To: CMS Coverage and Analysis Group

From: AHRQ Technology Assessment Program

Re: FOBT analysis

Date: August 20, 2003

Enclosed please find the final report on the comparison of the cost-effectiveness of several fecal occult blood tests (FOBT) in the context of annual screening in the Medicare population.

INTRODUCTION

This analysis compares the cost-effectiveness of commercially available guaiac-based FOBT (gFOBT) tests with immunochemical FOBT (iFOBT) tests in patients who have never been screened before age 65 and who use FOBT as the only method of screening after age 65. The analysis is based on the MISCAN-COLON computer model. This model was originally developed by researchers at Erasmus University and colleagues under contract to the National Cancer Institute.

RESULTS OF THE MODEL

- Threshold Payment: One of the results of the model is the threshold payment for iFOBT where the cost-effectiveness of the iFOBT would be equal to the cost-effectiveness of the gFOBT test. The clinical data suggest that iFOBT has a higher sensitivity than the most common gFOBT test, Hemoccult II. Therefore, using these data, the model predicts that iFOBT will prevent more cases of cancer and prevent more deaths due to cancer. However, the model also predicts that under most assumptions, the cost of using the iFOBT test is higher. The model calculates a wide range of price points for the threshold payment. For sensitivity estimates up to 80% and specificity estimate of 95%, the model calculates that the price of iFOBT would have to be less than $0 to have equal cost effectiveness to gFOBT. This is because a high cost is associated with follow

up tests for the large number of false positives generated by a lower specificity test. However, at the highest levels of sensitivity, the threshold price of iFOBT is $12. At this sensitivity, the iFOBT test is finding a larger number of additional cancers, improving the cost-effectiveness ratio. The threshold price may be even higher if the specificity is higher than 95%. Overall the model predicted a range of threshold prices of $-4.22 to +$29.02 using sensitivity estimates of 70-87% for cancer and specificity estimates of 95-98%. It is not possible to determine with further precision where the threshold payment would be given the data limitations discussed below.

- Incremental Cost-Effectiveness: Another result of the model is the incremental cost-effectiveness of iFOBT compared to gFOBT. The base case of the model predicts that the incremental cost-effectiveness ratio of iFOBT compared to gFOBT at $28 per test is under $30,000 per life year gained. This result is strongly dependent on the number of cancers avoided that is predicted by the model. The model predicts that under the base case assumptions, approximately 20 cancers and 11 deaths per 1000 patients would be avoided by the use of iFOBT compared to gFOBT over the 30 years of the model. As noted below, the overall number of cancer deaths avoided by gFOBT compared to no screening estimated by the model is high compared to the number measured in a screening trial, although there are many differences between the population studied in the model and in the trial that may explain the higher numbers in the model. Some of the assumptions in the model are not realistic, and may cause the model to overestimate the number of cancer deaths avoided and the incremental cost-effectiveness that would be achieved in a real-world population.

- Sensitivity Analysis: The analysis included several sensitivity analyses. One alternative assumption is more aggressive follow-up to positive FOBT tests (i.e., more frequent colonoscopies). Another alternative assumption is lower compliance levels; in this sensitivity analysis patients would be more compliant with iFOBT than gFOBT because of the relative ease of use of the test. Both of these assumptions lead to a

more favorable incremental cost effectiveness of iFOBT compared to gFOBT than the base case assumptions.

VALIDATION OF MODEL

The model predicts that gFOBT screening would lead to a decrease of 66 cancers per 1000 patients screened over 30 years compared to no screening. There are no data on a population reasonably similar to the Medicare population, as modeled for this analysis, so there is no way to validate whether the model is predicting the correct numbers of cancers. A screening study by Mandel et al.[1] found only 39 cancers per 1000 patients over 18 years in a population randomized to usual care. They found a decrease of 7 cancers per 1000 patients screened with gFOBT studied for 18 years compared to no screening. However, there were several differences between this population and the model population, including age range (50 and over), length of follow up (18 years), and that the real-world usual care population may have colonoscopy or other screening in additional to FOBT. Although the authors report that the MISCAN model accurately predicted certain results from Mandel et al. by using parameters similar to the population in the Mandel et al. trial, we do not know how well it models the population of interest to Medicare.

ASSUMPTIONS IN THE MODEL

The model depends on several input parameters estimated from clinical trial data:

- Sensitivity and specificity of the gFOBT and iFOBT tests: As can be seen from the literature review in Table 1 of the report, there has been substantial variation in the measured sensitivity and specificity in various trials published in the peer-reviewed literature. The sensitivity of the iFOBT test ranges from 70-90% for colon cancer and the specificity is generally estimated at about 95% in the majority of the studies. Published data on iFOBT are based on older tests, some of which are not currently being used. The only data available on the Insure test, which is the newest test under consideration here, are from the package insert and from a presentation at a scientific meeting. These data have not been published in peer review literature,

and therefore cannot be fully evaluated for methodological quality and relevance. In addition, because of the limited data available on the Insure test, we do not know the robustness of the estimates of sensitivity and specificity.

- Patient and provider behavior also introduce uncertainty into model results. These assumptions include 100% compliance with the FOBT test and optimal follow-up after a positive test. The model also assumes that patients have never received a screening test before age 65 and use FOBT as the only method of screening. In addition, there is substantial uncertainty around many input parameters to the model, including the underlying incidence of adenomas and other precancerous lesions, and the probability that these lesions will progress to cancer.

DISCUSSION

The model has simplifying assumptions that we know are not realistic, such as that no one in the population has any screening prior to age 65. These assumptions may lead the model to overestimate the benefit of FOBT screening in a real-world population. It is unknown what effects these assumptions would have on the ability of this model to accurately compare two tests. However, under the broad range of sensitivity analyses performed in the model, the incremental cost effectiveness of iFOBT was still low by most standards (i.e. below $50,000), even at $28 per test. The model predicts a wide range of threshold prices for iFOBT that would make the cost-effectiveness equal to gFOBT; it is not possible to narrow down this range further because of the uncertainty in the available data on the test.

[1]Mandel JS, Church TR, Bond JH, Ederer F, Geisser MS, Mongin SJ, Snover DC, Schuman LM The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med. 2000 Nov 30;343(22):1603-7.

Report to the Agency for Healthcare Research and Quality
A Comparison of the Cost-Effectiveness of Fecal Occult Blood Tests with Different Test Characteristics in the Context of Annual Screening in the Medicare Population

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Abstract/Executive Summary

Background. Colorectal cancer screening is now recommended in the general population beginning at age 50 for those at average risk. The most common colorectal cancer screening test in use in the United States is the guaiac based fecal occult blood test (FOBT). Colorectal cancer screening is now covered by Medicare with a reimbursement level of $4.50 for the guaiac test. Immunochemical fecal occult blood tests (IFOBT) have tended to be more expensive and have not yet been widely used in the US. In order to inform coverage and payment decisions related to the use of these tests, this report estimates the cost effectiveness of an immunochemical test with test performance parameters that are equivalent to or better than those associated with the guaiac test. We also report the threshold payment level of the immunochemical test relative to the guaiac test, the level of payment for the immunochemical test that would result in cost-effectiveness equivalent to that of the comparative guaiac test.

Methods. We use a micro-simulation model, MISCAN-COLON, developed and validated by Erasmus University to describe the natural history of the adenoma carcinoma sequence and the impact of screening on reducing colorectal cancer incidence and mortality. The cost effectiveness of life years gained relative to costs for screening are derived for screening tests with different test performance characteristics. We review the literature for guaiac and immunochemical tests to establish reasonable test performance levels of sensitivity and specificity for these tests. Although the efficacy of FOBT screening was established using the guaiac based Hemoccult II test, the guaiac based Hemoccult SENSA test has higher sensitivity but lower specificity than Hemoccult II and recently has increased in use. Consequently we consider both Hemoccult II and Hemoccult SENSA as base cases. We assume base case values for Hemoccult II of 40% sensitivity for colorectal cancer, 10% sensitivity for adenomas $\geq$1.0 cm, 5% sensitivity for adenomas < 1 cm, and 98% specificity (for not having cancers or adenomas). For base case values for Hemoccult SENSA we assume 70% sensitivity for colorectal cancer, 17% sensitivity for adenomas $\geq$ 1 cm, 9% sensitivity for adenomas < 1.0 cm and 92.5% specificity. We found less definitive evidence for establishing estimates of sensitivity and specificity for most of the immunochemical tests in a general population. Therefore we assumed a more favorable and a less favorable case for the immunochemical tests. We assumed that the immunochemical tests have sensitivities comparable to Hemoccult SENSA but with higher specificity (98% and 95%). Consequently we assumed that the immunochemical test had 70% sensitivity for colorectal cancer, 17% sensitivity for adenomas $\geq$ 1 cm, 9% sensitivity for adenomas < 1 cm, and 98% specificity for the more favorable case and 95% specificity for the less favorable case. We also assumed the same sensitivity parameters for the immunochemical tests but with 95% specificity. Furthermore in a sensitivity analysis, we assumed that the sensitivity of the immunochemical test increases 25%, 50%, 75%, and 100% over that of the Hemoccult II base case. In the base case we assumed extended intervals of surveillance for those with lower risk adenomas as specified in the most recent surveillance guidelines. We repeated these analyses, assuming a more intensive pattern of 3-year surveillance colonoscopy for all with adenomas detected. The cost and health effect outcomes were derived under the assumption that no colorectal cancer screening occurred prior to age 65 and all (100%) were compliant. In a sensitivity analysis, we assumed more realistic compliance rates and a higher compliance for immunochemical FOBT than for Hemoccult FOBT screening. We also determined the threshold analysis value for Hemoccult II and Hemoccult SENSA when an immunochemical test was the base case.

Results. The cost effectiveness of the Hemoccult II FOBT ($1,071 per life year gained) is a very favorable level of cost-effectiveness in comparison to other cancer screening modalities. Immunochemical tests, even with costs per test of $28 per test, still have a cost effectiveness ratio of no more than $4,500 per life year saved. At a paymemt level of $28 for IFOBT and $4.50 for Hemoccult II, the incremental cost effectiveness ratio (ICER) for IFOBT is $11,000 per additional life-year saved assuming a specificity of 98% for IFOBT and $21,000 per additional life-year saved assuming a specificity of 95% for IFOBT. The threshold payment level of the IFOBT, with 98% specificity for most test parameters considered, was in the range of $7.00 to $13.00, which is only somewhat higher than the $4.50 of the base case Hemoccult II. However when the IFOBT has specificity of 95%, then the threshold values for most test parameters considered were less than zero dollars. Results for IFOBT are much more favorable if Hemoccult SENSA is assumed to be the base case and especially if IFOBT is assumed to operate at the more favorable specificity value of 98%. A threshold payment level of $28 for IFOBT is exceeded if either or both of the following conditions are met: a) IFOBT is assumed to have the lower specificity value of 95% but much better values of sensitivity for the detection of adenomas than Hemoccult SENSA, or b) IFOBT is assumed to have sensitivity values equal to Hemoccult SENSA but the higher specificity value of 98%. If we assume payment rates of $18 and $27 for IFOBT, then the corresponding threshold payment levels are $10 and $17 for Hemoccult II when IFOBT has 98% specificity and $5 and $14 for Hemoccult SENSA when assuming 95% specificity for IFOBT.

Conclusion. Fecal occult blood tests, either guaiac based or immunochemical based, provide for a very cost effective intervention for reducing colorectal cancer incidence and mortality. If the immunochemical fecal occult blood test maintains the high specificity of Hemoccult II (98%) and increases sensitivity for colorectal cancer to 70% over that of Hemoccult II (40%), then a unit cost level of approximately $13.00 would provide a comparable cost-effectiveness to Hemoccult II at $4.50 per unit cost. If the specificity of the immunochemical fecal occult blood test is assumed to be 95% when the sensitivity for colorectal cancer increases to 70%, then the threshold payment level for IFOBT would actually be lower than the current $4.50. However, further threshold analysis using Hemoccult SENSA as the base case with a sensitivity of 70% for colorectal cancer and specificity of 92.5% indicates that the immunochemical test could achieve a threshold payment level in excess of $28 when the more favorable assumptions about IFOBT are made.

Evidence about the relative specificity and sensitivity of IFOBT in comparison to Hemoccult II and Hemoccult SENSA is sparse and highly uncertain. Therefore the scenarios under which the threshold payment level of $28 is exceeded for IFOBT, although potential possible, cannot be considered to be strongly evidence based. If payment level of $18 and $27 are assumed for IFOBT, corresponding threshold payment levels for Hemoccult II would be higher than current payment levels while this would be true for Hemoccult SENSA only if the lower specificity value of 95% is assumed for IFOBT.

INTRODUCTION

The 2002 statement of the U.S. Preventive Services Task Force (USPSTF 2002) strongly recommends that clinicians screen men and women 50 years of age or older for colorectal cancer and concludes that there is good evidence that periodic fecal occult blood testing (FOBT) reduces mortality from colorectal cancer. Three randomized controlled trials have demonstrated a 15% to 33% reduction in colorectal cancer mortality with FOBT screening (Mandel 1993; Hardcastle 1996; Kronborg 1996).

Colorectal cancer screening modalities, including guaiac FOBT, are currently covered services under the Medicare program. Medicare allows a payment of $4.50 for the guaiac based fecal occult blood test on an annual basis. The most commonly used guaiac tests under this coverage policy are Hemoccult II and Hemoccult-SENSA. Although the Hemoccult II test was used with rehydration in one of the randomized trials to increase sensitivity (Mandel 1993), this practice is not currently recommended. The practice of rehydration is thought to be associated with an unacceptably high rate of false positive tests, about 9% for rehydrated versus 2% for un-rehydrated FOBT, requiring expensive and invasive diagnostic follow-up. Hemoccult-SENSA has substantially better event test sensitivity than Hemoccult II, but at the cost of a false positive rate which is lower than that for rehydrated Hemoccult although it is higher than that for un-rehydrated Hemoccult II.

Immunochemical fecal occult blood tests (IFOBT) have been developed with the aim of achieving test sensitivity that is equivalent to or better than that of Hemoccult-SENSA while achieving false positive rates lower than SENSA but probably not as low as un-rehydrated FOBT. IFOBT may also be more expensive to produce than the traditional guaiac-based tests. The most recent American Cancer Society recommendations (2003) for colorectal cancer screening, include the statement that immunochemical tests are more patient-friendly, and are likely to be equal or better in sensitivity and specificity than guaiac based tests for the detection of fecal blood (Levin 2003).

A nationally representative survey of primary care physicians conducted in 1999 - 2000 found that Hemoccult-II represented 68% of all FOBT tests that were ordered by physicians, while Hemoccult-SENSA accounted for an additional 13%. The remaining 19% of tests used included some IFOBT tests (Klabunde 2003, Klabunde personal communication). The use of the more sensitive Hemoccult-SENSA or immunochemical tests are expected to increase in the future given the recent recommendations from the American Cancer Society.

The purpose of this report is to compare the guaiac and the immunochemcial fecal occult blood test with respect to the cancers detected, cancer deaths averted, and the costs and cost effectiveness (life years gained and costs) of both types of tests. Further the report is to provide an assessment of the cost-effectiveness of guaiac and immunochemical fecal occult blood tests at the same level of allowed Medicare payment for the test, $4.50, and at higher levels of payment for the IFOBT. Finally under different assumptions about test performance characteristics, we will determine payment levels of IFOBT that result in equivalent cost-effectiveness of IFOBT to guaiac FOBT paid at a level of $4.50. We will refer to this as a threshold payment analysis.

In this report, we will summarize evidence on the test performance characteristics of fecal occult blood tests, in particular measured sensitivity and specificity of the tests for the detection of invasive colorectal cancer and for pre-cancerous lesions. Based on this summary, we will specify the base case test parameter values that represent the best estimate of sensitivity and specificity for each type of test. Because the study designs used to obtain measured values of sensitivity and specificity vary widely and because the degree of available evidence varies across the different types of tests under consideration, we will also specify reasonable upper and lower uncertainty boundaries for the sensitivity and specificity parameter values for each type of test. We will then present a series of simulations that assess the cost-effectiveness of various fecal occult blood tests and produce threshold payment levels for IFOBT in comparison to the most cost effective guaiac FOBT test currently under use (Hemoccult II) and to the guaiac FOBT with the highest sensitivity (Hemoccult SENSA).

We recognize that the results of this analysis, cost-effective ratios and payment thresholds, are only one type of input to the complex decision making process that the Centers for Medicare and Medicaid Services (CMS) must consider in making its coverage policy decisions

SUMMARY OF EVIDENCE ABOUT TEST CHARACTERISTICS

Types of Fecal Occult Blood Tests

The fecal occult blood test (FOBT) is a test for blood or blood products in the stool. Neoplasia of the bowel mucosa, particularly larger neoplasia, has a tendency to bleed periodically. Consequently the test for blood in the stool is used as a marker for neoplasia. Van Deen in 1864 reported that gum guaiac, a natural resin extracted from wood, is useful in detecting occult blood. Greegor (1967) suggested the use of fecal occult blood tests in the diagnosis of colorectal cancer. In the 1970's the 3-window slide kit was developed (Fleisher 2003).

There are currently two major types of FOBT which are commercially available: guaiac and immunochemical tests. The guaiac-based test reacts positive to pseudoperoxidase activity of heme in the feces and is not specific for human blood. This is a limitation of this test because false positive tests can be due to the presence of plant and animal materials. In order to reduce the number of false positive tests, the guaiac-based test requires dietary restrictions (no red meat, certain uncooked vegetables, vitamin C, and nonsteroidal anti-inflammatory drugs (NSAIDS)) prior to and during administration of the test which requires specimens from 3 bowel movements. A meta-analysis based on Hemoccult II studies suggest that dietary restrictions are not required when using guaiac FOBT (Pignone 2001) but Young (2002) suggests that the Pignone review did not take into account dietary differences between different ethnic groups. In contrast the immunochemical fecal occult blood test is designed to detect the globin protein of *human* hemoglobin and is also specific for blood in the large intestines rather than for blood originating from other sources higher up in the gastrointestinal tract (Young 2002).

Guaiac tests such as Hemoccult can be developed and interpreted in an office setting whereas immunochemical tests may require development in a centralized laboratory setting (Australian Health Technology Advisory Committee, 1997). The two main guaiac tests in use in

the US are the Hemoccult II and Hemoccult SENSA tests. The newer Hemoccult SENSA test has improved readability and stability over that of the Hemoccult II test (Young 2003). However inaccurate training can lead to inaccurate reading of these tests (Fleisher 1991). Although the Clinical Laboratory Improvement Amendments (CLIA) of 1988 considered the guaiac tests (Hemoccult II and Hemoccult SENSA) as waived laboratory tests (Ransohoff and Lang 199&), new regulations are now requiring proficiency testing for those performing fecal occult blood tests. For example in New York State there are regulatory requirements regarding quality control and documentation for point of care testing. In order to mandate this requirements Memorial Sloan-Kettering Cancer Center has eliminated the performance of fecal occult blood tests at the point of care and has recommended processing for the FOBT's in a central facility which can be monitored for accuracy. The immunochemical tests are more amenable to standardized development and quality control (Young, 2002). Originally the immunochemical tests used enzyme-linked immunosorbent assay (ELISA) and double immunodiffusion methods. Latex agglutination tests and qualitative hemagglutination tests have been used more recently. Latex tests can be used in the physician's office (Young, 1996). Immunochemical tests include HemeSelect (Immudia Hem Sp, an older version of HemeSelect), FlexSure OBT, and Monahaem. Some immunochemical tests that have been evaluated are no longer marketed (i.e. FlexSure OBT) and some new tests are coming on the market (InSure). The FDA has registered over 50 types of FOBT in the United States but only a few tests have been evaluated for screening in population studies. (Young 2002)

In a review by Young, St. John, Winawer, and Rozen (2002) test positivity is reported to be highest with rehydrated Hemoccult II, and successively lower for Hemoccult SENSA, immunochemical FOBT, and then lowest for Hemoccult II (un-rehydrated). The order is reversed for specificity with Hemoccult II having the highest specificity. In regard to test sensitivity for the detection of colorectal cancer and other neoplasia, Hemoccult II results in the lowest values, while sensitivity is highest for Hemoccult SENSA and rehydrated Hemoccult and IFOBT's yield intermediate sensitivities. Another characteristic of the IFOBT, as mentioned, is that it is specific for occult blood in the large intestine. Consequently a positive IFOBT with no detectable colon or rectal problem (polyps or hemorrhoids) will not result in a further upper GI series work-up.

There is a third type of fecal occult blood test based on the technology of heme-porphyrin assays which are specific for dicarboxylic porphisa and detect heme in any form and its degradation products. Hemoquant is a test based on this method. The heme-porphyrin assays require fluorescent spectrometry which makes this a more complex type of fecal occult test (Young 1996). The heme-porphyrin assay tests are not discussed further in this report.

<u>Study designs for estimating FOBT sensitivity and specificity for colorectal cancer and adenomatous polyps used in available studies.</u>

FOBT followed by colonoscopy as the gold standard for all.

The probability that a one-time fecal occult blood test (and follow-up diagnostic procedures) will detect a lesion, e.g. colorectal cancer, when such a lesion is actually present, is the <u>event sensitivity</u> of FOBT. The empirical measure that most directly corresponds to this concept of event sensitivity is the performance of a gold-standard test for the presence of colorectal cancer or adenomas, such as colonoscopy, immediately following the performance of

an FOBT. Even this approach falls short of measuring true event sensitivity because it is known that colonoscopy, itself, does not have 100% sensitivity to detect all colorectal cancers and adenomas. Evidence from back to back colonoscopy examinations (Rex 1997) and follow-up colonoscopy (Ee 2002) indicates that colonoscopy achieves close to 100% sensitivity for detection of colorectal cancer while at least 6% of large adenomas ($\geq$1 cm), 13% of moderate sized adenomas (0.6-0.9 cm) and 27% of small adenomas ($\leq$ 0.5 cm) are missed (Rex 1997). Nevertheless, high quality colonoscopy is the best gold standard available.

Studies using contemporaneous colonoscopy as a gold standard however are modest in size. The majority of findings at colonoscopy are adenomas rather than cancer. Due to the small number of colorectal cancers detected, sensitivity estimates for cancers may be imprecise or the sensitivity estimate may be based on combining colorectal cancers and adenomas rather than for colorectal cancer alone. Further these types of studies are usually based on high-risk populations atypical for screening populations. Therefore these sensitivity values are difficult to directly compare to sensitivity values for cancer derived from very large screening trials.

Follow-up of positive tests with colonoscopy and negative tests with surveillance of at least one year.

Another type of study relies on follow-up of positive FOBT's with colonoscopy and then monitoring patient's records for a year or more following negative FOBT and recording instances of clinically detected cancer. Such studies are likely to over-estimate sensitivity for cancer compared to studies that use contemporaneous colonoscopy as a gold standard. This is because some cancers present at the time of FOBT testing have not yet become clinically manifest**.** On the other hand, new cancers may have developed after the FOBT testing and become evident during the follow-up period. These studies are generally not suitable for estimating sensitivity for adenomas because most adenomas are asymptomatic. Studies, which employ different follow-up periods, i.e. one year following FOBT versus 2 or 3 years, can provide different measures of sensitivity and are not directly comparable. In some of these surveillance studies multiple fecal occult blood tests are compared and a positive on any of the tests would be followed by a colonoscopic evaluation. Such studies provide relative sensitivity of one test to another but not an absolute measure of sensitivity. Such relative comparisons over-estimate sensitivity because false negatives are under-represented. A listing of studies which use relative sensitivity is given in Table 1F.

Randomized controlled trials of screening

Finally, sensitivity is also estimated from randomized controlled trials of screening involving periodic screening, counting "interval" cancers, cancers clinically detected between the screening interval following a negative screening test, as evidence of a false negative test. Sensitivity directly observed by this last method does not correspond to event sensitivity but, rather, is a measure of "program sensitivity". In most cases, program sensitivity will be higher than event sensitivity. This is because for trials of annual or biennial FOBT screening, the average interval between screening tests is shorter than the average sojourn time, the time that it takes an undetected lesion (i.e. a preclinical invasive colorectal cancer) to develop into a clinically detectable cancer. Thus, a lesion that is missed by a first screening test may have some probability of being detected by a second or third test before it would have, in the absence of screening, been clinically detected. For example Church (1997), shows that high program sensitivity for FOBT of 90% in the context of a single cohort clinical trial of periodic screening

can be consistent with an event sensitivity of less than 30%. Mathematical methods can be used to simultaneously estimate event sensitivity and the preclinical duration of the lesion from screening trial data. (Gyrd-Hansen 1997, Prevost 1997). Notice that the sensitivity measured in trials is not only affected by test sensitivity for cancers but also by sensitivity of adenomas – which when removed, reduce the risk of subsequent cancers. The mathematical model can and should account for this mechanism.

Summary of the evidence on sensitivity and specificity of FOBT

Table 1 summarizes estimates of FOBT test sensitivity and specificity (for any neoplasia - cancer or adenomas) for Hemoccult II, Hemoccult SENSA, and immunochemical FOBT. Sensitivity is presented for colorectal cancer, for large adenomas (>1 cm) and for small adenomas (<1 cm). There was generally insufficient data to provide separate sensitivity estimates for Duke's A/B and for Duke's C/D stage of cancer. The estimates are derived from several different types of sources including clinical series that monitor for positive follow-up tests and surveillance for at least one year following the initial FOBT and clinical series or studies that compare the results of FOBT to colonoscopy conducted immediately following FOBT and large randomized controlled screening studies. In addition we present values of FOBT sensitivity and specificity that have been assumed in other cost-effectiveness studies, in clinical guideline documents and in package insert literature from the manufacturer.

HEMOCCULT II

Sensitivity for colorectal cancer

The Hemoccult II guaiac based test has been the most widely used colorectal cancer screening test. Although some screening programs in the past used the rehydrated Hemoccult II test with the aim of increasing test sensitivity, rehydration is not considered to be an acceptable means of increasing the sensitivity of the FOBT because of deteriorating specificity (Winawer, 2003). Consequently this report focuses on the estimated value for sensitivity and specificity for the un-rehydrated FOBT. The estimates from the literature for rehydrated FOBT are provided as a reference point but are not the focus for test-parameter estimates. The sensitivity of a single un-rehydrated FOBT is relatively low (range from 11% to 86%) with most estimates around 40% sensitivity for cancer. All persons with a positive Hemoccult II test should be referred for diagnostic colonoscopy.

Sensitivity for adenomas

Data for the sensitivity for large and for small adenomas are much more sparse than for colorectal cancer and primarily depend on studies with colonoscopic evaluation following fecal occult blood testing. As noted above these studies tend to be based on higher risk individuals who are already scheduled to have colonoscopy (Table 1). The VA Cooperative Study is a colonoscopy screening study in asymptomatic persons in the VA system (primarily men) with *rehydrated* FOBT preceding the scheduled colonoscopy. One-time FOBT sensitivity was 23.9% for large adenomas or cancer (50% sensitivity for colorectal cancers and 21.6% for adenomas $\geq$1.0 cm) (Lieberman 2001). In the National Polyp Study *un-rehydrated* Hemoccult II tests were performed annually for patients who were under surveillance following initial colonoscopic

removal of adenomatous polyps (Zauber 2002). In this surveillance study, Hemoccult II sensitivity for adenomas ≥ 1.cm was 23%. A multi-national trial was conducted of 4 FOBT tests (un-rehydrated Hemoccult II, Hemoccult SENSA, and the immunochemical tests of HemeSelect and FlexSure OBT) on patients referred for colonoscopy for predetermined indications (Greenberg, 2000). Un-rehydrated Hemoccult II sensitivity for cancers was 85.7% and for large adenomas was 20.5%. Some earlier cost-effectiveness studies have assumed lower sensitivity of guaiac FOBT for adenomas. (Wagner 1996, Loeve 2000). We assume that sensitivity of Hemoccult II (un-rehydrated) for large adenomas is 10% which is approximately half that reported in these higher risk screening cohorts and reported for rehydrated Hemoccult II in asymptomatic veterans. We also assume that Hemoccult II sensitivity for smaller adenomas (<1 cm) is only 5% or half that of the assumed value for the larger adenomas. We recognized that there is little data in the literature on sensitivity for adenomas, of larger size (≥ 1 cm) or of smaller size (< 1 cm).

Program sensitivity

Values of program sensitivity derived from large randomized trials only apply to guaiac FOBT Hemoccult II (Table 1). The sensitivities reported from the Minnesota screening trial, of 92% for annual screening with rehydrated FOBT and 81% for annual un-rehydrated FOBT are program sensitivities for annual screening. The corresponding specificity values are about 90% and 98%. Event sensitivity and specificity values derived from two European trials, using un-rehydrated FOBT for biennial screening, are in the range of 47%-66% and 97%-99% respectively. Estimates, from other studies, of programmatic sensitivity for rehydrated FOBT range from 68% to 96% with corresponding specificity in the range of 86%-97%.

Other cost-effectiveness analyses

Other cost-effective studies, after reviewing similar data, have assumed values for guaiac FOBT sensitivity in the range of 33%-60% for un-rehydrated FOBT and 60%-70% for rehydrated FOBT, with corresponding ranges of specificity of 97%-98% and 90%.

Summary of assumptions on un-rehydrated Hemoccult II

Sensitivity

We will adopt a conservative assumption for un-rehydrated Hemoccult II of 40% sensitivity for colorectal cancer, 10% sensitivity for adenomas ≥ 1cm, and 5% sensitivity for adenomas < 1 cm. We do not consider rehydrated FOBT in our analysis since its use is currently not recommended by U.S. clinical guidelines (Winawer, 2003).

Specificity

Specificity for the un-rehydrated Hemoccult II test for colorectal cancer has been consistently reported as high, between 95.2% to 98.9%. We assume that specificity for not having cancer or adenomas for the Hemoccult II test is 98% on the basis of what has been measured in the randomized trials.

HEMOCCULT-SENSA

Data on the test characteristics of the guaiac Hemoccult-SENSA and IFOBT are also relatively sparse, with no data for these tests available from large, controlled screening trials. From studies conducted using modest samples of selected patients, some consisting of direct comparisons of these tests and guaiac FOBT, it seems clear that Hemoccult-SENSA results in better sensitivity than un-rehydrated Hemoccult, but with specificity somewhere between that of un-rehydrated and rehydrated Hemoccult. It appears that SENSA may have sensitivity for cancer in the range of 80% with specificity in the range of 90%-94%. We use a conservative estimate of sentitivity and assume in this report that Hemoccult SENSA sensitivity for colorectal cancer is 70%, sensitivity for adenomas $\geq$ 1 cm is 17%, and sensitivity for adenomas < 1 cm is 9% and a specificity of 92.5%.

IMMUNOCHEMICAL FECAL OCCULT BLOOD TESTS (IFOBT)

The various studies of IFOBT indicate sensitivity in the same range as for Hemoccult SENSA with perhaps somewhat better specificity, i.e., sensitivity in the range of 70% - 90% with specificity of about 95% in the majority of studies. Other reviews of the literature have come to similar conclusions. (Young 1996, Young 2002). Consequently we consider an immunochemical test with sensitivity of 70% for colorectal cancer and 17% sensitivity for large adenomas and 9% sensitivity for smaller adenomas (the same sensitivities assumed for Hemoccult SENSA) but with higher specificity. We consider IFOBT specificities of 98% and of 95%.

We recognize that there are varying types of IFOBT's by different manufacturers and that the estimates of sensitivity and specificity vary for each particular type of IFOBT. For example, unlike the chemical-based guaiac tests, immunochemical tests use biological components, particularly antibodies, that can be quite variable. The FlexSure test manufactured by Beckman-Coulter used polyclonal antibodies for both capture and labeling of globin from the stool sample. The InSure test by Enterix uses a monoclonal antibody to always capture globin by the same epitope and with the same affinity consistently from batch to batch of the test manufacture (Young 2003 – personal communication). Also the immunochemical tests are quantitative with respect to the detection of hemoglobin. Consequently the positivity threshold adopted may vary for different tests or in different studies. The positivity threshold adopted can be varied to achieve different postiivity levels for an increased sensitivity with lowered specificty or a decreased sensitivity with an increased specificity. The optimal positivity threshold for IFOBT's has to address the capacity of the health care system to evalute the postive tests with colonoscopy as well as an assessment in the tradeoffs of life years gained with higher sensitivty and costs incured due to evaluation of false positives if specficity is decreased. For example Ransohff and Lang (1996) suggest that a FOBT should have a specificty of 95% or higher in order to avoid an excessive number of colonoscopy examinations.

Of particular interest is the InSure immunochemical fecal occult blood test (Enterix Corporation) which is recently introduced in the US. This test does not require dietary restrictions, uses a novel brush sampling method for collection, and requires two days of stool sampling rather than the 3 for Hemoccult II or Hemoccult SENSA. The participant samples the stool by briefly burshing the surfce of the stool while immersed in the toilet bowl water. The test has been compared with another immunochemical test (FlexSure OBT) in patients scheduled to undergo diagnostic colonoscopy (Young, in press 2003). The sensitivity and specificity for the

two tests were comparable. Also a relative comparison of InSure with Hemocult SENSA showed that InSure had sensitivity of 85% for cancer, 77% for significant neoplasia (cancer or adenomas $\geq$ 1. 0 cm), and 68% for all neoplasia compared to Hemoccult SENSA with sensitivity of 38% for cancer, 50% for significant neoplasia, and 50% for all neoplasia (Cole 2003). These results were based on an average risk screening cohort (n=284), a high risk surveillance cohort (n=158), and a symptomatic diagnostic group (n=18). These results as presented in abstract form stated that InSure provided significantly better sensitivity for colorectal neoplasia without any loss of specificity when compared to Hemoccult SENSA. Also in a randomized trial InSure had a higher participation rate (40%) for completing screening than Hemoccult SENSA (23%) or FlexSure OBT (30%) (Cole, in press 2003).

New data on immunochemical fecal occult blood test sensitivity and specificity is expected in the near future from newer tests. We recognize that the estimates for IFOBT would benefit from upcoming publications on these tests. Consequently for the purposes of this report we present simulations for an immunochemical test with sensitivity 25%, 50%,75%, and 100% higher than that of Hemoccult II. Specificity of 98% and of 95% are considered for the IFOBT with these levels of sensitivities. An immunochemical test with sensitivity 75% greater than the Hemocult II test is the sensitivity level of 70% for colorectal cancer, 17% for large adenomas and 9% for small adenomas which is assumed for the Hemoccult SENSA test and is used as the main assumption for the IFOBTs with a more favorable specificity (98%) and a less favorable specificity (95%).

A two-tier approach combining a sensitive guaiac with an immunochemical test have been considered by Allison (1996, 2002) and Greenberg (2003). A two-tier approach is not included in this report.

The sensitivity and specificity assumptions for the simulation analyses for Hemoccult II, Hemoccult SENSA, and immunochemical tests are given in Table 2.

METHODS

Description of MISCAN-COLON Simulation Model

The MISCAN-COLON model is a Micro-simulation Screening Analysis Cancer model designed to simulate the natural history of the adenoma-carcinoma sequence in a population with and without colorectal cancer screening. A large number of fictitious individual life histories are simulated and each life has a risk of developing one or more adenomas. The life history is first simulated by drawing a date of birth and subsequent date and cause of death (other than due to colorectal cancer) for each member of the simulated cohort. Simulated life histories are created for a population with the age distribution of the U.S. population at the beginning of the screening program. For a screening program beginning in 2000 for those ages 65-79, these life histories should include cohorts born in 1921 and later. From a simulated population of 1 million, the number of simulated individuals surviving to age 65-79 to the beginning of the screening program is about 72,000 per simulation. Individuals age into and out of this population over the course of the screening program.

This approach simulates an age-structured dynamic population which is used to assess the impact of a new intervention within a population of varying ages. The risk of developing an adenoma differs within a population and is a function of a risk index and the age-specific risk of developing an adenoma. Some adenomas will progress on to cancer and some of these will cause death due to colorectal cancer. Some people will never develop a lesion, while others may develop more than one lesion. An individual is at risk of developing an adenoma up until time of death. This simulated cohort represents persons without any participation in colorectal cancer screening. Next, a program of periodic screening for colorectal cancer is simulated for this dynamic cohort and these screening tests will change some of the life histories, depending on whether a detectable but preclinical adenoma or cancer is present in each hypothetical individual, depending on the sensitivity and specificity of the test and depending on stage of cancer that would have been clinically detected in the absense of screening and depending on whether the individual would have died of cancer sooner than other causes of death in the absence of screening. MISCAN-COLON and other simulation models use estimates of "event sensitivity" as a model assumption and input. Separate event sensitivities can be incorporated into the MISCAN model for detection of large ($\geq$1.0 cm) and for small adenomas (< 1cm) as well as for colorectal cancer. As noted below, the availability of information on event sensitivity for cancers and for adenomas vary depending on the study design to assess sensitivity.

Input assumptions affecting adenoma prevalence, colorectal cancer incidence and mortality, are calibrated so that the observed adenoma prevalence, colorectal cancer incidence and colorectal cancer mortality (USA) are reproduced by the model. A summary of the model's assumptions for screening and surveillance are given in Table 3. For those hypothetical individuals exposed to screening the additional costs of screening are added and for all positive test results, including false positive results, the additional costs of diagnostic and surveillance procedures are added. For those individuals in which preclinical adenomas or cancer are detected by screening, time of death is changed if, for that person, the individual would have died of colorectal cancer in the absence of screening. Medical costs are also added or subtracted depending on the change in stage of disease detected and the change in the individual's life span after colorectal cancer diagnosis. All changes in costs and life time due to the screening program are accumulated over the entire life-span of all individuals who have been subjected to the screening program.

Details of the parameter estimation and validation for the MISCAN-COLON model are given in several published articles (Loeve 1999; 2000; 2001) that are attached as Appendix 1. In addition during the initial development of the MISCAN-colon model a validation study was performed comparing MISCAN-colon simulations against the results of the Minnesota Colon Cancer Control (MCCC) trial (Mandel 1993 and 1999; Loeve 1998) . As much as possible the simulation was specified to replicate the conditions of MCCC trial, which was complicated by several factors, including switching from unredydrated to rehydrated FOBT, by an initial 2 year recruitment phase in the trial and by two phase of screening in the trial, from 1975 to 1982 and 1986 to 1992. In 1993 the MCCC reported an observed statistically significant mortality reduction from annual FOBT of 32%. With additional follow-up MCCC reported a mortality reduction of 33% for annual FOBT and 21% for biennial FOBT. The MISCAN-colon simulation of the trial predicted a mortality reduction of 34.6% for annual FOBT and 20% for biennial FOBT.

In these papers and reports validating the MISCAN model we made the assumption that the sensitivity of Hemoccult II for cancer was 60% which is higher than that assumed for this report (40% for Hemoccult II for colorectal cancer). In assuming a lower sensitivity for cancer we have not recalibrated the estimate of preclinical cancer duration to assure global consistencey with observed age specific cancer incidence as was done in the original model. However, we believe that this will not have an important efect relative to the outcomes modeled here.

The simulation model is used to derive the number of colorectal cancer cases and deaths, life years and the costs with and without screening options.

Assumptions of the model and simulations

For the purposes of this report, the following assumptions were made:

Screening Program:

- The economic evaluations were conducted in the context of a program of annual FOBT screening for Medicare recipients.
- It was assumed that the program of screening was initiated in 2000 and was in effect for the duration of 30 years.
- All persons between the ages of 65 and 79 were assumed to receive annual FOBT screening during the duration of the screening program.
- The health effects and costs associated with the screening program, however, were followed for the entire life of each person.
- No person had received any type of colorectal screening procedure prior to age 65.
- All individuals were 100% compliant with screening and follow-up diagnostic and surveillance procedures.
- Individuals with an adenoma detected will continue to have surveillance colonoscopies until a diagnosis of colorectal cancer or death from other causes. The timing of the surveillance interval will depend on the number, size, and histology findings of the initial findings (Winawer, 2003)

While the assumed screening program is clearly unrealistic, this “what-if” scenario has utility for making relative cost effectiveness comparisons between different tests. We use sensitivity analysis with variation in the range of these parameters and assessed how much these changes in parameter estimates changed the outcomes from the model.

Costs: The allowed payment level of guaiac FOBT was set at $4.50 and included the 20% co-payment from the patient. The allowed payment level of IFOBT was varied across a range of values in the threshold payment analysis. Cost of diagnostic follow-up, surveillance and treatment procedures based on actual Medicare payment levels, were assumed to be as follows. The estimated costs for colonoscopy and polypectomy are based on information provided by CMS on Medicare payment rates for 2002 for colonoscopy procedures (CPT 45378 and CPT 45380) and polypectomy procedures (CPT 45383, 45385, 45385) performed in free standing clinic settings, on outpatient hospital settings and in ambulatory surgical settings. The weighted average payment across these settings was $646 for diagnostic colonoscopy and $683 for diagnostic colonoscopy plus biopsy. Average payment levels for polypectomy ranged from $691

to $760 depending on the specific CPT code. Based on this information we assumed an average payment level of $650 for diagnostic colonoscopy and $750 for polypectomy.

Estimates of costs for initial, continuing and terminal treatment for colorectal cancer were based on Medicare payment data from the SEER-Medicare database (Brown 1999). Cost estimates for colorectal cancer cases diagnosed between 1990 and 1994 were updated to 2002 using price adjusters from CMS, the PPS index for Part A payments, the MEI index for Part B payments, and an added 15% to take out of pocket costs into account. Based on this information we assume that the average payment level is $26,800 for the initial treatment of colorectal cancer, $2,100 annually for continuing care cost following initial cancer treatment, and $21,700 for terminal care costs for those who die of colorectal cancer.

Discounting: In the main analyses both heath effects and costs are discounted at 3% per year.

Cost-effectiveness measures

For purposes of this report the cost-effectiveness of FOBT is expressed as dollars per life-year gained from an ongoing program of annual screening for persons age 65-79, compared to no screening. Life-years gained result from reduced mortality from colorectal cancer due to the early detection of colorectal cancer and to the detection and removal of pre-cancerous lesions, some of which would have developed into invasive clinical cancer in the absence of their detection and removal. Costs included in the analysis include the cost of the screening test itself, the cost of any subsequent diagnostic follow-up and surveillance procedures, and the cost of cancer treatment either curative or palliative. Cost for the guaiac based tests is $4.50, the Medicare approved level for a guaiac test. For comparison purposes we first set the cost values for a new immunochemical test at $4.50 (the current value for the guaiac test) and then consider higher values as well.

Cost effectiveness ratios are described for Hemoccult II and Hemoccult SENSA at a payment level of $4.50 and IFOBT at payment levels of $4.50 and $28.00. We also describe threshold payment levels for IFOBT that result in cost-effectiveness ratios equal to those for Hemoccult II and Hemoccult SENSA at payment levels of $4.50 for these two tests. Finally, we describe threshold payment levels for Hemoccult II and Hemoccult SENSA that would result in cost-effectiveness ratios equal to those for IFOBT at payment for IFOBT of $18 and $27.

In the case of screening, compared to no screening, additional costs are incurred from screening and follow-up procedures, but there is also the potential for some off-setting cost-savings because the treatment cost for pre-invasive and less advanced disease is less expensive compared to more advanced disease. This analysis includes only direct medical costs paid for by the Medicare program and Medicare recipients in the form of co-payment and deductible payments. We do not include such indirect costs as the time-cost incurred by patients in undergoing screening and treatment and indirect costs attributable to family care-giving. Nor do we include the cost of medical care unrelated to colorectal cancer associated with life-years gained from screening.

We also have not incorporated quality of life considerations into the analysis because the quality of life literature in regard to all phases of colorectal cancer screening and treatment is still

very preliminary and beyond the scope of this current work. Loeve (1998) did do an exploratory study on the potential effects of taking quality of life into account in the MISCAN-Colon model. Using estimates of quality of life decrements from screening similar to those documented for breast cancer screening and preliminary estimates of quality of life following diagnosis and treatment simulations were run with and without quality of life considerations. The quality of life impact was relatively small. For example for annual unrehydrated FOBT the simulated life-years gained from screening was 9% less quality-adjusted life years compared to unadjusted life-years, using a 3% discount rate. While this difference is not negligible, differences of this magnitude are unlikely to have a substantial impact on the kinds of analyses presented in this report. The results from this exploratory analysis are similar to those obtained by De Koning (1991) in assessing the impact of quality of life on cost-effectiveness for breast cancer. He used quality of life estimates for screening and treatment based on a survey of clinical experts and found that that the quality of life considerations had only a modest impact on cost-effectiveness estimates for mammography screening.

We use the simulation model to derive the costs per life year saved for different screening options. The cost-effectiveness ratios are based on a comparison of a screening intervention compared to no screening intervention. This measure is also called the average cost-effectiveness ratio (ACER). Alternatively a cost-effectiveness ratio can be derived comparing the costs and effectiveness of one screening program to the costs and effectiveness of another screening program. These relative cost effectiveness ratios are the incremental cost effective ratios (ICER). In this setting the ACER and ICER values are similar and we only report the ACER values for the cost-effectiveness ratios in the tables and give the ICER in the tables of Appendix 3.

We also use the ACER and ICER values to derive threshold values for the cost of a new immunochemical test which would provide equivalent effectiveness (life years gained) for cost expended as that for the base case guaiac tests with a reimbursement of $4.50. The threshold value for IFOBT can be derived iteratively. Alternatively a graphical solution to deriving a threshold value is illustrated in the Appendix 2.

RESULTS

We use the simulation model to derive the costs per life year gained for a screening strategy compared to no screening (the average cost effectiveness ratio or ACER) and for one screening strategy compared to another screening strategy (the incremental cost effectiveness ratio or ICER). Difference in colorectal cancer cases and colorectal cancer deaths, total costs, life years gained, and cost-effectiveness ratios (costs per life years saved) with and without discounting are derived for all simulations. Further the simulated results provide for an assessment of different prices for the guaiac FOBT and the IFOBT that will deliver equivalent cost effectiveness ratios. This price is the threshold analysis value.

Dynamic Results of a Screening Program

The simulation is based on a 30-year period of annual screening. Figure 1 shows the dynamic effects of a typical screening program using annual screening with Hemoccult II. The line labeled “no screening” shows the number of new cases of colorectal cancer that would be detected in the absence of screening. The line labeled “all” shows that total cases of colorectal

cancer would decrease during the 30 years of a screening program and after the termination of screening, in 2030, would eventually recover to the no screening level. The lines labeled "clinical," "scr. det.", and "surveil. det." show the number of cases of colorectal cancer that would be detected following clinical symptoms, following positive screening test results and following positive surveillance test results. The mortality benefit from screening occurs because fewer total invasive cancers occur during a screening program, because of the removal of pre-cancerous adenomas, and because cancer detected by screening and surveillance tend to be diagnosed at an earlier and more treatable stage than those that are clinically detected. Cancers that are prevented or those detected at an earlier stage may also result in avoided treatment costs.

Results of Screening: Life Years Saved, Costs, and Cost-Effectiveness

In Table 4 we consider the results of the simulation model for Hemoccult II and Hemoccult SENSA compared to an IFOBT with sensitivity of the Hemoccult SENSA (70%) and specificity of the un-rehydrated Hemoccult II FOBT (98%) or lower (95%). Two costs, $4.50 and $28, are considered for all scenarios. We also consider costs of $18 and $27 for the main assumptions. The cost effectiveness ratios portrayed in Table 4 are very favorable by conventional standards for all fecal occult blood test options. The ACER for programs using Hemoccult II with 40% sensitivity and 98% specificity is approximately $1000 per life year gained when FOBT costs $4.50. IFOBTs with 98% specificity have an ACER lower ($357) than that of Hemoccult II when IFOBT costs $4.50 and still very favorable with an ACER of $2834 if IFOBT costs $28. The more unfavorable ACER is obtained for Hemoccult SENSA which is the test with the lowest assumed specificity (92.5%). However even if Hemoccult SENSA costs $28 per test, the ACER is $5827. Our lowest cost-effectiveness estimates are more favorable than those that have been reported in most other cost-effectiveness studies, but this can be explained by the lower value we have used for the payment level for the test. Compared to the $4.50 level have assumed, other studies assumed test cost from $7.50 to $38.00 (Pignone 2002).

Incremental cost-effectiveness ratios can be easily calculated from the data provided in Table 4. For example, at a discount rate of 3%, the ICER for IFOBT with 98% specificity, and assuming equal unit cost of $4.50, is negative, that is, it is cost-saving compared to Hemoccult II, it results in more life-years gained at lower cost. This follows from the fact that we are assuming increased sensitivity at equal specificity, resulting in more life years saved and treatment costs avoided with about the same level of diagnostic and surveillance costs. At a unit cost of $28.00 for this IFOBT compared to $4.50 for Hemoccult II the ICER increases to about $11,000 per additional life-year gained as a result of using IFOBT instead of Hemoccult II. Assuming a specificity of 95% for IFOBT the ICER when compared to Hemoccult II is about $6,000 per added life-year assuming a unit cost of $4.50 and about $21,000 per added life-year assuming a unit cost of $28.00 for IFOBT. When compared to Hemoccult Sensa, IFOBT with a specificity of 98% is cost-saving even at a unit cost of $28.00. However, for IFOBT with a specificity of 95%, the ICER at $28, compared to Hemoccult Sensa at $4.50, adds very high costs for essentially the same level of life-years gained. In this last case, the modest cost advantage of somewhat better specificity is out-weighed by the cost-disadvantage of the much high unit cost of the screening test.

Clearly, if we assume a specificity of 98% for IFOBT, it is a test that would be economically preferred to Hemoccult II at the current level of payment and be preferred to

Hemoccult Sensa even at a much high payment level. When we assume a payment level of $28 for IFOBT the additional benefits of the test, compared to Hemoccult II come at various levels of additional economic costs depending on the assumed level of specificity. While the ICER values in this case are multiples of the cost-effectiveness of Hemoccult II compared to no screening, they are well within the range of what is conventionally considered to be economically reasonable.

Figure 2 displays the life years gained per costs in a sensitivity analysis for IFOBT with specificities of 98% and 95% with increasing sensitivity for colorectal cancers and adenomas compared to the base case of Hemoccult II with 40% sensitivity for colorectal cancer and 98% specificity. Tests that have higher sensitivity and equal specificity (colored symbols to the left and above the base-case) result in more life-years gained and lower net cost (because of more savings in treatment costs avoided) while tests that have higher sensitivity but lower specificity (open symbols to the right and above the base-case) result in more life-years gained but substantially higher net cost because of higher costs related to diagnostic follow-up of false positive screening tests. These effects are also reflected numerically in Table 4. For example, comparing row 2 and row 4 for Table 4, it can be seen, that everything else equal, the test with 95% specificity (row 4) results in substantially greater costs and a substantially less favorable ACER that the test with 98% specificity (row 2).

Additional sensitivity analyses are given in Table 4 for more frequent surveillance compared to current guidelines and with lower compliance for Hemoccult II versus IFOBT. Even with more extensive surveillance every 3 years for all with adenomas detected, the ACER's range from $2728 to $6617.

Threshold Payment Analysis

Table 5 tells us that if we make the more favorable assumption about the specificity (98%) for IFOBT, a payment level in the range of $10 to $14 but no higher, might be justifiable. But if the true specificity of IFOBT is closer to 95%, a payment greater than the current $4.50 could not be justified on comparative cost-effectiveness grounds, even though the absolute cost effectiveness ratios may fall within boundaries that are conventionally considered reasonable (Table 4). If the true specificity of IFOBT is closer to 95%, the threshold value payment level is less than $4.50 and even less than zero when sensitivity ranges from 40% to 80% and the sensitivity for colorectal cancer is four times that for adenomas of size $\geq$ 1.0 cm. However a threshold value of $18 is obtained for IFOBT if sensitivity for colorectal cancer increases to 87% and the sensitivity for colorectal cancer is 1.75 times that for adenomas of size $\geq$1.0 .

It could be argued that IFOBT should be compared to Hemoccult-SENSA as the base case rather than Hemoccult-II because Hemoccult-SENSA is available and increasingly used in the United States at the current Medicare reimbursement level of $4.50. While the higher sensitivity of SENSA is a desirable characteristic, this advantage is somewhat blunted in the context of a program of annual screening, and there is a cost disadvantage associated with the lower specificity in the range of 90- 94%. Assuming specificity of 92.5% for Hemoccult SENSA would have a cost effectiveness about double that of Hemoccult II. If we assume the lower bound of 94% for the Hemoccult SENSA, the tests are essentially equivalent and the threshold payment level of IFBOT would not be much greater than the $4.50 for Hemoccult II SENSA Still, in

absolute terms this is within the range of cost effectiveness at $4270 per life years gained which is far under $50,000 per life years gained that is often cited as a reasonable benchmark for reasonable value for money. So it could be argued that is reasonable for those with a preference for higher sensitivity to use Hemoccult-SENSA. Most studies suggest that Hemoccult SENSA and IFOBT have roughly similar sensitivity values so the point of comparison between the two is the difference in specificity. If we assume the lower bound value of 95% for IFOBT and the upper bound value of 94% for Hemoccult SENSA, the two tests are essentially equivalent and the threshold payment level of IFOBT would not be much greater than $4.50. But if we assume the less favorable value of 92.5% specificity for Hemoccult SENSA, and the 95% - 98% range of specificity for IFOBT, the threshold payment level for IFOBT would be considerably higher, as shown in Table 5. At the lower value of 95% specificity for IFOBT the threshold payment level would be about $17.00 when compared to SENSA at 92.5% specificity. At the upper value of 98% specificity for IFOBT, the threshold payment level would be almost $33.00. Figure 3 shows the costs and health effects of these scenarios compared to the Hemoccult II base case. Note, assuming a lower value of specificity for Hemoccult SENSA relative to IFOBT increases the estimated threshold payment for IFOBT but also decreases the rationale for adopting Hemoccult SENSA, rather than Hemoccult II as the base case.

Sensitivity Analyses

Best Case for IFOBT

We consider that the package insert claims for InSure to be the best-case assumptions that could be made for sensitivity and specificity for this particular IFOBT. These results are similar to those presented in May 2003 (Cole, 2003) and described above. The estimates of sensitivity are based on very small clinical series (n=240) of high-risk individuals. The estimate of specificity is based on a small sample (n=90) of individuals who had previously received negative colonoscopy examinations. The values estimated from these studies are: specificity = 98% (95% Confidence Interval: 92% - 100%), sensitivity for cancer = 87% (95% Confidence Interval: 70% - 97%), sensitivity for large adenomas = 48% (95% Confidence Interval: 25% - 71%). The reported sensitivity is based on relative sensitivity compared to Hemoccult SENSA. These results suggest that the sensitivity of IFOBT for adenomas of size $\geq$ 1.0 is approximately half the level as for detecting colorectal cancer. This assumption for sensitivity for adenomas of size $\geq$ 1.0 cm is a much higher rate of detection of the large adenomas than assumed previously (25% of the colorectal cancer rate). As shown in Table 5, when compared to the base case that we have associated with Hemoccult II, the payment level that yields equivalent cost-effectiveness for this best case scenario is about $29. When compared to Hemoccult SENSA as the base case, the threshold payment level associated with IFOBT, assuming the package insert claims, would be about $60. It is worth noting that this particular scenario uses test performance characteristics estimated in a single study for an IFOBT performed in a small and possibly atypical patient population, while the performance characteristics for the base case Hemoccult II and Hemoccult SENSA are based on a conservative reading of a broad range of studies. There are no studies that we know of that confirm this result through large studies have average risk individuals in a screening setting comparing IFOBT directly to Hemoccult. This best case scenario for IFOBT is illustrated in Figure 4.

IFOBT as the Base Case

Here we consider the situation where a payment level of IFOBT has been established and we ask the question: what would be the corresponding threshold payment level of Hemoccult II and Hemoccult SENSA. We performed threshold analyses assuming payments levels of $18 and $27 for IFOBT. Results of this analysis are shown in the bottom panel of Table 5. If a specificity of 98% is assumed for IFOBT, the threshold payment levels corresponding to $18 and $27 payment levels for IFOBT are about $10 and $17 for Hemoccult II. At a specificity of 98% for IFOBT corresponding threshold payment levels of Hemoccult SENSA would be less than the current payment of $4.50. But if a specificity of 95% were assumed for IFOBT than the corresponding threshold payments levels for Hemoccult SENSA would be about $5 (corresponding to the $18 payment for IFOBT) and about $14 (corresponding to the $27 payment for IFOBT).

Non-Guideline Surveillance (More intensive surveillance)

We have assumed that surveillance in performed in compliance with current clinical guidelines. However, there is evidence that surveillance procedures may often be performed more intensively than currently recommended (Knopf 2001, Mysliwiec 2003). Figure 5 shows the affect of more intensive surveillance. Life-years saved are increased slightly while costs are increased substantially. The relative cost-effectiveness advantage of screening tests that are more sensitive for the detection of adenomas would diminish with more intensive surveillance practices.

Less Than 100% Compliance

Because dietary restrictions are not required prior to the administration of IFOBTs, it is possible that compliance may be higher for these tests, especially compared to SENSA (Young, 2002). Also the InSure IFOBT test uses a novel brush collection method which can increase willingness to complete the test (Cole 2003). In order to explore the implications of differing test compliance, we assume (using test sensitivity and specificity values shown in Table 2) that only 60% of the population complies per year with screening in a situation with annual screening in the base case. For any individual, compliance with the current test is assumed to be independent of compliance in the past tests, i.e., we assume random compliance. We also assume that with the new test, compliance increases from 60% to 90% compliance (50% increase in compliance for IFOBT compared to Hemoccult II), again random. We assume that Medicare pays $4.50 for 100% of test kits that are given to patients, for an effective cost of $6.75 per kit in the case of 60% compliance.

The last panel (rows) of Table 4 shows the results of differing assumptions about compliance in completion of the FOBT test. The next to last panel of Table 5 shows that the threshold payment level of a high compliance IFOBT with 98% specificity would be almost $15 rather than almost $11 in the case where compliance is equal for both tests. Figure 6 illustrates these affects of compliance.

LIMITATIONS

Several limitations to this analysis should be noted:

Screening Program

For our main analysis, we have assumed a screening program consisting of annual FOBT only. The benefit of increased sensitivity is likely to be greater for screening programs characterized by longer screening intervals, e.g. biennial or triennial screening or by sporadic schedules of screening. We chose to focus on annual screening because this is allowed under current Medicare coverage policy. Nevertheless, it is possible that the threshold payment level of IFOBT might be somewhat higher in the context of other screening schedules.

We have assumed that no screening takes place prior to age 65 and that there is no use of endoscopy, e.g. screening sigmoidoscopy, in combination with FOBT as allowed under current Medicare coverage policy. If screening sigmoidoscopy were assumed to be used in the screening program, the incremental cost-effectiveness of FOBT in addition to sigmoidoscopy would likely be much less favorable than in this report. For example, in the study of Lieberman et al. (2001) the addition of rehydrated FOBT to a one-time screening sigmoidoscopy examination resulted in a statistically non-significant increase in sensitivity (using colonoscopy as the gold standard) for advanced neoplasia from 70.3% to 75.8%. This would clearly result in large increases in the absolute cost-effectiveness ratios for all FOBTs and lower incremental benefits for more sensitive tests.

There is evidence that compliance to diagnostic follow-up and surveillance is much lower than 100%. (Winawer 2003) This would reduce the cost saving associated with a screening program with higher specificity but it would also reduce the effective sensitivity of any test. We also assume a protocol of diagnostic follow-up and surveillance in accordance with current U.S. clinical guidelines. There is evidence that much more intensive and costly patterns of surveillance are often used in community practice. This factor would increase the cost savings associated with screening programs of higher specificity.

Other Considerations

IFOBT tests are less likely that the guaiac tests of Hemoccult II or Hemoccult SENSA to result in false positive tests due to the detection of blood originating from the upper gastrointestinal tract. This may result in the performance of upper gastrointestinal endoscopy examinations following some false positive FOBT tests. We have not included this consideration in our simulations. To do so we would have to add additional costs related to false positive FOBT tests. Nevertheless, it is likely that consideration of this factor could result in somewhat more favorable threshold payment levels for IFOBT. Upper gastrointestinal endoscopy is recommended for these patients (Zuckerman 2000) even though several authors have reported a low yield for this procedure when the patient has no symptoms. Thomas and Hardcastle (1990) used the data from the Nottingham fecal occult blood test randomized trial to suggest that upper gastrointestinal investigations need not be performed routinely in asymptomatic persons with positive FOBT's but negative colonoscopies. They suggest that this procedure be reserved for

those with symptoms. Retrospective studies suggest that there is a low clinical yield for upper gastrointestinal endoscopy for such patients. (Chen 1993; Ali 2003).

These analyses have been conducted from the perspective of medical payments allowed by the Medicare program. Significantly, this excludes the time cost that accrues to both patients to undergo the screening and diagnostic procedures and the uncompensated physician time that might be associated with advising the patient to participate in screening. If these costs were counted the absolute cost effectiveness estimates would increase by substantial margins and this would affect the rationale for considering Hemoccult SENSA as an alternative base case.

When adjusting the duration of pre-clinical cancer to observed colorectal cancer detection rate in the trials 60% sensitivity was assumed. However in these analyses we have made the assumption of 40% sensitivity for colorectal cancer for Hemoccult II. For this report we have not recalibrated the model. This would suggest that in this report there could be an underestimate of the screening effect. But this does not clearly affect the comparison between higher and lower sensitivity in this report.

If recalibrated we would have a longer duration for preclinical cancer but this is neutralized by the lower sensitivity. The shorter duration of preclinical cancer the more higher sensitivity helps. We didn't underestimate the extra benefits of higher sensitivity. We had a shorter duration now than if we recalibrated, so if anything we have underestimated rather than over estimated the benefits of increased sensitivity.

Finally, it is clear that a large element of uncertainty is associated with this analysis because of the paucity of reliable data on the test characteristics of IFOBT and Hemoccult-SENSA. The first large screening trial to report a mortality benefit from FOBT screening relied primarily on rehydrated Hemoccult. But rehydrated Hemoccult is no longer recommended for use. Several large European screening trials used un-rehydrated FOBT. There are few, if any, studies of Hemoccult-SENSA and the IFOBTs that fulfill the features of an optimal study design for determining the true performance characteristics of these tests relative to un-rehydrated FOBT: a large prospective study involving previously unscreened, a symptomatic individuals with contemporaneous confirmation by a gold standard procedure where alternatives tests are administered to the same individual or randomly assigned to subsets of individuals from the same study population. Of recent studies the one that comes closest to fulfilling these conditions is the Veterans Administration study reported by Lieberman et al. (2001). In this study, the study population was asymptomatic and unscreened. This population was of higher than average risk but numerous correlates of risk were also collected. Colonoscopy was used as a gold standard. Several screening modalities were tested contemporaneously, but only one FOBT test was considered and, due to the prominence of the Minnesota FOBT trial when the VA study was initiated, this was rehydrated FOBT. Such studies are expensive and logistically complex but additional studies of this type comparing the newer FOBTs may be worth considering as long as several alternative types of FOBT tests remain under consideration as primary modalities for colorectal cancer screening.

CONCLUSIONS

Because of the high degree of uncertainty about the true test characteristics of the various types of FOBTs, we have conducted a variety of simulations to cover the most plausible combinations of these characteristics for various test combinations, including the most favorable assumptions about the characteristics for IFOBT supported by any evidence.

For each of these assumptions we determined the threshold payment level for IFOBT, the payment level that would result in cost effectiveness equal to that for the comparison base case test with a payment level of $4.50. For less favorable, but plausible, assumptions about the specificity of IFOBT compared to Hemoccult II, the threshold payment is less than $4.50. For more favorable assumptions about the specificity of IFOBT compared to Hemoccult II the threshold payment is in the range of $13 - $14. If the less cost-effective Hemoccult SENSA, rather than Hemoccult II, is considered to be the base case the threshold payment level of IFOBT can be in the range of $17 - $33 depending on whether the lower 95% or the higher 98% specificity value is assumed for IFOBT. Substantially higher threshold payment levels for IFOBT could be obtained if IFOBT test performance characteristics as specified by InSure package insert literature are assumed. However, it is doubtful that these values are truly comparable to the conservative values we have assumed for Hemoccult II and Hemoccult SENSA.

Table 1. Summary of Studies Reporting Sensitivity and Specificity for FOBT

Table 1 A. GUAIAC Hemoccult II (un-rehydrated and rehydrated)								
Author	**Ref**	**Year**	**N in Study**	**Country**	**Sensitivity CRC**	**Sensitivity Large Aden**	**Sensitivity Small Aden**	**Specificity**
Literature with follow-up of positive tests with colonoscopy and negative tests with surveillance of at least one year								
Hemoccult II un-rehydrated								
Allison	N Eng J Med	1996	8065	US	37.1	30.1		98.1
Petrilli	Surg Onc	1994	8933	US	37.1			98.1
Robinson	BrJ Surg	1994	1489	UK	11.1			98.9
Hemoccult II rehydrated								
Castiglione	BrJCa	1996	8008	Italy	68.2	52.9		94.1
Randomized controlled trials								
Hemoccult II un-rehydrated								
Mandel	N Engl J Med	1993	45,000	US	80.8			97.7

Hardcastle	Lancet	1996	150,000	UK	58.6			96.8
Kronborg	Lancet	1996	60,000	Den mark	55.5 (62.1)			99.3
Gyrd-Hansen	In J Epi	1997	(60,000)	Den mark	62.1			
Hemoccult II rehydrated								
Mandel	N Engl J Med	1993	45,000	US	92.2			90.4
Church	JNCI	1997	(45,000)	US	90.0			
Literature with FOBT followed by Colonoscopy for all								
Hemoccult II un-rehydrated								
Greenberg	AmJ Gast	2000	554	9 centers in world	85.7	20.5		92.8
Zauber	DDW	2002	881	US		23		91
Hemoccult II rehydrated								
Lieberman	N Engl J Med	2001	2885	US	50%	21.6	7.0	93.8

Table 1 B. GUAIAC Hemoccult SENSA

Author	Ref	Year	N in Study	Country	Sensitivity CRC	Sensitivity Large Aden	Sensitivity Small Aden	Specificity
Literature with follow-up of positive tests with colonoscopy and negative tests with or without* surveillance of at least one year								
Allison	N Engl J Med	1996	8065	US	79.4	68.6		87.5
Cole*	Gastro Enterolgy	2003	460	Australia	38.5			Not reported
Literature with FOBT followed by Colonoscopy for all								

Greenberg	AmJ Gast	2000	554	9 centers in world	78.6	35.9		90.5

Table 1 C. Immunochemical								
Author	*Ref*	Year	**N in Study**	Country	Sensitivity **CRC**	**Sensitivity Large Aden**	**Sensitivity Small Aden**	**Specificity**
Literature with follow-up of positive tests with colonoscopy and negative tests with surveillance of at least one year								
HemeSelect								
Allison	N Engl J Med	1996	8065		68.8	66.7		95.2
Robinson	BrJSurg	1994	1489	UK	100			90.8 (94.9)
Castiglione*	BrJCa	1996	8008	Italy	95.5	78.6		92.0 (92.7) (
(Castiglione**)	BrJCa	1996	8008	Italy	77.3	51.4		97.1 (97.6)
Monahaem								
Nakama	Prev Med	1994	3365	Japan	91			96
Nakama	JmedSc	1996	3365	Japan	71.4			95.6
Nakama	Hep-Gastr	1999	4611	Japan	88.9			93.1
*1 day positive plus borderline ***1 day positive only*								
Insure								
Cole	Gastro	2003	460	Australia	85			Not given in abstract
Randomized controlled trials								
None								
Literature with FOBT followed by colonoscopy (or flexible sigmoidoscopy*) for all								
Flexsure								
Young	J Med Sc	2003		Austral	80			97.2
Greenberg	AmJ Gast	2003	554	World	87.5			86.2
HemeSelect								
Allison	Gastro	2002	5356	US	81.8	25.4		97.5
Greenberg	AmJ Gast	2003	554	World	83.3			88.2
Allsion	Gastro	2002	5356	US	82 for left	25		97.5

					crc			
Nakama	Hepato Gas	1999	4611	Japan	83.3	50.7		96.0
Magstream 1000/Hem SP								
Wong	Cancer	2003	250	China	62 OR 100?	47		93
Insure								
Young	J Med Scr	2003		Austra	75			97.8

Table 1D Package Inserts							
Company	**Year**	**Country**	**Sensitivity CRC**	**Sensitivity Large Aden**	**Sensitivity Small Adenomas**	**Specificity**	
Guaiac Tests							
Hemoccult II un-rehydrated							
Beckman-Coulter	2000	US	86	53	32	98	
Hemoccult SENSA							
Beckman-Coulter	2000	US	92	67	43	96.5	
Immunochemical Test							
Insure							
Enterix	2003	US	87	47.4		97.7	

Table 1E Estimates from cost-effectiveness assumptions and guidelines						
Author	**Ref**	**Year**	**Sensitivity CRC**	**Sensitivity Large Aden**	**Sensitivity Small Aden**	**Specificity**
Cost-Effectiveness Models						
Hemoccult II un-rehydrated						
Frazier/ Kuntz	JAMA	2000	33		2	97
MISCAN	Compu	1999	60	5	2	98
Sonnenberg	Ann Int Med	2000	40			97.5
Wagner	Prev	1996	60			90
Hemoccult II rehydrated						
Frazier/ Kuntz	JAMA	2000	60			90
MISCAN	Compu	1999	70	20		90
Kanneker	Int J Tech	2000	60	10	6	92
Guidelines Recommendations						
Hemoccult II un-rehydrated						
Winawer	Gastroent	1997	60			90
Australian	Austral	1997	50	10		92

	Health Tech					

Table 1F. Studies Comparing Multiple FOBT"s

Author	Hemoccult II Unrehydrated	Hemoccult II rehydrated	Hemoccult SENSA	Immuno-chemical
Allison (1996)	X		X	HemeSelect
Allison (2002)			X	HemeSelect or FlexSure
Castilgone		X		HemeSelect (1 day + and +/-)
Robinson	X			Hemeselect 3 day
Greenberg	X		X	HemeSelect and FlexSure
Young				InSure and FlexSure
Cole			X	InSure

Table 2. Estimates of sensitivity and specificity for Hemoccult II, Hemoccult SENSA and immunochemical tests assumed for the simulations

FOBT Test	Sensitivity for CRC	Sensitivity for ≥1 cm adenomas	Sensitivity for <1 cm adenomas	Specificity	Base case
Main analyses					
Hemoccult II FOBT 40,10,5_98	40%	10%	5%	98%	Base
Hemoccult SENSA FOBT 70, 17,9_92.5	70%	17%	9%	92.5%	Base
IFOBT70,17,9_98	70%	17%	9%	98%	New test
IFOBT_70,17,9_95	70%	17%	9%	95%	New test
Sensitivity Analyses of Test Parameters of IFOBT					
IFOBT with increased sensitivity compared to Hemoccult II					
IFOBT 50,12.5,6.25_98 *25% ↑Se*	50%	12%	6%	98%	New test
IFOBT 50,12.5,6.25_95	50%	12%	12%	95%	New test
IFOBT 60,12.5,6.25_98 *50% ↑Se*	60%	15%	7%	98%	New test
IFOBT 60,12.5,6.25_95	60%	15%	7%	95%	New test
IFOBT 70,17,9_98 *75% ↑Se*	70%	17%	9%	98%	New test MAIN comparison

IFOBT 70,17,9_95	70%	17%	9%	95%	New test MAIN
IFOBT 80,20,10_98 *100% ↑Se*	80%	20%	10%	98%	New test
IFOBT 80,20,10_95	80%	20%	10%	95%	New test
Best case for IFOBT(package insert)					
IFOBT 87,48,24_95%	87	48%	24%	98%	New test

Table 3. Main assumptions in the expert MISCAN-COLON model, established in expert meetings at the National Cancer Institute in 1996 and 1997

Parameter	Value	Based on
Distribution birth over calendar years		Age distribution in SEER data
Life tables of deaths from other causes than colorectal cancer		Age-specific mortality rates in US population in 1989-1991
Adenoma incidence	Age dependent: 40-49 yrs: 0.9% per yr 50-59 yrs: 1.9% per yr 60-69 yrs: 3.3% per yr 70-79 yrs: 2.6% per yr	Adenoma prevalence in autopsy and colonoscopy studies of 15% in age group 50-59 to 33% in age group 70+, cancer incidence in SEER registry in 1978 (before screening started NCI, SEER 2001)
Distribution of risk for adenomas over the general population	Gamma distributed, mean 1, variance 2	Multiplicity distribution of adenomas in autopsy studies (Koreas 1993)
Duration distributions in preclinical stages	Exponential	Expert opinion, other cancer models (Walter 1983; Gyrd-Hansen 1997; Launoy 1997)
Mean duration of non-progressive adenomas	Lifelong	Expert opinion

Parameter	Value	Based on
mean duration of progressive adenomas	16.4 yrs on average, exponentially distributed	Expert opinion
Site distribution, transition from each preclinical invasive stage	Calibrated to:	site distribution of clinical cancers in SEER data in 1978 (before screening started)
mean duration of preclinical cancer	3.6 yrs on average, exponential distributed	Cancer detection rate at first screening and background cancer incidence in FOBT trials (Hardcastle 1989; Kronborg 1989)
Correlation between durations	100% between durations in preclinical stages	
Probability to develop cancer from removed adenoma	0%	Expert opinion
Sensitivity of FOBT tests for carcinomas and for adenomas of various size, and specificities of FOBT tests	Varied	See this report
Sensitivity of diagnostic and surveillance colonoscopy for adenomas	≤5mm: 80% 6-9mm: 85% 10+mm: 95%	Back-to-back colonoscopy studies (Hixson 1991; Rex, Cutler, Lemmel, et al 1997; Rex, Rahmani, Haseman, et

Parameter	Value	Based on
		al)
Sensitivity of diagnostic and surveillance colonoscopy for cancer	95%	Back-to-back colonoscopy studies
Dependency between tests	No dependency	
Site dependency	No site dependency	
Diagnostic follow-up after positive result for each test and each preclinical stage	Yes	
Prognosis after screening	After screen detection of a polyp: 100% cure After screen detection of a cancer: new survival based on stage-specific survival of clinical cancer	
Surveillance: follow-up interval after detection of adenomas at screening or surveillance (surveillance test: colonoscopy)	1 or 2 <1cm adenomas: after 5 years; 3+ adenomas or 1+ adenoma ≥1cm: after 3 years;	New AGA recommendations (Winawer, 2003)

Parameter	Value	Based on
	after negative surveillance: 5 years; sensitivity analysis: surveillance every 5 year life-long	
Attendance to screening	100%; sensitivity analysis: HCII 60% (costs of the FOBT kit is accounted for 100%) and IFOBT 90%	

Table 4: Simulated cancers prevented, CRC deaths prevented, life years gained, costs and costs per life year gained from different scenario's. Simulations with MISCAN-colon. Results per 1 million individuals age 65-79 at the beginning of the screening program.

			no discounting				3% discounting	
		Difference	Diff. in	Total Cost	Life Years	Total Cost 3%	Life Years	ACER 3%
Test	**Scenario**	**in CRC's**	**CRC deaths**		**Gained**		**Gained 3%**	
100% compliance:								
	guideline surveillance							
Hemoccult II	40,10,05-98/$4,50	-65,949	-52,055	-418,291,105	470,434	205,556,566	192,007	1,071
IFOBT 98% specificity	70,17,09-98/$4.50	-88,030	-63,304	-826,064,174	573,709	83,110,600	232,909	357
IFOBT 98% specificity	70,17,09-98/$18	-88,030	-63,304	-297,163,502	573,709	414,541,652	232,909	1,780
IFOBT 98% specificity	70,17,09-98/$27	-88,030	-63,304	55,436,947	573,709	635,495,687	232,909	2,729
IFOBT 98% specificity	70,17,09-98/$28	-88,030	-63,304	94,614,774	573,709	660,046,135	232,909	2,834
IFOBT 95% specificity	70,17,09-95/$4.50	-87,891	-63,207	-218,659,200	572,154	462,794,391	232,138	1,994
IFOBT 95% specificity	70,17,09-95/$18	-87,891	-63,207	310,200,312	572,154	794,206,329	232,138	3,421
IFOBT 95% specificity	70,17,09-95/$27	-87,891	-63,207	662,773,320	572,154	1,015,147,621	232,138	4,373
IFOBT 95% specificity	70,17,09-95/$28	-87,891	-63,207	701,948,098	572,154	1,039,696,653	232,138	4,479
Hemoccult – SENSA	70,17,09-92.5/$4.50	-87,737	-63,165	284,602,919	571,815	775,643,892	232,107	3,342
Hemoccult – SENSA	70,17,09-92.5/$28	-87,737	-63,165	1,205,219,051	571,815	1,352,544,256	232,107	5,827

Table 4: continued

	More surveillance: (every 3 years)							
Hemoccult II	40,10,05-98/$4,50	-76,474	-56,747	46,967,784	498,244	453,692,724	202,108	2,245
IFOBT 98% specificity	70,17,09-98/$4.50	-101,646	-69,221	-141,402,524	608,292	449,039,461	245,381	1,830
IFOBT 98% specificity	70,17,09-98/$28	-101,646	-69,221	770,673,804	608,292	1,021,113,112	245,381	4,161
IFOBT 95% specificity	70,17,09-95/$4.50	-101,506	-69,110	463,741,807	606,808	826,542,231	244,693	3,378
IFOBT 95% specificity	70,17,09-95/$28	-101,506	-69,110	1,375,741,577	606,808	1,398,580,548	244,693	5,716
	Other compliance levels:							
Hemoccult II	40,10,05-98/$6,75/60% compl.	-45,553	-38,119	-212,286,055	338,027	197,556,556	136,817	1,444
IFOBT 98% specificity	70,17,09-98/$4.50/90% compl.	-82,781	-60,436	-770,072,214	542,142	89,198,446	219,931	406
IFOBT 98% specificity	70,17,09--98/$28/90%compl.	-82,781	-60,436	65,421,034	542,142	612,654,174	219,931	2,786

Table 5: Threshold analysis: unit costs in $US for iFOBT costs resulting in equal cost-effectiveness (ACER and ICER) compared to the base case (Hemoccult II or Sensa) test for different combinations of test sensitivity and specificity. Simulations with MISCAN-colon.

base (hemoccult)	**Comparison: iFOBT**					
HCII: 40,10,05-98	**40,10,05-98**	**50,12,06-98**	**60,15,07-98**	**70,17,09-98**	**80, 20,10-98**	**87,48,24-98**
Guideline surveillance						
for equal ACER	*4.50*	*7.08*	*8.99*	*11.27*	*12.44*	*29.02*
for equal ICER	*4.50*	*7.08*	*9.00*	*11.28*	*12.45*	*29.04*
	40,10,05-95	**50,12,06-95**	**60,15,07-95**	**70,17,09-95**	**80, 20,10-95**	**87,48,24-95**
for equal ACER	*-10.55*	*-8.17*	*-6.30*	*-4.23*	*-3.22*	*12.08*
for equal ICER	*-10.55*	*-8.17*	*-6.29*	*-4.22*	*-3.21*	*12.10*
Sensa: 70,17,09-92.5%				**70,17,09-98**		**87,48,24-98**
Guideline surveillance						
for equal ACER				*32.82*		*56.88*
for equal ICER				*32.93*		*63.71*
				70,17,09-95		**87,48,24-95**
for equal ACER				*17.25*		*39.90*
for equal ICER				*17.25*		*46.68*
Sensitivity analyses:						
1. More surveillance (every 3 years)						
HCII: 40,10,05-98	**40,10,05-98**	**50,12,06-98**	**60,15,07-98**	**70,17,09-98**	**80, 20,10-98**	
for equal ACER	4.50	*6.25*	*7.55*	*8.68*	*8.93*	
for equal ICER	4.50	*6.47*	*7.95*	*9.19*	*9.53*	
2. Higher (50%) compliance for iFOBT						
40,10,05-98/60% compliance/6.75$				**70,17,09-98/90%compl.**		
for equal ACER				*14.75*		
for equal ICER				*15.03*		

Table 5: continued						
Base: iFOBT 70,17,09	**Comparison: Hemoccult II and Hemoccult Sensa**					
Guideline surveillance						
(all results for equal ACER)	**HCII: 40,10,05-98/new surveil.**					
IFOBT 70,17,09-98/$27	*16.98*					
IFOBT 70,17,09-98/$18	*9.84*					
	Sensa: 70,17,09-92.5%/new surveil.					
IFOBT 70,17,09-98/$27	*-1.30*					
IFOBT 70,17,09-98/$18	*-10.27*					
IFOBT 70,17,09-95/$27	*14.25*					
IFOBT 70,17,09-95/$18	*5.25*					

Appendix 1.

This appendix consists of three published papers that describe the MISCAN-COLON model:

Loeve F, Boer R, van Oortmarssen GJ, van Ballegooijen M, Habbema JDF. The MISCAN-COLON simulation model for the evaluation of colorectal cancer screening. Computers and Biomedical Research 1999;32:13-33.

Loeve F, Brown ML, Boer R, van Ballegooijen M, vanOortmarssen GJ, Habbema JDF. Endoscopic colorectal cancer screening: a cost-saving analysis. J Natl Cancer Inst 2000;92:557–63

Loeve F, Boer R, van Oortmarssen GJ, van Ballegooijen M, Habbema JDF. Impact of systematic false-negative test results on the performance of faecal occult blood screening. European Journal of Cancer 2001; 37:912-917

Appendix 2. Graphical representation of threshold analysis values

A graphical solution to the threshold analysis value is presented in Appendix 2.

Figure A1 shows the life years gained (y-axis) relative to the costs of screening (x-axis) for each strategy. Line 1 represents the change in the life years gained relative to the cost of screening annually with a test with 40% sensitivity for colorectal cancer, 20% for large adenomas, and 10% for small adenomas and with specificity of 98% as compared to no screening. Line 2 represents the change in the life years gained relative to the cost of screening with a test with these same test characteristics but compared to a test administered biennially rather than annually. Line 3 compares a test with performance characteristics, which are 75% higher than 40% sensitivity for colorectal cancer as compared to no screening. Line 4 compares a test with 75% higher sensitivity for colorectal cancer as compared to the base case of 40% sensitivity. The inverse of the lines represents the ACER when compared to no screening and the ICER when compared to another screening test. All the points presented represent situations in which the unit cost per FOBT is $4.50. The test with the higher sensitivity has a lower CER (steeper slope) of the line through that point. The question now is how much the unit cost of this test with the 75% higher sensitivity may increase and still result in a CER no greater than the initial CER of the test with the lower sensitivity. The horizontal arrows in Figure A2 show how the cost effectiveness lines change as the unit cost of a screening test is increased. The test cost increase but the life years gained are not affected. Figure A2 also shows the new cost effectiveness line that represents the situation where the unit cost has increased to the point that the CER of the more sensitive test equals the CER of the test with the lower sensitivity at the original, lower, unit cost. This threshold analysis can be applied to CER's from screening compared to no screening (ACER's) or to changes in costs and effects from screening compared to alternative screening strategies (ICER's). Figure A2 also shows a lined that represents the situation in which the unit cost of the more sensitive test has been increased such that the CER is now equal to twice the CER of the less sensitive test at the original cost.

Figure A3 adds lines for the ACER and ICER when the new IFOBT has the lower sensitivity value of 95%. In this situation, we draw the horizontal line from the new test to the older test with 98% specificity to illustrate that a decrease in specificity results in a lower cost for the FOBT than for the base of Hemoccult II to achieve comparable cost effectiveness.

Appendix 3

Technical Addendum

This technical addendum contains intermediate outputs for all the simulations conducted for this report. These extensive spreadsheets are best viewed on a computer screen, but they can also be printed out as explained below.

- There are six work books that contain the follow types of spread-sheets:

Grafiek 1 – A graph showing the life-years gained and cost associated with the various scenarios. These graphs are unlabeled. Corresponding labeled graphs are contained in the main report.

Chart 1 – A graph showing threshold payment levels as a function of assumed sensitivity of the comparison test.

Spread-sheets – A series of spread-sheets. Sheet 1 summarizes, for each scenario, numbers of procedures, changes in colorectal cancer cases, deaths and life-years, total costs, average and incremental cost effectiveness ratios and threshold payment levels. Each additional spreadsheet corresponds to a different assumption about the comparison test. In most cases this is different levels of sensitivity. In the case of compliance comparisons this is different levels of compliance. Each spreadsheet provides all the input assumptions, intermediate output values and final output values that correspond to each of the single points shown on Grafiek 1 and Chart 1. Intermediate output values include numbers and costs of all medical procedures for the non-screening and screening simulation and health states, such as clinical and preclinical occurrences of cancer and adenomas, that occur in the non-screening and screening simulations. For a more detailed list of inputs, intermediate outputs and final outputs see column 1 of the spreadsheets.

When printed out the spreadsheets will require 4 or 6 pages. The first 2 or 3 pages correspond the first column panel and all the rows of the spreadsheet. The second 2 or 3 pages correspond to the second column panel and all the rows of the spreadsheet. The first column panel lists all input assumptions for the simulations and contains all intermediate and final output values for a discount rate of zero percent. The second column panel lists all intermediate and final output values for discount rates of 3% and 5%.

The spreadsheet workbooks are labeled as follows:

Workbook 4010059898s – For base case, sensitivity is 40% of cancer, 10% for large adenomas, 5% for small adenomas, specificity is 98%. For comparison test, specificity is 98%, sensitivity is varied over a range of up to 100% greater than the base case and according package insert claims for IFOBT. (See Figure 2).

Colonoscopic surveillance for recurrence is performed once every three years following detection of an advanced adenoma, once every five years following the detection of a small adenoma and one every ten years otherwise.

Workbook 4010059895s – Same as above but for indicated values of sensitivity and specificity.
Workbook 7017099295s - Same as above but for indicated values of sensitivity and specificity.
Workbook 7017099298s - Same as above but for indicated values of sensitivity and specificity.
Workbook 4010509898 – Same as above but surveillance is performed once every three years.
Workbook 4010059898opk6090 – Values of sensitivity and specificity for base case as indicated; sensitivity/specificity of comparison test is 70170998. Compliance for base case test is 60% and compliance for comparison test is 90%.

The correspondence between these document files and material in the main text is as follows:

Figures 1,2 and 4 are based on workbook 4010059898s and workbook 4010059895s;
Figure 3 is based on workbook 7017099295s and workbook 7017099298s
Figure 5 is based on workbook 4010509898
Figure 6 is based on workbook 4010059898opk6090

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Main Text Figures

Figure 1. Cases of colorectal cancer with no screening program and with a screening Program using Hemoccult II.

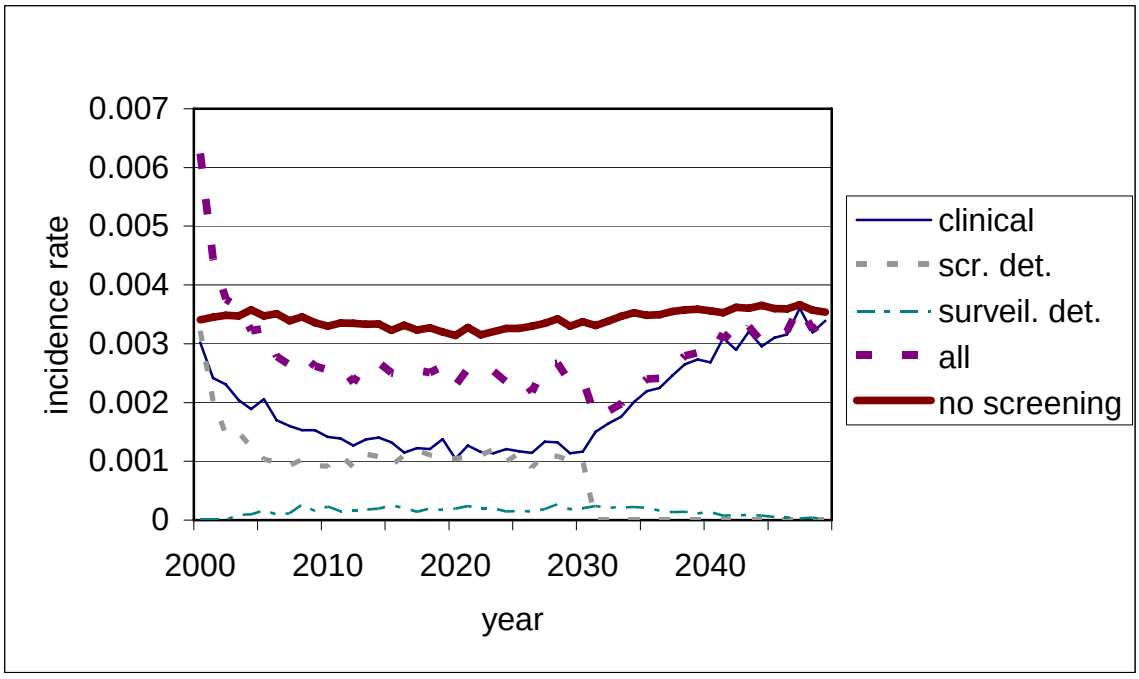


Figure 2: Simulated costs and effects per mln individuals age 65-79 alive at the start of the program.
Base case: HCII (40,10,05-98), to which iFOBT with +25, +50, +75% and +100% higher sensitivity and 98%/ 95% specificity is compared.

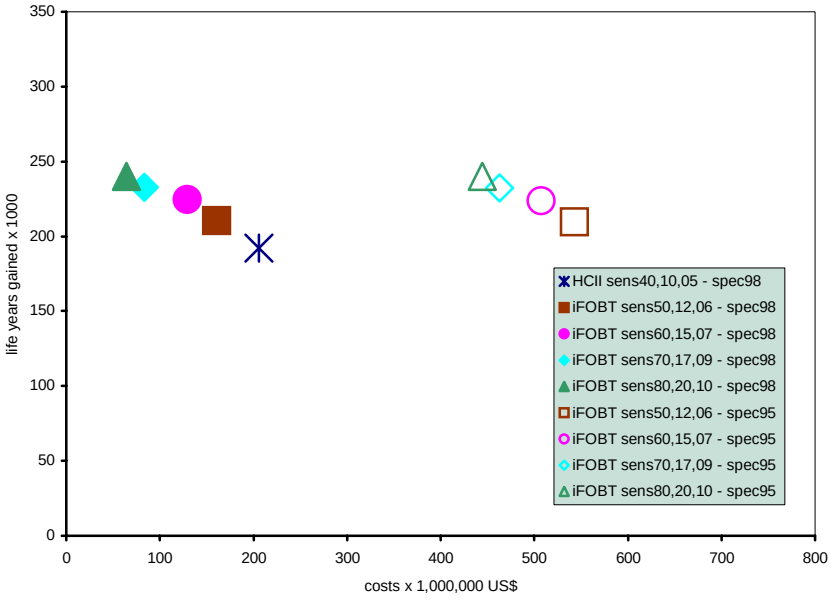


Figure 3: Simulated costs and effects per mln individuals age 65-79 alive at the start of the program.
Base case: Sensa (70,17,09-92.5), to which iFOBT with the same sensitivity (70,17,09) and 98/95% specificity is compared.

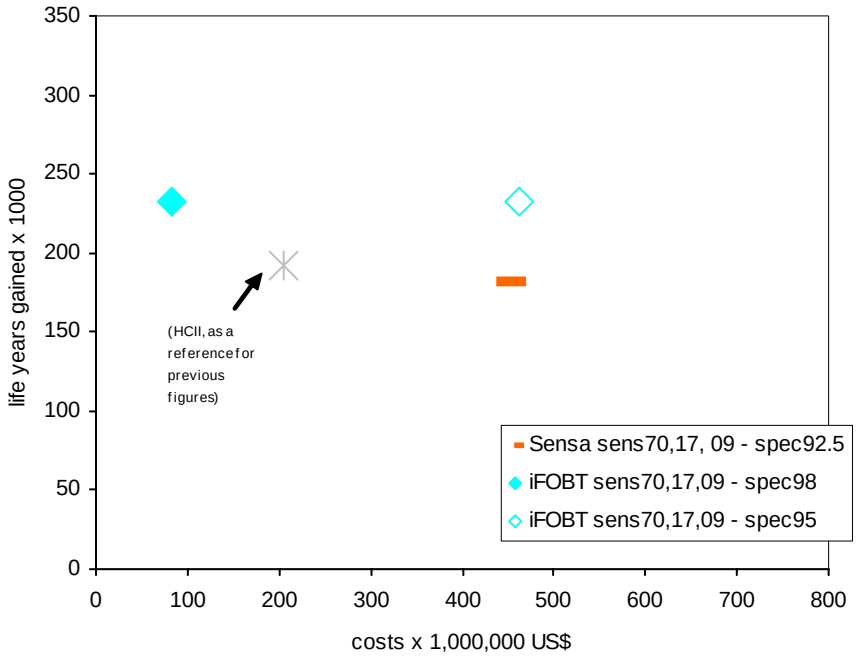


Figure 4: Simulated costs and effects per mln individuals age 65-79 alive at the start of the program.
Base case: HCII (40,10,05-98), to which the "claimed" iFOBT with sensitivity 87, 48, 24 and 98/95% specificity is compared.

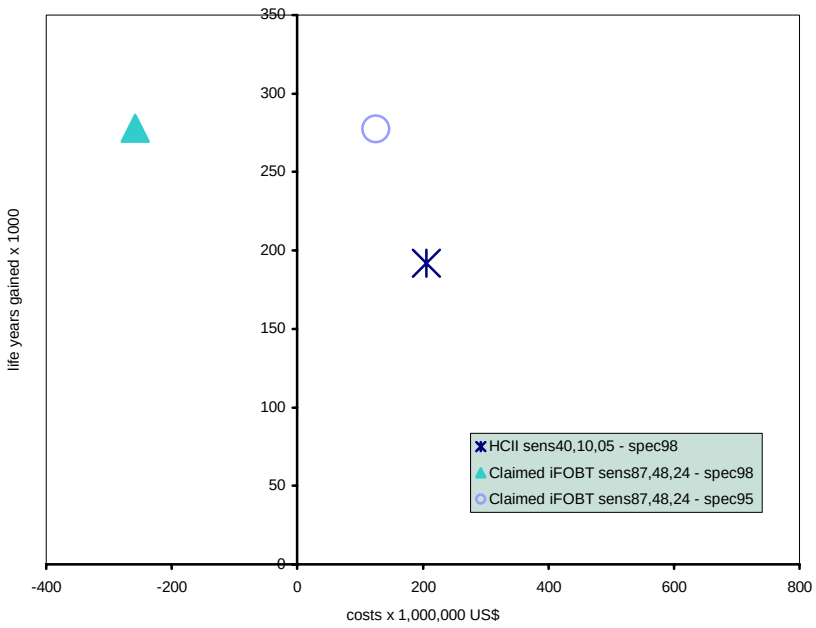


Figure 5: Simulated costs and effects per mln individuals age 65-79 alive at the start of the program.
Sensitivity analysis: iFOBT compared with HCII with **more surveillance** (every 3 years)

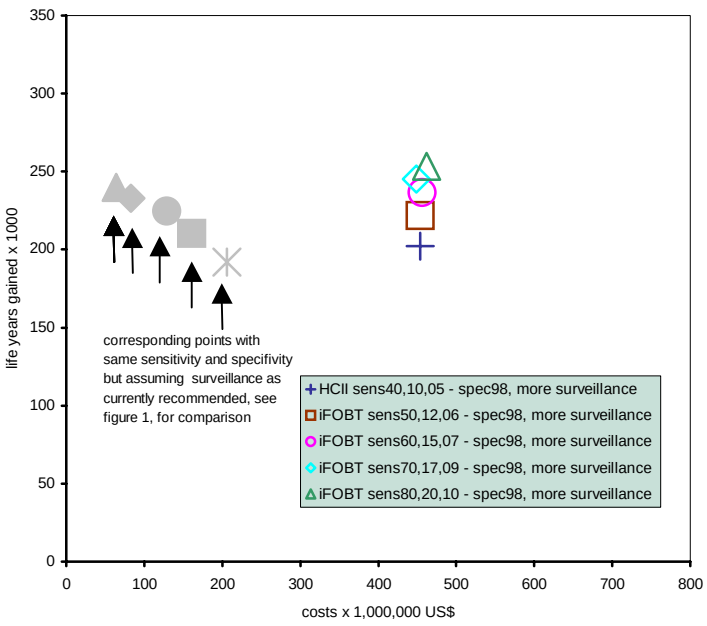


Figure 6: Simulated costs and effects per mln individuals age 65-79 alive at the start of the program.
Sensitivity analysis: iFOBT compared with HCII with 50% higher compliance for iFOBT

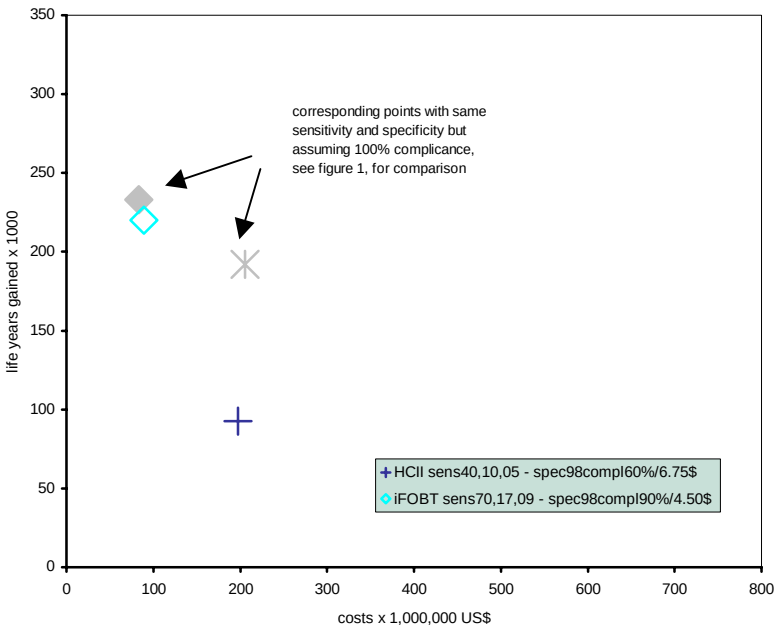
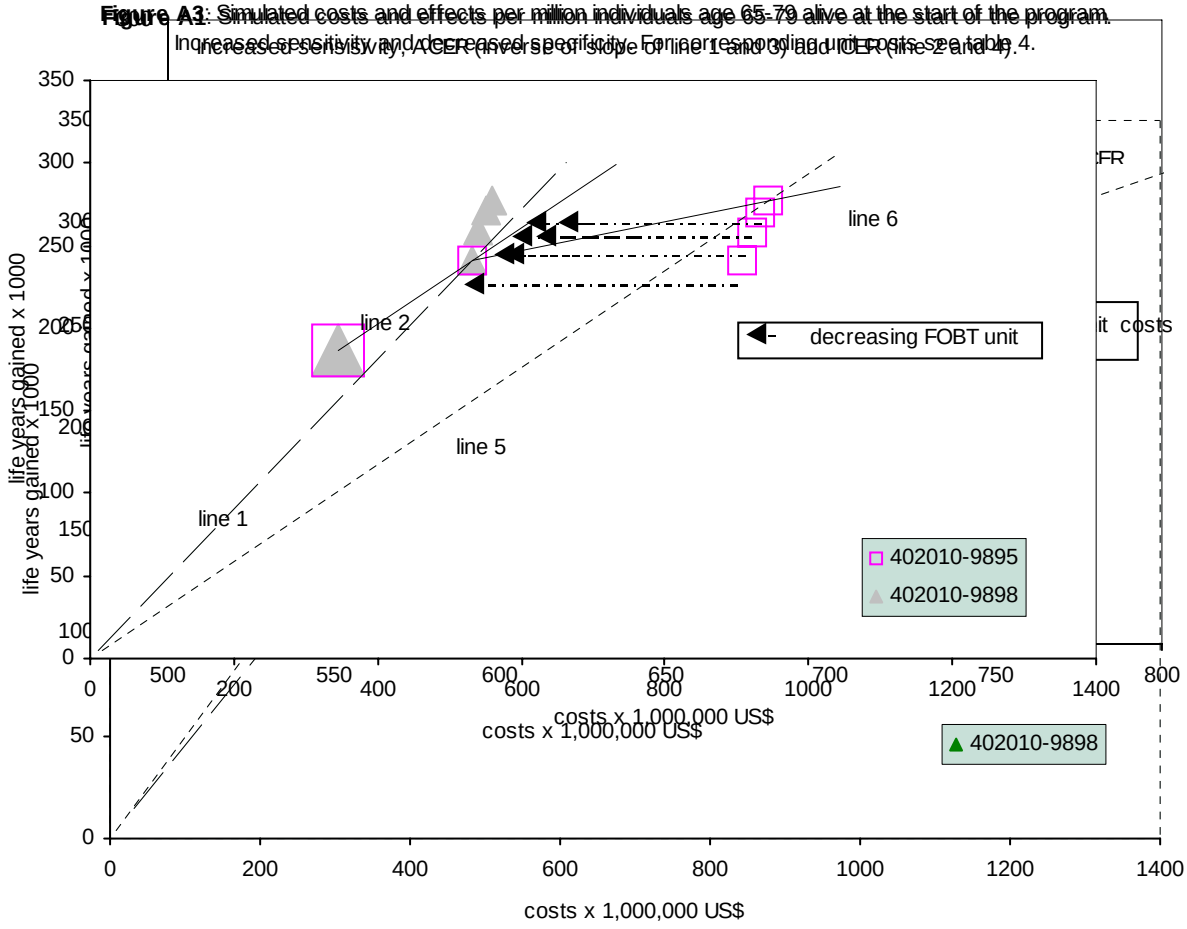


Figure A2: Simulated costs and effects per million individuals age 65-79 alive at the start of the program. Higher sensitivity allows for higher FOBT unit cost if equal CER is the criteria.

Figure A3: Simulated costs and effects per million individuals age 65-79 alive at the start of the program. Increased sensitivity and decreased specificity. For corresponding unit costs see table 4.



Appendix 2 Figures