of disease occurrence usually associated with screening for cancer in the general population. Age-specific incidence rates for colorectal cancer are known to increase sharply after age 50 years (Giles et al, 1987) as shown in Figure 1. The increase is most pronounced for cancer of the rectum but the incidence of cancer located in the proximal region i.e., the ascending colon and caecum also rises quite sharply beyond age 60 years, especially among women, as Figure 2 shows. One may reasonably expect that the undetected prevalence of this cancer would likewise rise with age. Since the PPV for any population screened will obviously be quite sensitive to the age composition of that population, especially the proportion of those screened under 50 years (if any), it is disappointing that published findings from clinical trials do not include age-specific PPVs. This would certainly aid the comparison of results across trials. As it is, data from the initial screening rounds of these controlled studies indicate that there is a 10-18% chance that an asymptomatic individual with a positive Hemoccult result has cancer. The positive predictive value of the test for cancer and/or polyps is about 40-50% (see Table 1 which summarises some of the key results of the controlled trials now underway).

Table 2 details the high, medium and low estimates of the Hemoccult test's PPV for diagnoses of miscellaneous bleeding (e.g., diverticulosis, internal haemorrhoids, ulcers, etc.), cancer, polyps and no bleeding (i.e., false positive). They are the prior probabilities that are revised on the basis of the findings of subsequent confirmatory diagnostic tests.

2.2 Confirmatory Tests

In screening individuals for colorectal cancer, both the costs incurred and the health benefits realized will depend on the diagnostic work-up strategy adopted in response to a positive Hemoccult test. There are many ways in which the diagnostic tests available - rigid sigmoidoscopy, flexible sigmoidoscopy, colonoscopy and barium enema examination - could be combined. And the number of clinical paradigms reported in the literature suggests a lack of consensus among experts regarding the most appropriate strategy. Needless to say, most seem to have been devised with the aim of maximizing the yield of true positives, without any direct

3 Such data are also critical to policy decisions about screening that may be based in part on the test's risk/benefit ratio, as reflected in the PPV. The point here is that for the benefits of being diagnosed with early colorectal cancer to be realised by true positives in FOBT screening programs, they must be willing and able to undergo extensive follow-up testing and treatment. Many persons over 70 years of age may not meet these requirements. Moreover, especially when the definition of the target condition is broadened to include adenomas, there is the added factor that many individuals are not destined to develop symptomatic cancer in their lifetime, either because they will die from another cause or because the neoplasia will not progress.
consideration of the costs and risks associated with confirmatory testing or any formal calculation of the number of cases liable to be detected.

Decisions about which diagnostic tests to use, and in what order, are not straightforward. The tests examine different regions of the bowel and, as a result, have different diagnostic accuracies. In particular, the length of the sigmoidoscope has a direct effect on case detection since only 30% of colorectal cancers occur in the distal 20cm of the bowel, and only 50-60% occur in or distal to the sigmoid colon (see Figure 3). Second, the relationship between flexible sigmoidoscopy and colonoscopy, and the barium enema study, may be complementary (e.g., Thoeni and Menuck, 1979; Fork, 1981; Thoeni and Petras, 1982; Jensen, Kewenter, Haglind et al, 1986); by identifying the possible location of abnormal lesions, the results of a barium enema study can improve the sensitivity of a subsequent flexible sigmoidoscopy or colonoscopy. Third, the tests have different diagnostic powers and therapeutic potential. With endoscopic procedures, concurrent polypectomy or biopsy of lesions is possible. Where a lesion is suspected on barium enema examination, an additional procedure (usually colonoscopy) is required to make a definitive diagnosis. Fourth, each of the tests has different financial costs. Finally, the frequency and nature of complications varies across this set of tests.

2.2.1 Rigid Sigmoidoscopy

The average depth of insertion of the standard 25 cm rigid sigmoidoscope is 18-20 cm (Winan, Berci, Panish et al, 1980; Nivatvongs and Fryd, 1980; Nicholls and Dube, 1982), and allows examination to just above the rectosigmoid junction. It has been estimated that 25-35% of all colorectal cancers are located within reach of the rigid sigmoidoscope (Bassett, Bennett and Goulston, 1979; Hardcastle, Balfour and Amar, 1980; Chapius, Dent and Goulston, 1982; Greene, 1982; Maglinte, Keller, Miller and Cherhish, 1983). Figure 3 provides an indication of the reach of the rigid sigmoidoscope vis-a-vis other instruments and the distribution of colorectal lesions in the large bowel.


It is sometimes stated that flexible sigmoidoscopy is better tolerated by patients than rigid sigmoidoscopy (e.g., Fleischer, Goldberg, Browning, et al, 1989). In fact, among comparison studies of different sigmoidoscopes, the evidence is mixed. A number of studies indicate that the 30 or 35 cm flexible sigmoidoscope seems to be more acceptable to patients than either rigid or the 60 cm flexible sigmoidoscopes, which rank about equally in terms of patient tolerance or expressions of degree of discomfort (Bohlman, et al, 1977; Winawer, Leidner, Boyle et al, 1979; Winnan et al, 1980; Grobe, Kozarck and Sanowski, 1983; Zucker, Madura, Chmiel, et al, 1984; Dubow, Katon, Benner, et al, 1985). Vellacott, Amar and Hardcastle (1982) found that 76 percent of patients preferred rigid sigmoidoscopy over flexible sigmoidoscopy.

Large series of rigid sigmoidoscopic examinations indicate that there is a negligible risk of colonic perforation (about 1.2-1.8 per 10,000 examinations) where experienced examiners perform
sigmoidoscopy (Bolt, 1971; Nelson, Abcarian and Prasad, 1982). The risk of minor morbidity (bleeding) is assumed to be 0.16%.

### 2.2.2 Flexible Sigmoidoscopy

The long (60 to 65 cm) flexible sigmoidoscope, when fully inserted, can reach the proximal end of the sigmoid or higher in 80% of patients examined, and can therefore reach about 50-60% of colorectal lesions (Marks et al, 1979; Tedesco, Waye and Avella et al, 1980). A number of studies have estimated the sensitivity of cancer to be about 60-90% in the range of the colon the instrument can reach (Winawer et al, 1978; Ott, Wu, and Gelford, 1982; Thoeni and Petras, 1982; Jensen et al, 1986). Other studies indicate that a fibreoptic sigmoidoscope will examine two to three times as much bowel, and detect two to six times as many polyps and two to three times as many cancers, as the rigid sigmoidoscope (Johnson, Quan and Rodney, 1984; Bohlman et al, 1977; Marks, et al, 1979; Protell et al, 1978; Winnan et al, 1980; Grobe et al, 1982; Vellacott et al, 1982; Farrands et al, 1983; Rozen, Ron, Fireman, et al, 1987; Warden, Petrelli, Herrera and Mittleman, 1987). Insofar as flexible sigmoidoscopy parallels colonoscopy within range, its overall sensitivity for cancer and polyps is assumed to be 40-60%.

Because all potential lesions are directly visualized and can be biopsied and removed, a lack of specificity, or the problem of false-positive tests, is not an issue with sigmoidoscopic examination - except where the clinical significance of diminutive (< 5-6 mm) adenomatous polyps is concerned (Feczko, Bernstein, Halpert, et al, 1984; Ott, Gelfand and Wu, 1986). This relates to the problem of the definition of the target condition discussed above. By detecting polyps that are unlikely to become malignant in the patient's lifetime, technically sigmoidoscopy can yield false-positive results (Selby and Friedman, 1989; US Preventive Services Task Force, 1989a, 1989b). It is recommended practice to remove and histologically examine all polyps greater than 5 mm in diameter (Lambert, Sobin, Waye and Stadler, 1984; Stroehlein, Goulston and Hunt, 1984; Fleischer, Goldberg, Browning et al, 1989).

Although fewer data are available for flexible versus rigid sigmoidoscopy, the potential iatrogenic risk associated with flexible sigmoidoscopy seems to be comparable to that quoted above in respect of rigid sigmoidoscopy (Rogers, Silvis, Nebel, et al, 1975; Winnan et al, 1980; Traul, Davis, Pollock and Scudmore, 1983; Rosevelt and Frankl, 1984; Rodney and Albers, 1986). Accordingly, a perforation rate of 0.0125% is assumed for both rigid and flexible sigmoidoscopy.

### 2.2.3 Colonoscopy

The colonoscope can examine the entire colon, although even experienced endoscopists do not reach the caecum in about 10% of procedures (Abrams, 1982; Knutson and Max, 1979; Webb, McDaniel and Jones, 1985). About 10-15% of cancers are located in the caecum (Tedesco, Waye, Avella and Villalobos, 1980; Schottenfeld and Fraumeni, 1982; Fork et al, 1983; Maglinte et al, 1983; Webb et al, 1985). The sensitivity of colonoscopy for cancer and polyps has been estimated to be 90-98% when the results of the barium study are available to the endoscopist (Wolff, Shinya, Geffen et al, 1975; Laufer, Smith and Mullens, 1976; Winawer et al, 1978; Williams, Macrae and Bartram, 1982; Beggs and Thomas, 1983). The sensitivity of colonoscopy without prior barium enema examination is in the order of 80-90% (Abrams, 1982; Thoeni and Petras, 1982; Leinicke, Dodds, Hogan et al, 1979; Knoepp and Suits, 1984; Knutson and Max, 1979; Kronberg and Ostergaard, 1975; Thorpe, Grayson and Wingfield, 1981; Hogan, Stewart, 1984).

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4 The shorter 30 to 35 cm instrument is not included in this analysis.
Greenen et al, 1977). Complications include bleeding in about 2-4.7% of cases (Frickmorgen and Demling, 1979; Williams and Tan, 1979; Abrams, 1982) and perforation when combined with biopsy in 0.3-0.6% of cases (Rogers et al, 1975; Frickmorgen and Demling, 1979; Schwesinger, Levine and Ramos, 1979; Macrae, Tan and Williams, 1983; Abrams, 1982). There is also about a 0.01-0.04% mortality rate associated with colonoscopy (Frickmorgen and Demling, 1979; Macrae, Tan and Williams, 1983). Based on a weighted average of these findings, we assume the risk of major morbidity is 0.2% and the risk of bleeding is 0.25%. Fatal complications are assumed to occur at the rate of 0.04%.

2.2.4 Double-Contrast Barium Enema

Provided patients are prepared carefully, the double contrast barium enema (DCBE) examination can achieve 92-95% sensitivity for cancer and 85-92% sensitivity for polyps (Williams, Hunt, Loose, et al, 1974; Laufer et al, 1976; Thoeni and Menuck, 1977; Winawer, 1978; Ott, Gelfand, Wu and Kerr, 1980; Fork, 1981; Kelvin, Gardner, Vas, et al, 1981; Vellacott et al, 1982; Beggs and Thomas, 1983; Farrands et al, 1983; Fork et al, 1983; Johnson, Carson, Taylor, et al, 1983; Leicester, Lightfoot, Millar, et al, 1983; de Roos, Hermans, Shaw et al, 1985; Jensen et al, 1986; Bolin et al, 1988). Problems in interpretation are most often due to poor preparation and inadequate filling. Because endoscopic examination of the proximal portion of the colon is not always possible, and because blind endoscopic areas can exist in the caecum, splenic flexure and hepatic flexure, DCBE is often described as a useful complement to colonoscopy in particular. On the other hand, it is often assumed that an experienced endoscopist can achieve 100% specificity for neoplasia with colonoscopy\(^5\), compared to a specificity level of 95-98% for a barium enema study. Barium enema examination is assumed to have a 0.02 risk of perforation (Han and Tishler, 1982; Winawer, 1980).

In the only study of patients’ preferences for double-contrast barium enema examination versus colonoscopy, patients expressed a strong preference for colonoscopy in terms of its overall comfort and acceptability (Van Ness, Chobanian, Winters et al, 1987).

\(^5\) The single contrast barium enema examination is not considered in this analysis due to its higher false negative rate vis-a-vis the double contrast barium enema study.

\(^6\) In principle, the validity of this assumption can be checked by determining the frequency of “normal” colonic mucosal biopsies obtained during sigmoidoscopic examination.
3. METHODS

Many protocols for the diagnostic work-up of Hemoccult positive patients have been proposed in the literature, and there are many other clinically defensible protocols that can be constructed using the diagnostic procedures described in the preceding section. With one exception, they all involve the use of multiple tests which are performed in a series, i.e. tests are ordered sequentially, with the performance of subsequent tests being contingent on the results of earlier studies. The "if positive, then this; if negative, then this" nature of the protocols lends itself to their being represented as probability trees. In this context a probability tree is simply a way of displaying the proper temporal and logical sequence of the diagnostic work-up and of identifying the probability paths associated with each type of diagnostic classification or misclassification.

Figure 4 shows the full range of diagnostic strategies examined. A subset of these strategies is recommended in the literature, viz. workup strategies S1-S10 inclusive. The other plausible work-ups included in the evaluation reflect the following guidelines: both rigid and flexible sigmoidoscopy cannot be included in the same protocol; a patient cannot undergo the same test more than twice; if sigmoidoscopy and colonoscopy are both included, then sigmoidoscopy is used first; if barium enema and colonoscopy are both included, then barium enema is used first; a positive barium enema study is always followed by colonoscopy; and a positive colonoscopy is never followed by another test ((Brandeau and Eddy, 1987).

Figure 5 provides an example of a probability tree. It focuses on work-up strategy S5 and begins with a rigid sigmoidoscopy which, if negative, is followed by a barium enema examination and subsequently by a colonoscopy if positive. Calculating the probability of an outcome involves multiplying together the probabilities of the events along each of the paths that lead to that outcome and then adding together the resultant products. For example, to calculate the probability of detecting a cancer, it is necessary to know: (1) the prior probability of cancer in a Hemoccult positive individual; (2) the probability that the cancer is within reach of the sigmoidoscope; (3) the sensitivity of the rigid sigmoidoscope within range; (4) the probability that the cancer will be detected by a barium enema study given a negative sigmoidoscopy result; and (5) the probability that the cancer can be detected by colonoscopy given the results of the barium enema study.

3.1 Procedural Costs

In calculating the cost-effectiveness of the alternative work-up strategies described below, this analysis adopts the perspective of the insurer/health care system, as reflected in the difference between the Medical Benefit Schedule fee and the out-of-pocket cost to the patient. That is, our aim is to identify the protocol that maximizes the number of cases of colorectal cancer (and polyps?) detected, at least cost to Medicare. This approach befits the prospective character of our endeavour but does not gainsay the need for a more fully-fledged analysis should the colorectal cancer screening prove efficacious. Our remit, as we define it, is simply to clarify the

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7 Willingness to entertain this perspective is, of course, not universal as the following quotation indicates: 'In the reductionist model costs and benefits are quantified objectively to assist logic in selecting a best answer. Objective benefits must pass through the subjective gate of perceived value. Programs and services produce costs, and the costs are borne by those who value the perceived benefits. It is acknowledged that increased quantities of life will increase medical costs, but from the patients' point of view the goal is "to die young at as old an age as possible". The primary allegiance of the physician is to the patient, not the insurer' (Rodney, 1987, p. 603).
relative roles that endoscopy and barium radiography might play in examinations of the gastrointestinal tract if the introduction of screening for colorectal cancer is contemplated under a fee structure like the present one. In a sense, this analysis is an attempt to pre-empt the kind of "creeping determinism" hinted at by NHTAP (1987) in its discussion of future trends in the usage of endoscopy in Australia.

The present fee structure differentiates between diagnostic and therapeutic endoscopy, and implicitly assumes that ‘endoscopy is usually performed in hospital (such that) bed charges, theatre fees and sometimes extra fees for anaesthetists, radiologists and assistants must be added to the procedural fee'. We assume that these ‘add-on costs are quite unnecessary' (Goy, 1985, p. 179) and that endoscopy can be performed as an outpatient procedure with minimal sedation (i.e., without anaesthesia), consistent with what is common practice overseas (Marks et al, 1979; Lipshutz et al, 1979; Winnan et al, 1980; Leicester, 1982; Hillsabeck, 1983; Aberg, Ling, Breland and Norlund, 1985; Fleischer et al, 1989) and recommended practice in Australia (Faithfull and Goulston, 1985; Goy, 1985). This assumption tends to level the rather uneven "playing field" between radiology and endoscopy (Gadiel, 1989). To the extent that it is controversial, the consequences can be examined using sensitivity analysis, though, realistically, one would have to anticipate the development of dedicated gastrointestinal clinics in the event that colorectal cancer screening is introduced.

We assume that therapeutic endoscopy is performed in the event that polyps are found, and that diagnostic endoscopy is followed by surgical treatment in the event that colorectal cancer is found (Stroehlein et al, 1984; Ackroyd and Hedberg, 1985; Lambert et al, 1984; Fleischer et al, 1989). In point of fact, some polyps may require surgical excision and some tumours can be removed endoscopically. We do not know the magnitude of the bias introduced by these patient management assumptions, but we suspect it is not great judging from the literature. In the event that polyps are detected in patients who undergo flexible sigmoidoscopy then colonoscopy (immediately, or after a subsequent barium enema study), it is assumed that the procedures are diagnostic and therapeutic, respectively. If the protocol indicates that there is no follow-up colonoscopy after a positive flexible sigmoidoscopy test in a patient with polyps, that test is assumed to be therapeutic. That is, polyps detected are removed during the final endoscopic procedure performed.

In accordance with current recommendations, we also assume that all polyps are examined histologically and that a fee for biopsy is incurred in respect of all colorectal neoplasia detected.

The net cost to Medicare (85% of scheduled fee with a maximum cost of $20 to the patient) of each of the procedures discussed in Sections 2.2.1 to 2.2.4 is summarized in Table 3 together with the assumptions made about the sensitivity and specificity of the tests. Our baseline assumptions reflect a weighted average of the sensitivity and specificity of the tests calculated from values in the literature cited. These data are broadly comparable with those used in previous economic analyses of colorectal cancer screening (Barry, Mulley and Richter, 1987; England, Halls and Hunt, 1987; Brandeau and Eddy, 1987). Also included in Table 3 are data pertaining to two further tests - repeat faecal occult blood test and upper gastrointestinal series - which are included in some of the diagnostic workup protocols described in Figure 4 (see below). In respect of the sensitivity and specificity of these tests, we made the same assumptions as Brandeau and Eddy (1987) as a first approximation, since we obtained similar results independently for the other diagnostic tests.
4. RESULTS

Each of the confirmatory testing strategies shown in Figure 4 are evaluated using the method and data described above. The strategies can be compared with each other in terms of their average cost to Medicare (for a cohort of 1,000 Hemoccult positive individuals requiring diagnostic assessment), the fraction of cancer found, the fraction of polyps found, a measure of test efficiency (viz. the ratio of true positive plus true negative classifications to the total number of tests performed) and complications. Detailed results are summarized in Table 4.

Which protocols appear to be the most efficient and effective? At a conceptual level, the answer is not altogether straightforward. Evaluating the cost-effectiveness of alternative protocols for the work-up of Hemoccult positive individuals is complicated by the definition of the target condition. One solution is to "convert" polyps into the number of cancers that will develop, assuming the cancer-polyp sequence can be accepted as a working hypothesis (Brandeau and Eddy, 1987). This is problematic, however, since "depending on the type of adenomatous polyp, an estimated 5 to 40 percent eventually become malignant [Muto, Bussey and Morson, 1975], a process that takes an average of ten to fifteen years [Morson, 1974; 1984]" (US Preventive Services Task Force, 1989c, pp. 120-121). The uncertainty surrounding the rate of transformation from polyps to cancer can be handled via sensitivity analysis. But, it seems to us inappropriate to equate the diagnosis and treatment of some proportion of adenomas with the diagnosis and treatment of colorectal carcinoma. Expected future cancers are simply not the same as cancers detected now, and if it made sense to do so, discounting would simply add decimal dust to the fraction of cancers detected. Another problem with the "equivalence" approach is that it ignores the significant long-term follow-up costs that may be incurred in the management of individuals with polyps identified as a result of initial screening (Kinzie, Silverman, Gupta et al, 1988; Lambert et al, 1984).

A second concern we have (in a sense the opposite of the one above ) is with the use of the proportion of cases detected as the denominator of the cost-effectiveness ratio. This maximand neglects altogether one of the purposes of follow-up testing among individuals with positive screening test results, viz. identifying true versus false positive cases. The logical fallacy involved is obvious, on reflection. The number of cases of colorectal cancer detected is maximized by not doing any further diagnostic tests on individuals who screen positive. With imperfect tests, each additional test decreases the number of true positive classifications - and increases the number of true negatives identified.

By way of an attempt to address this problem, we also consider the ratio of the average cost of follow-up testing per Hemoccult positive patient to test efficiency (as defined above), as well as the cost per colorectal cancer, and per polyp detected. However, it should be noted that inclusion of the first-mentioned cost-effectiveness ratio serves to broaden the picture rather than to resolve the problem. It goes too far in the opposite direction by effectively giving equal weight to false positive and false negative classifications.

As it happens, in this case, the maximand chosen has a limited effect on the determination of the dominant strategies, as shown in Figures 6, 7 and 8. Using either the proportion of cancers detected or the proportion of colorectal neoplasia detected (defined as colorectal cancer plus 10 percent of polyps), there are only two strategies that are either more effective and/or less expensive. These strategies, S7 and S21, are located on the "efficient frontier". The selection of the preferred workup between these strategies involves a tradeoff between cost and diagnostic
yield, and hence is a value judgement. However, the other twenty strategies are clearly identified as "not optimal", because for each there is a dominant protocol on the frontier that is either cheaper, more effective, or both cheaper and more effective. In general, there is a lack of correlation between the cost and any of the measures of effectiveness for the twenty-two strategies examined.

The two dominant strategies range in expected costs from $83 to $174 per case worked up, and in fractions of cancerous lesions detected from approximately 50 percent to 99.6 percent. The range for polyps detected is from 46 percent to 99.2 percent. The two strategies are dissimilar. Strategy S7 involves the use of a repeat FOBT, followed by rigid sigmoidoscopy among those with positive results, followed by barium enema examination regardless of the result. Strategy S21, on the other hand, consists of flexible sigmoidoscopy followed by colonoscopy in the event that it is negative.

Where the measure of effectiveness used is correct classifications (true positives and true negatives) in relation to total diagnostic tests the efficient frontier is again limited to two diagnostic workup protocols. Significantly, however, only one of the strategies, S7, is common to Figures 6 to 8. Strategy S21 is displaced by S6 from the frontier of least cost/maximum effect alternatives, though it remains superior to all other dominated strategies except S4, S5 and S22 which are all more efficient (in terms of the ratio of correct classifications to diagnostic tests performed) and more costly than strategy S21. On the other hand, strategy S6 lies on the efficient frontier of Figure 8 where it was clearly dominated by strategy S21 in Figures 6 and 7.

This said the dilemma presented by this set of contradictory results is not great. Strategy S21 lies quite near to the efficient frontier of Figure 8 and we certainly would not choose to argue that the error costs of false positive and false negative diagnoses are symmetrical (as implied by the definition of test efficiency used). Thus, it seems reasonable to regard S7 and S21 as efficient strategies in the sense of having a greater diagnostic yield and/or lower cost. Nonetheless, it does seem reasonable to have regard to the identification of false positives as a legitimate indicator of the performance of a diagnostic follow-up strategy in screening contexts. Traditionally, this dimension has been paid scant attention in formal analyses of screening programs, notwithstanding the fact that continued participation in, and ultimately the success of, screening programs may depend on the way in which the false positive experience is handled. In this case, although the identification of the superior workup strategies is not greatly affected by the choice of maximand, the performance of the dominated strategies is seen to be more variable when the measure of effectiveness adopted is test efficiency rather than proportion of colorectal neoplasia detected.

Significantly, the same two strategies are included in the efficient frontier when correct classifications (true positives and true negatives) in relation to total diagnostic tests undertaken is adopted as the measure of effectiveness. Not surprisingly, the performance of the remaining strategies is seen to be more variable than when they are evaluated only in terms of colorectal neoplasia detected. As shown in Figure 8, the use of this criterion also results in the addition of strategy S22, a protocol that is well-dominated in terms of its performance in detecting colorectal neoplasia, to the efficient frontier. Strategy S22 consists of colonoscopy only and hence it not

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8 We are grateful to our discussant, Phil Potterton, for pointing out an error in our plot of Figure 8 (from the data in Table 4) as presented at the Conference. The corrected version of Figure 8 is included herein and the relevant text has been amended accordingly.
unexpectedly yields more false negatives and fewer false positives than strategy S21, at a greater average cost per case worked up.

In examining these results it is important to note that the cost shown for each protocol represents the average workup cost for a cohort of 1,000 individuals with positive screening test results. The net cost to Medicare will be greater for some individuals and less for others. To assess the importance of differences in workup costs for the health care system it is helpful to consider the economic impact of working up every patient with a particular protocol. If the one-fifth of the Australian population aged between 50 and 75 were to be screened every year, and if 2% obtain positive results, then there will be about 68,000 workups per year, and a $100 increase in the cost per workup will cost a total of $6.8 million. On the basis of the results summarized in Table 4, identifying in excess of 90 percent of colorectal neoplasia could cost anywhere from $11.83 million to $30.26 million, depending on whether a protocol like S21, at one extreme, to a protocol like S1, at the other extreme, were adopted. And making due allowance for less than 100 percent participation in the screening program will only scale down proportionately the costs of diagnostic follow-up.

Table 5 shows the incremental costs and effectiveness of the two dominant protocols, S7 and S21. If workup strategy S21 is used instead of S7, as one would imagine to be the case, then the expected cost to Medicare would increase by $91 per case for an additional 49 percent chance of finding an existing cancer. This corresponds to a marginal cost of $1.857 per one percent increase in the chance of detection. Otherwise put, it costs an extra $91,000 to find about 60 extra cases of colorectal cancer among a cohort of 1,000 individuals with positive FOBT screening results.

Brief reflection indicates that the avenues for sensitivity analysis are numerous given the many assumptions that underpin these results. Thusfar, we have examined only the effects of varying the positive predictive value of a positive screening test result for colorectal cancer versus polyps, and of increasing the sensitivity of repeat faecal occult blood testing. In both cases, strategies S7 and S21 remain dominant. It remains to determine whether the efficient frontier is affected by increasing the net costs to Medicare of confirmatory testing where endoscopy is assumed not to be an office-based procedure.

As indicated in Figure 4, strategies S1 to S10 are based on workup protocols recommended in the literature. Only S7 turns out to be an efficient strategy with respect to all workups considered, but we note that it detects only about 50 percent of cancerous lesions, compared with about 99 percent for the other efficient strategy, S21. Part of the explanation for the fact that literature-based workup protocols do not fare well in the present analysis is that, in a number of instances, the strategies include probability tree branches that have negative marginal costs i.e., cost increases but diagnostic yield decreases. To a degree this may be an artefact of the fact that our analysis does not take into account the probability of synchronous lesions. However, we do note that even when such branches are pruned in such a way as to eliminate this anomaly, the workup strategies concerned do not lie on the efficient frontier. In a subsequent analysis we plan to examine the extra costs and benefits associated with the search for synchronous lesions. This is tantamount to examining the marginal cost of branches associated with further diagnostic testing in respect of individuals who have obtained positive results from tests that do not examine the entire colon (cf. Aberg et al, 1985). What we predict is that the clinical and economic significance of including versus not including synchronous lesions will depend on the definition of the target condition. Thus, Brandeau and Eddy (1987) estimated that 96% of Hemoccult positive individuals who have cancer have only one cancer; 22% of individuals with cancer have a co-existing benign
polyp; and 40% of Hemoccult positive individuals with polyps have more than one polyp. For now we note that our findings are consistent with those of Brandeau and Eddy (1987), Barry, Mulley, and Richter (1987) and England, Halls and Hunt (1987). The entire colon should be evaluated following a positive faecal occult blood test.
5. DISCUSSION

Our analysis addresses the question: How should a prudent buyer of preventive health care choose among the various procedures for diagnosing asymptomatic individuals with colorectal neoplasia? Many authorities have made recommendations but little explicit information is available to physicians and policy makers concerning the actual benefits and costs of the many possible combinations of the diagnostic procedures. Such information is necessary to determine the appropriate tradeoff between costs and effectiveness.

In the Australian context it may be objected that the question is premature given that colorectal cancer screening has not been incorporated into physicians’ practices. We would argue to the contrary. First, there are indications that screening programs using faecal occult blood testing are being promoted in Australia, through community groups such as service clubs and on a commercial basis (via the availability of over-the-counter or home test kits). And, in a recent article in the *Australian Doctor Weekly* (23 March, 1990) a doctor was quoted as saying that ‘the GP should be aware of how common bowel cancer is, that it may be symptomless in the early stages and that screening at yearly intervals for patients over 40 was essential.’ NHTAP (1987) has noted that, given the high incidence of bowel cancer, and the potential for the prevention of this disease, the role of endoscopy in investigations of the lower gastrointestinal tract is likely to increase further. Further, the implications of colorectal cancer screening for public health were also examined in a special article in *The Medical Journal of Australia* (Woodward and Weller, 1990) that seems to have been prompted, at least in part, by the increased interest in Australia in screening by faecal occult blood testing.

In the light of these developments, this study seeks to provide an indication (albeit a conservative one) of the order of magnitude of the “downstream costs” of screening - and of the folly of the suggestion that faecal occult blood testing is inexpensive. The direct costs of materials and of the actual delivery and development of test-slides are low but there are many "hidden" monetary and other costs. Even so, it should be noted that the estimated average costs of the diagnostic workup of FOBT positive individuals is quite conservative. To begin with, the costing assumes that all endoscopic procedures are office-based and are performed under minimal sedation, rather than in day procedure centres or public/private hospitals and under anaesthesia. It does not include the added cost of long-term intensive follow-up currently recommended for patients found to have polyps. Nor are the costs arising from complications included. And, it should be reiterated, that no consideration is given to the direct costs of FOBT screening per se or the cost of the infrastructure necessary to promote and sustain community participation in the program.

There is a more general point to be made, too. It is that economic evaluation of health programs is relevant at the time that a choice (between alternatives) is to be made. For policy making purposes opportunity costs are an ex ante concept. There is no point in waiting until the introduction of a health care program is a fait accompli to do an economic evaluation because many alternatives may not be, by then, effectively available. One of the main deficiencies in the practice of economic evaluation is the lack of a clear link between the results of evaluation and decisions. In health care there are two parallel decision making processes: planning decisions about which programs or therapies to reimburse or fund; and clinical decisions about what care to provide for the individual patient. Mechanisms for encouraging a rational diffusion and use of health care technology, and by implication economic evaluation need to have an impact on both decision processes (Haan and Rutten, 1987; Drummond, 1987). Prospective economic analyses
that focus on the nature of the clinical decision-making process have a very good chance of doing both - assuming that regulation by directive (or incentive?) is feasible for small ticket items.

Our approach stands in contrast to the only recent Australian study of diagnostic tests of the colon, i.e. Doessel's (1986) econometric analysis of utilisation rates. The essence of this approach is explained by the following statements: `has the per capita utilization of the "old" diagnostic tests of the colon fallen as the "new" fiber optic procedures have been adopted? On a priori grounds it would be expected that, as per capita use of the "new" technology increased, other things being equal, the per capita use of the old technology would fall' (p. 499). We see problems with this type of "black-box" approach to diagnostic/therapeutic technologies. Doessel's study treats the new and emerging technologies as alternatives to those in common use (e.g. barium enema examination). However, if one recognises that the technologies are, at least in part, complementary and not perfectly accurate, then it is to be expected that there will not necessarily be a replacement of the old by the new. Indeed, in the context of a population-based analysis, precisely because some of the older technologies, when they are alternatives, are cheaper, they may play a legitimate "screening" role in the diagnostic workup. For example, among protocols in which sigmoidoscopy is used, using rigid rather than flexible sigmoidoscopy may be more effective - despite the fact that flexible sigmoidoscopy is apparently more sensitive within range than rigid sigmoidoscopy, and has the potential to reach more lesions. Because rigid sigmoidoscopy is cheaper and detects fewer cancers and polyps it may figure in more effective diagnostic workups; using it may result in more patients going on to have more effective tests (e.g. barium enema and colonoscopy). For this reason it is important to consider the decisions that underlie the behaviour of those who, in large measure, determine the utilisation of medical procedures. It is only when the evaluation of medical technology is linked to specific classes of decisions - and a given technology may be used in support of a number of diagnostic and patient management decisions - that it can hope to have an impact on clinical practice.
**TABLE 1**
RESULTS OF INITIAL SCREENING FOR COLORECTAL CANCER: CONTROLLED TRIALS OF FAECAL OCCULT BLOOD TESTING

<table>
<thead>
<tr>
<th>Study</th>
<th>Age Criterion</th>
<th>Number screened (% of invited)</th>
<th>Number (5) screened positive</th>
<th>Number of workups (% of screened positive)</th>
<th>Number with polyps or cancer (PPV(^1) for either)</th>
<th>Number with Cancer (PPV(^1))</th>
<th>Cancer Prevalence Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sloan-Kettering(^2)</td>
<td>Over 40</td>
<td>11,505 (-)</td>
<td>115 (1.0%)</td>
<td>81 (70%)</td>
<td>41 (51%)</td>
<td>10 (12%)</td>
<td>0.10%</td>
</tr>
<tr>
<td>Minnesota</td>
<td>Over 50</td>
<td>30,000 (-)</td>
<td>540 (1.8%)</td>
<td>190 (35%)</td>
<td>85 (44%)</td>
<td>28 (14%)</td>
<td>0.09%</td>
</tr>
<tr>
<td>Nottingham</td>
<td>Over 45</td>
<td>3,613 (35%)</td>
<td>77 (2.1%)</td>
<td>77 (100%)</td>
<td>39 (51%)</td>
<td>12 (16%)</td>
<td>0.33%</td>
</tr>
<tr>
<td>Funen</td>
<td>Over 45</td>
<td>20,672 (67%)</td>
<td>215 (1.0%)</td>
<td>215 (100%)</td>
<td>123 (59%)</td>
<td>37 (18%)</td>
<td>0.18%</td>
</tr>
<tr>
<td>Goteborg</td>
<td>Over 60</td>
<td>4,436 (67%)</td>
<td>76 (1.9%)</td>
<td>76 (90%)</td>
<td>24 (32%)</td>
<td>4 (5%)</td>
<td>0.09%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4,604 (64%)</td>
<td>256 (5.8%)</td>
<td>228 (89%)</td>
<td>50 (22%)</td>
<td>12 (5%)</td>
<td>0.26%</td>
</tr>
</tbody>
</table>

---

**Notes:**

1. PPV = Positive predictive value

2. The New York study is atypical of the trials in that study groups were not assigned by random allocation, and the intervention consists of faecal occult blood testing plus proctosigmoidoscopy, compared with proctosigmoidoscopy alone.

3. Rehydrated test group.
<table>
<thead>
<tr>
<th>Disease Condition</th>
<th>Proportion 1 (0.06)</th>
<th>Proportion 2 (0.12)</th>
<th>Proportion 3 (0.16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer</td>
<td>0.06</td>
<td>0.12</td>
<td>0.16</td>
</tr>
<tr>
<td>Polyps</td>
<td>0.44</td>
<td>0.38</td>
<td>0.34</td>
</tr>
<tr>
<td>Miscellaneous Bleeding</td>
<td>0.20</td>
<td>0.36</td>
<td>0.30</td>
</tr>
<tr>
<td>No Disease</td>
<td>0.30</td>
<td>0.14</td>
<td>0.20</td>
</tr>
</tbody>
</table>

**Notes:**
1. The frequency of colorectal neoplasia (cancer and polyps) has been held constant at 50%.
2. High, medium and low estimates.
<table>
<thead>
<tr>
<th>Test</th>
<th>Overall Sensitivity for</th>
<th>False Positive Rate</th>
<th>Net Cost to Medicare</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Miscellaneous Bleeding</td>
<td>Polyps</td>
<td>Cancer</td>
</tr>
<tr>
<td>Repeat hemoccult</td>
<td>0.8/0.95</td>
<td>0.55/0.9</td>
<td>0.55/0.9</td>
</tr>
<tr>
<td>Upper GI series</td>
<td>0.05</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rigid Sigmoidoscopy</td>
<td>0.33</td>
<td>0.22</td>
<td>0.22</td>
</tr>
<tr>
<td>Flexible Sigmoidoscopy</td>
<td>0.33</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Double Contrast Barium Enema</td>
<td>0.75</td>
<td>0.84</td>
<td>0.92</td>
</tr>
<tr>
<td>Colonoscopy without DCBE</td>
<td>0.86</td>
<td>0.92</td>
<td>0.92</td>
</tr>
<tr>
<td>Colonoscopy with DCBE</td>
<td>0.90</td>
<td>0.95</td>
<td>0.95</td>
</tr>
</tbody>
</table>

**Notes:**

1. These are the overall sensitivities for polyps and cancers; sensitivities for polyps and cancers within range of rigid and flexible sigmoidoscopes can be calculated by dividing by the proportion of lesions each instrument can reach - 45% and 65%, respectively.

2. Sensitivity is positively correlated with polyp size. The analysis assumes polyps are greater than 2cm.

3. Net cost to Medicare of diagnostic procedure, excluding histopathological examination of biopsy material ($114).

4. Net cost to Medicare of therapeutic procedure, excluding histopathological examination of biopsy material ($114).
### TABLE 4

**PERFORMANCE OF ALTERNATIVE DIAGNOSTIC STRATEGIES FOR WORKUP OF FOBT POSITIVE INDIVIDUALS: PPV FOR CANCER = 12% AND PPV FOR POLYPS = 38%.

<table>
<thead>
<tr>
<th>Diagnostic Workup</th>
<th>Proportion of Cancers Found</th>
<th>Proportion of Polyps Found</th>
<th>Efficiency</th>
<th>Average Proportion of Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cost ($)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perforation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1</td>
<td>0.9500</td>
<td>0.9500</td>
<td>0.2900</td>
<td>447</td>
</tr>
<tr>
<td>S2</td>
<td>0.9610</td>
<td>0.9610</td>
<td>0.3504</td>
<td>366</td>
</tr>
<tr>
<td>S3</td>
<td>0.6276</td>
<td>0.6276</td>
<td>0.2836</td>
<td>218</td>
</tr>
<tr>
<td>S4</td>
<td>0.9545</td>
<td>0.9365</td>
<td>0.9502</td>
<td>346</td>
</tr>
<tr>
<td>S5</td>
<td>0.9017</td>
<td>0.8424</td>
<td>0.8874</td>
<td>315</td>
</tr>
<tr>
<td>S6</td>
<td>0.9600</td>
<td>0.9200</td>
<td>0.9504</td>
<td>210</td>
</tr>
<tr>
<td>S7</td>
<td>0.5060</td>
<td>0.4620</td>
<td>0.4952</td>
<td>83</td>
</tr>
<tr>
<td>S8</td>
<td>0.9280</td>
<td>0.9120</td>
<td>0.6118</td>
<td>303</td>
</tr>
<tr>
<td>S9</td>
<td>0.9179</td>
<td>0.9008</td>
<td>0.3231</td>
<td>387</td>
</tr>
<tr>
<td>S10</td>
<td>0.9960</td>
<td>0.9920</td>
<td>0.2852</td>
<td>227</td>
</tr>
<tr>
<td>S11</td>
<td>0.9896</td>
<td>0.9871</td>
<td>0.3774</td>
<td>356</td>
</tr>
<tr>
<td>S12</td>
<td>0.9951</td>
<td>0.9911</td>
<td>0.4239</td>
<td>350</td>
</tr>
<tr>
<td>S13</td>
<td>0.9331</td>
<td>0.8686</td>
<td>0.2757</td>
<td>295</td>
</tr>
<tr>
<td>S14</td>
<td>0.9571</td>
<td>0.9158</td>
<td>0.4284</td>
<td>295</td>
</tr>
<tr>
<td>S15</td>
<td>0.9921</td>
<td>0.9874</td>
<td>0.3962</td>
<td>356</td>
</tr>
<tr>
<td>S16</td>
<td>0.9950</td>
<td>0.9919</td>
<td>0.4161</td>
<td>316</td>
</tr>
<tr>
<td>S17</td>
<td>0.9899</td>
<td>0.9838</td>
<td>0.7455</td>
<td>343</td>
</tr>
<tr>
<td>S18</td>
<td>0.9120</td>
<td>0.8740</td>
<td>0.4122</td>
<td>352</td>
</tr>
<tr>
<td>S19</td>
<td>0.9370</td>
<td>0.8990</td>
<td>0.4305</td>
<td>285</td>
</tr>
<tr>
<td>S20</td>
<td>0.9600</td>
<td>0.9600</td>
<td>0.5801</td>
<td>273</td>
</tr>
<tr>
<td>S21</td>
<td>0.9960</td>
<td>0.9920</td>
<td>0.7587</td>
<td>174</td>
</tr>
<tr>
<td>S22</td>
<td>0.9200</td>
<td>0.9200</td>
<td>0.9096</td>
<td>301</td>
</tr>
</tbody>
</table>

---

**Notes:**

1. Efficiency = (True Positives + True Negatives)/Total Tests (excluding biopsy examination)
### TABLE 5
MARGINAL COSTS AND EFFECTIVENESS OF DOMINANT PROTOCOLS

<table>
<thead>
<tr>
<th>Incremental Workup Strategy</th>
<th>Average Cost per Case</th>
<th>Percent of Worked up Cancers Found</th>
<th>Marginal Cost(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S7(^2)</td>
<td>$83</td>
<td>50.6%</td>
<td>$1,640</td>
</tr>
<tr>
<td>S21</td>
<td>$91</td>
<td>49.0%</td>
<td>$1,857</td>
</tr>
</tbody>
</table>

**Notes:**

1. Expected incremental cost to Medicare for an additional one percent chance of finding colorectal cancer among 1,000 individuals with positive screening results.

2. Compared with no screening program.
FIGURE 1

AGE-SPECIFIC INCIDENCE RATES FOR COLORECTAL CANCER

Colorectal cancer: Australia -- 1982

- Colon Ca
- Rectal Ca
- Colorectal Ca

Source: Quis, Armstrong & Smith (1)

Colon cancer: Australia -- 1982

- Males
- Females
- Total

Rectal cancer: Australia -- 1982

- Males
- Females
- Total
FIGURE 2

DISTRIBUTION OF COLORECTAL CANCERS BY ANATOMIC LOCATION AND REACH OF SIGMOIDOSCOPY INSTRUMENTS (measurements in centimetres)

Source: Maglinte, Keller, Miller & Chernish (1983), Table 1
FIGURE 3
AGE-SPECIFIC INCIDENCE RATES FOR COLORECTAL CANCER BY ANATOMIC LOCATION

Source: Kune, Kune & Watson (1988)
FIGURE 4

ALTERNATIVE DIAGNOSTIC WORKUP STRATEGIES FOR THE DETECTION OF COLORECTAL NEOPLASIA IN FOBT POSITIVE INDIVIDUALS

WORKUP S1
Bralow & Kopel (1979)

WORKUP S2
Greenlaw & Norfleet (1980)

WORKUP S3
Hardcastle et al (1980)

WORKUP S4
Hardcastle et al (1988)

WORKUP S5
Hendrix & Saba (1980)

WORKUP S6
Kewenter et al (1985)

WORKUP S7
Miller & Knight (1977)

WORKUP S8

WORKUP S9

LEGEND
RSig: Rigid sigmoidoscopy
FSig: Flexible sigmoidoscopy
CScope: Colonoscopy
DCBE: Double-contrast barium enema
FOBT2: Repeat faecal occult blood test
Upper GI: Upper gastrointestinal series
FIGURE 4 (continued)

WORKUP S10
Stuart et al (1961)

WORKUP S15
WORKUP S16: Same as S15, except FSig

WORKUP S19

WORKUP S20

WORKUP S17

WORKUP S21

WORKUP S18

WORKUP S22

WORKUP S11
WORKUP S12: Same as S11, except FSig

WORKUP S13
WORKUP S14: Same as S13, except FSig
FIGURE 5
EXAMPLE OF A PROBABILITY TREE FOR DIAGNOSTIC WORKUP STRATEGY S5

Individuals with positive FOBT screening tests

Cancer

0.12

Positive
FSig 0.50

Positive
DSBE 0.92

Positive
Cscopec 0.65

Cancer
found

Negative
FSig 0.50

Negative
DSBE 0.08

Negative
Cscopec 0.03

Cancer
missed

Benign
polyp

0.38

Positive
FSig 0.50

Positive
DSBE 0.92

Positive
Cscopec 0.65

Poly
found

Negative
FSig 0.50

Negative
DSBE 0.08

Negative
Cscopec 0.03

Poly
missed

Miscellaneous
Bleeding
Source

0.36

Positive
FSig 0.33

Positive
DSBE 0.79

Positive
Cscopec 0.10

M.B.s
found

Negative
FSig 0.67

Negative
DSBE 0.25

Negative
Cscopec 0.10

M.B.s
missed

No disease

0.14

Positive
FSig 0.50

Positive
DSBE 0.95

Positive
Cscopec 1.0

No disease

Negative
FSig 1.0

Negative
DSBE 0.05

Negative
Cscopec 1.0

No disease
FIGURE 6
AVERAGE COST TO MEDICARE AND EFFECTIVENESS
(FRACTION OF COLORECTAL CANCERS DETECTED)
OF ALTERNATIVE DIAGNOSTIC WORKUP STRATEGIES
FOR FOBT POSITIVE INDIVIDUALS

Fraction of cancers detected

Average Cost ($) to Medicare
(per 1,000 FOBT Positive Individuals)

efficient frontier
FIGURE 7

AVERAGE COST TO MEDICARE AND EFFECTIVENESS
(FRACTION OF COLORECTAL NEOPLASIA DETECTED)
OF ALTERNATIVE DIAGNOSTIC STRATEGIES FOR FOBT
POSITIVE INDIVIDUALS

*Estimated fraction of colorectal neoplasia detected is defined as (number of cancers found + 10% of number of polyps found)/(total number of cancers + 10% of total number of polyps).
FIGURE 8
AVERAGE COST TO MEDICARE AND TEST EFFICIENCY OF
ALTERNATIVE DIAGNOSTIC WORKUP PROTOCOLS FOR
FOBT POSITIVE INDIVIDUALS

Average Cost ($) to Medicare
(per 1,000 FOBT Positive Individuals)
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