Screening for Colorectal Neoplasms With New Fecal Occult Blood Tests: Update on Performance Characteristics

James E. Allison, Lori C. Sakoda, Theodore R. Levin, Jo P. Tucker, Irene S. Tekawa, Thomas Cuff, Mary Pat Pauly, Lyle Shlager, Albert M. Palitz, Wei K. Zhao, J. Sanford Schwartz, David F. Ransohoff, Joseph V. Selby

Background One type of fecal occult blood test (FOBT), the unrehydrated guaiac fecal occult blood test (GT), is recommended by the United States Preventive Services Task Force and the Institute of Medicine for use in screening programs, but it has relatively low sensitivity as a single test for detecting advanced colonic neoplasms (cancer and adenomatous polyps ≥1 cm in diameter). Thus, improving the sensitivity of FOBT should make colon cancer screening programs that use these tests more effective.

Methods We assessed prospectively the performance characteristics of two newer FOBTs in 5841 subjects at average risk for colorectal cancer in a large group–model managed care organization. The tests evaluated included a sensitive GT, a fecal immunochemical test (FIT), and the combination of both tests. Patients with positive and negative test results were advised to have colonoscopy and sigmoidoscopy, respectively. Sensitivity and specificity for detecting advanced neoplasms in the left colon within 2 years after the FOBT screening were evaluated for the two tests administered separately and in combination.

Results A total of 139 patients were diagnosed with advanced colorectal neoplasms (n = 14 cancers, n = 128 adenomas) within the 2 years following their initial FOBT screening. Sensitivity for detecting cancer was 81.8% (95% confidence interval [CI] = 47.8% to 96.8%) for the FIT alone and 64.3% (95% CI = 35.6% to 86.0%) for the sensitive GT and the combination test. Sensitivity for detecting advanced colorectal adenomas was 41.3% (95% CI = 32.7% to 50.4%) for the sensitive GT, 29.5% (95% CI = 21.4% to 38.9%) for the FIT, and 22.8% (95% CI =16.1% to 31.3%) for the combination test. Specificity for detecting cancer and adenomas was 98.1% (95% CI = 97.7% to 98.4%) and 98.4% (95% CI = 98.0% to 98.7%), respectively, for the combination test; 96.9% (95% CI = 96.4% to 97.4%) and 97.3% (95% CI = 96.8% to 97.7%), respectively, for the FIT; and 90.1% (95% CI = 89.3% to 90.8%) and 90.6% (95% CI = 89.8% to 91.4%), respectively, for the sensitive GT.

Conclusions The FIT has high sensitivity and specificity for detecting left-sided colorectal cancer, and it may be a useful replacement for the GT.

J Natl Cancer Inst 2007;99:1462–70

Most guidelines for colorectal cancer screening recommend selecting from a menu of possible screening tests (1–3). This recommendation is based in part on studies showing that no single colon cancer screening test is superior to any other (4,5). The fecal occult blood test (FOBT) remains one of the recommended options.

Although FOBT screening has been shown to decrease colorectal cancer incidence and mortality (6–9), the FOBT used currently is an unrehydrated guaiac test (GT). This test has limited sensitivity for advanced colonic neoplasms (24%) and, in primary care community practice, is frequently not used as recommended in the guidelines (10,11). The GT detects the peroxidase activity of

Affiliations of authors: Division of Research, Kaiser Permanente Northern California Region, Oakland, CA (JEA, TRL, JPT, IST, WKZ, JVS); Division of Gastroenterology University of California, San Francisco General Hospital Campus, San Francisco, CA (JEA); Department of Gastroenterology, Kaiser Permanente Medical Center, Walnut Creek, CA (TRL, AMP); Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, WA (LCS); Department of Medicine, Kaiser Permanente Medical Center, Richmond, CA (TC); Department of Medicine, Kaiser Permanente Medical Center, Sacramento, CA (MPP); Department of Internal Medicine, Kaiser Permanente Medical Center, San Francisco, CA (LS); Department of Medicine, School of Medicine; Health Care Systems Department, The Wharton School; Leonard Davis Institute of Health Economics; Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, PA (JSS); Departments of Medicine and Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC (DFR).

Correspondence to: James E. Allison, MD, Division of Research, Kaiser Permanente Northern California Region, 2000 Broadway, Oakland, CA 94612-2304 (e-mail: jea@dor.kaiser.org or jallison@medsfgh.ucsf.edu).

See "Funding" and "Notes" following "References."

DOI: 10.1093/jnci/djm150

heme, either as intact hemoglobin or free heme. In the presence of heme and a developer (hydrogen peroxide), guaiac acid is oxidized, producing a blue color. Heme is present in red meat, and peroxidase activity is present in fresh fruits and vegetables, such as radishes, turnips, and broccoli. These foods, therefore, have the potential to produce false-positive results.

A search for a better FOBT has led to the development of a sensitive GT, which detects lower levels of peroxidase activity than the previous GT, and fecal immunochemical tests (FITs) (12). The FITs use antibodies specific to human hemoglobin, albumin, or other blood components (e.g., globin) and therefore represent a technologic advance over the guaiac-based tests that are currently available (13,14). Unlike the GT, FITs do not depend on peroxidase activity and are highly specific for detecting human blood of colonic origin; this specificity eliminates the need for pretest restriction of diet or medication. Furthermore, some FITs use an automated analysis for reading test results, removing the qualitative error that is associated with human interpretation (15–20).

A study published in 1996 (21) showed that FITs had promise for use in screening for colorectal cancer, but test performance characteristics were estimated using 2-year clinical follow-up—not endoscopy—in the test-negative patients (22). Thus, estimates of the sensitivity of FIT for detecting carcinoma or large polyps may have been overestimated to the extent that these lesions may not have become clinically apparent during the 2 years after a negative test result.

As part of a study to determine the benefit of adding an improved FOBT to an established sigmoidoscopy screening program, we were able to accurately determine the performance characteristics of several new FOBTs for advanced neoplasms in the left colon. Nearly 6000 average-risk subjects were screened for advanced colorectal neoplasms using two new FOBTs—a sensitive GT and an FIT. All patients with positive test results were advised to have colonoscopy, and patients with negative test results were advised to have sigmoidoscopy. Our results provide important information on the performance characteristics of these newer stool tests in detecting advanced left-sided colorectal neoplasms.

CONTEXT AND CAVEATS

Prior knowledge

The unrehydrated guaiac fecal occult blood test (FOBT), as a single test, is currently recommended for use in screening programs because it has been proven in randomized trials to decrease colorectal cancer mortality. Nevertheless, it has a somewhat low sensitivity for detecting colorectal cancer and advanced colorectal neoplasms.

Study design

The sensitivity and specificity of two newer FOBTs—a sensitive guaiac test (GT), which detects lower levels of the peroxidase activity of heme than the older test, and a fecal immunochemical test (FIT), which detects components of blood—to detect advanced adenomas and cancers in the left colon were compared in average-risk individuals.

Contributions

The FIT was more sensitive and specific than the sensitive GT for detecting cancer in the left colon.

Implications

The FIT might be more useful than the currently used FOBT for colorectal cancer screening.

Limitations

The newer tests were not directly compared with the currently recommended FOBT. The ability of the new tests to detect neoplasias of the right colon was not tested because not all patients were offered colonoscopy.

Subjects and Methods

The study was approved by the Kaiser Permanente Northern California Region Institutional Review Board. All participants provided written informed consent.

Setting

Participants were enrolled in the study at three Northern California Kaiser Permanente medical centers from April 1, 1997, through October 31, 1999 (Fig. 1). Patients at average risk for colorectal cancer were recruited either by telephone or by referral from their primary care physician. Patients who expressed interest in participating were sent a letter that described the rationale for colorectal cancer screening and invited them to a study information session. Kaiser Foundation Health Plan members aged 50 years and older were eligible for participation if they had none of the following: history of inflammatory bowel disease, active rectal bleeding or positive FOBT in the past 12 months, history of colon polyps or colon cancer, colonoscopy or sigmoidoscopy within the past 5 years, family history of colon cancer with either a single affected first-degree relative aged 55 years or older or at least two affected first-degree relatives of any age, or language or other barrier to understanding the consent form.

Colorectal Cancer Screening

Eligible patients (n = 7394) who provided informed consent received a study packet consisting of three test cards (Supplementary Fig. 1, available online). A separate card was to be used for each of three bowel movements. Each test card allowed for testing with the sensitive GT, Hemoccult Sensa (Beckman Coulter, Inc, Fullerton, CA); an FIT, FlexSure OBT (currently marketed as Hemoccult ICT; Beckman Coulter, Inc); and a combination of these two tests. This arrangement allowed the performance characteristics of each FOBT and the combination to be determined using the same stool specimen. The advantage of using a combination test is that it saves costs on the FIT assay because the FIT is developed only if the GT result is positive. Beckman Coulter, Inc (formerly SmithKline Diagnostics Inc, Palo Alto, CA), supplied all FOBT cards.

Participants were instructed to collect stool samples from one bowel movement for each test card and to send the completed test cards to the Kaiser Permanente Northern California Regional Laboratory in Berkeley, CA, within 5 days after collection of the first sample. The only dietary restriction was to avoid vitamin C for 3 days before and during the period of stool collection. Stool samples were collected in collection tissue before contact with the toilet bowl water.

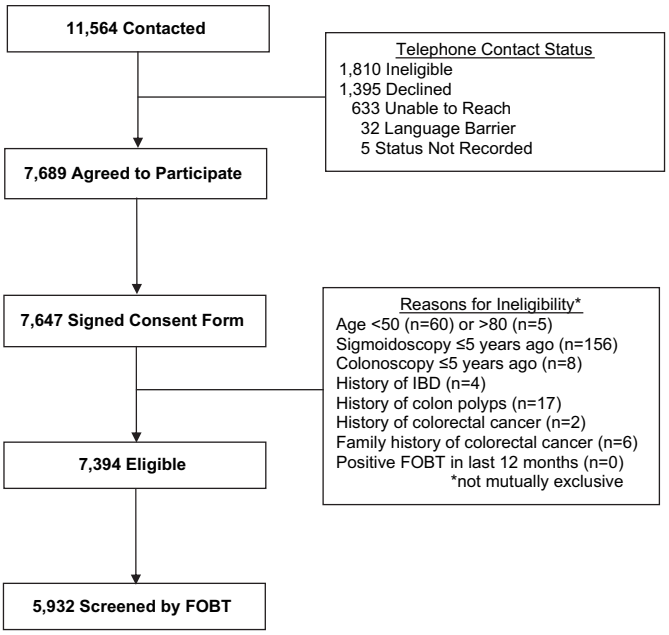

Fig. 1. Flow chart of study participant enrollment and eligibility. IBD = inflammatory bowel disease; FOBT = fecal occult blood test.

Completed test cards were separated into component tests on receipt at the Kaiser Permanente laboratory and were developed within 48 hours. The Hemoccult Sensa test specimen was always developed first. No Hemoccult Sensa test was developed earlier than 3 days after preparation, and no FOBT was developed more than 14 days after specimen collection. When the study was initiated, the FlexSure OBT from the same stool specimen was developed only if the Hemoccult Sensa test results were positive or inconclusive. In October 1997, the study protocol was changed to include assessment with the FlexSure OBT, regardless of the Hemoccult Sensa test result. This change was made at the request of the manufacturer. By changing the protocol, we were able to obtain much more information on the FlexSure OBT alone. A member of the scientific staff of SmithKline Diagnostics (now Beckman Coulter Primary Care Diagnostics) trained and oversaw laboratory development of the FlexSure OBT test card at the Kaiser Permanente laboratory. The manufacturer's cutoff value for the immunochemical FOBT is 0.3 mg hemoglobin per gram of feces, and 95% of the time a positive result will be obtained at that level. Laboratory technicians developed each test individually and were blinded to test results for the other tests on the card. Manufacturer representatives periodically monitored performance of the technicians and the quality of the tests.

Study participants were required to submit all three test cards. Those who tested positive using either Hemoccult Sensa or FlexSure OBT were considered to be positive if at least one of the three stool samples collected for that test gave a positive result and were considered to be negative if all three samples gave a clearly negative result. Results of the combination test were considered to be positive if both the Hemoccult Sensa test and FlexSure OBT gave positive results; otherwise results of the combination test were considered to be negative, except when both the Hemoccult Sensa test and FlexSure OBT yielded inconclusive results. Patients with indeterminate results were encouraged to repeat both tests.

Participants' physicians were notified of all positive test results. All patients who tested positive using either FlexSure OBT or the combination test were recommended by the study staff to undergo further clinical examination, preferably colonoscopy. For all patients with negative test results, flexible sigmoidoscopy was recommended; patients with advanced colorectal neoplasms found at sigmoidoscopy were advised to have colonoscopy. Patients with negative results of stool tests and patients with positive test results but negative endoscopic examination results were encouraged to repeat FOBT after 1 year. Patients were followed using administrative databases for at least 2 years after having the initial screening test.

Data Sources

Demographic information, including age, sex, and race, was obtained from all patients at enrollment. Electronic data files of study FOBT results were received monthly by the laboratory and were compiled into a single database. Copies of standardized sigmoidoscopy and colonoscopy reports, along with corresponding pathology reports, were routinely collected from each participating Kaiser Permanente facility. From those clinical records, information on endoscopic procedure date and lesions detected (i.e., number, location, depth, size, and histopathology) was abstracted, coded, and entered into a separate database. FOBT-screened patients with advanced colorectal neoplasms that were detected at endoscopic screening were identified by a computerized search of the data files. To ensure completeness of data across 2 years of follow-up, we also conducted electronic searches of several databases that were maintained by Kaiser Permanente to identify any missed reports of colorectal cancers, missed pathology records, and additional endoscopic visits. For 93% of study participants, follow-up was complete either for 2 years of continuous health plan membership, until discovery of a colorectal neoplasm, or until death.

Statistical Analysis

Our analysis included FOBT-screened patients who had at least one valid test result (positive or negative) for the Hemoccult Sensa test, the FlexSure OBT, or the combination test. The primary reason for an invalid test result was that the amount of specimen collected for testing was either excessive or insufficient. Because valid results were not obtained with the Hemoccult Sensa test and FlexSure OBT for every study participant, the number of participants screened differed for each test. The analyses presented for FlexSure OBT alone included only the 5356 patients who were tested on or after October 1, 1997, when FlexSure OBTs were processed independent of Hemoccult Sensa test results.

Test performance was evaluated by identifying screened patients who had advanced neoplasia in the left side of the colon (rectum, sigmoid colon, descending colon) that was detected within 2 years after initial screening. Advanced neoplasia was defined as colorectal carcinoma or villous, tubulovillous, or tubular adenoma that was 1 cm in diameter or larger. Carcinomas were characterized by histopathology and classified according to Dukes' stage (23–25) and location. Polyps were classified by histopathologic characteristics, size, and location (26).

Interpretation of test performance was based on four underlying assumptions: 1) any neoplasm that was discovered after evaluation

of a positive FOBT was the cause of the positive result; 2) all advanced polyps or carcinoma distal to the splenic flexure were identified at sigmoidoscopy; 3) any advanced colorectal lesions that were present but not identified by the initial FOBT and sigmoidoscopy screening were discovered within the next 2 years, either by colonoscopy prompted by clinical symptoms or by positive results of FOBT administered after 1 year; and 4) the frequency of advanced neoplasms did not differ between persons who did and did not undergo sigmoidoscopy. The 2-year follow-up period was used as a means of determining the "miss" rate of advanced colorectal neoplasms for participants who had negative FOBT, negative sigmoidoscopy result, or both. It was also used for determining colonoscopy miss rates in patients with a positive FOBT and a negative colonoscopy. A generally accepted direct relationship between the size of a neoplasm and the likelihood of bleeding exists; thus, it is reasonable to expect that a cancer in a test-negative patient would become apparent by repeat testing or symptoms by 2 years after an initial negative screening examination. This relationship is less likely to apply to most advanced adenomas, which are usually only 1–2 cm in diameter when detected by a screening endoscopy and grow slowly. To the extent that assumption 3 was incorrect, test sensitivity estimates were overestimated.

Test performance was evaluated by ability of the test to detect advanced neoplasms in the left side of the colon. Test results were classified according to whether a colorectal neoplasm—carcinoma or polyp measuring at least 1 cm in diameter or both—was found in the left colon during a 2-year follow-up period. The total number of advanced neoplasms did not equal the sum of cancers and advanced polyps detected because both cancer and polyps were discovered in the left colon in some patients. A positive test result was considered to be a true positive if a neoplasm was detected during the 2-year follow-up period; a positive test result was considered to be a false positive if no neoplasm was detected. A negative test result was considered to be a false negative if a neoplasm was detected; a negative test result was considered to be a true negative if no neoplasm was detected within 2 years of initial testing. Sensitivity, specificity, and positive predictive values were expressed as percentages (27,28), with sensitivity defined as the proportion of patients with a given pathology who tested positive, specificity defined as the proportion of patients without a given pathology who tested negative, and positive predictive value defined as the proportion of patients with a positive test who had a given pathology. Ninety-five percent confidence intervals (CIs) were calculated by methods for proportions (29). In addition, the likelihood ratio for a positive test—defined as the probability of obtaining a positive test result among patients with a given pathology divided by the probability of obtaining a positive test result among patients without the given pathology—was determined (30). All statistical tests were two-sided. Analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

Results

During the 30-month study period, 5932 of the 7394 persons who met the eligibility criteria completed FOBT screening. The Hemoccult Sensa test or FlexSure OBT was considered to have been prepared satisfactorily by an individual if either a positive or negative result was determined from his or her three test cards. Because persons who were screened before October 1, 1997, were screened only with the FlexSure OBT if they first had a positive or inconclusive result with Hemoccult Sensa, persons screened before this date were excluded from analyses pertaining to the FlexSure OBT alone. However, persons could be scored as positive or negative for the combination test even if they had an inconclusive result with the Hemoccult Sensa test or if they were not screened or had an inconclusive result with the FlexSure OBT (Table 1). The Hemoccult Sensa test was prepared satisfactorily by 5799 (97.8%) of the 5932 persons screened. The FlexSure OBT was prepared

Table 1. Number of persons satisfactorily screened for each test among participants in a population at average risk for colorectal cancer

Distribution of test results				No. of individuals satisfactorily screened			
Hemoccult Sensa	FlexSure OBT	Combination	Screened on or after 10/1/97	Hemoccult Sensa*	FlexSure OBT†	Combination‡	Any test
Negative	Negative	Negative	Yes	4738	4738	4738	4738
Negative	Positive	Negative	Yes	55	55	55	55
Negative	Inconclusive	Negative	Yes	31		31	31
Negative	Not screened	Negative	No	391		391	391
Positive	Negative	Negative	Yes	410	410	410	410
Positive	Positive	Positive	Yes	113	113	113	113
Positive	Inconclusive	Inconclusive	Yes	16			16
Positive	Negative	Negative	No	36		36	36
Positive	Positive	Positive	No	8		8	8
Positive	Inconclusive	Inconclusive	No	1			1
Inconclusive	Negative	Negative	Yes		35	35	35
Inconclusive	Positive	Inconclusive	Yes		5		5
Inconclusive	Negative	Negative	No			2	2
Total				5799	5356	5819	5841

* Excluded persons who had inconclusive Hemoccult Sensa results.

† Excluded persons who were screened before October 1, 1997, or were screened on or after October 1, 1997 and had inconclusive FlexSure OBT results.

‡ Excluded persons whose results on the combination test were inconclusive.

Table 2. Demographic characteristics of the 5841 participants with valid fecal occult blood test screening

Characteristic	No. (%) of participants
Sex	
Male	2772 (47.5)
Female	3069 (52.5)
Age, y	
50–59	3428 (58.7)
60–69	1774 (30.4)
≥70	639 (10.9)
Race	
White	4327 (74.1)
Black	291 (5.0)
Asian	687 (11.8)
Hispanic	305 (5.2)
Other/unknown	231 (3.9)

satisfactorily by 5356 (97.7%) of the 5481 persons screened after October 1, 1997. For the combination test of Hemoccult Sensa and FlexSure OBT, a positive or negative result could be determined for 5819 (98.1%) of the 5932 persons screened. Overall, 5841 participants had at least one valid result for any of the three tests.

The study population was representative of the Northern California Kaiser Permanente membership aged 50 years and older with respect to sex and race (Table 2). There was an overrepresentation of patients aged 50–59 years and an underrepresentation of patients aged 70 years and older due in part to the selection of individuals at average risk for colorectal cancer.

Of the 5841 participants, 644 (11.0%) had at least one positive FOBT result. The proportion of participants testing positive was 10.1% (584 of 5799 screened) for the Hemoccult Sensa test, 3.2% (173 of 5356 screened) for FlexSure OBT alone, and 2.1% (121 of 5819 screened) for the combination test. Approximately 72% of participants with positive test results screened positive with Hemoccult Sensa only.

Of the 181 participants with positive results on the FlexSure OBT alone or the combination test, 172 subsequently received either colonoscopy (n = 168) or sigmoidoscopy (n = 4). Endoscopic evaluation, primarily by sigmoidoscopy, was performed in 4546 of the 5643 participants (81%) with negative results on both the FlexSure OBT and the combination test. Neoplasms in the left colon were detected in 139 study participants: 14 patients had colorectal carcinoma, and 128 patients had adenomas 1 cm or larger in diameter. Of the cancerous lesions, nine were classified as Dukes' stage A, three as Dukes' stage B, and two as Dukes' stage C.

We next determined the performance characteristics of the FOBTs (Table 3). The sensitivity of Hemoccult Sensa test for detecting colorectal carcinoma (64.3%, 95% CI = 35.6% to 86.0%) was similar to that of the combination test (64.3%, 95% CI = 35.6% to 86.0%) but was lower than that of the FlexSure OBT (81.8%, 95% CI = 47.8% to 96.8%). The sensitivities of the Hemoccult Sensa (41.3%, 95% CI = 32.7% to 50.4%) and FlexSure OBT (29.5%, 95% CI = 21.4% to 38.9%) tests for detecting advanced colorectal adenomas were superior to that of the combination test (22.8%, 95% CI = 16.1% to 31.3%); however, for all tests, the sensitivity for detecting advanced colorectal adenomas was less than previously reported (19). Specificities for detecting colorectal cancer and advanced colorectal adenomas were 98.1% (95% CI = 97.7% to 98.4%) and 98.4% (95% CI = 98.0% to 98.7%), respectively, for the combination test; 96.9% (95% CI = 96.4% to 97.4%) and 97.3% (95% CI = 96.8% to 97.7%), respectively, for the FlexSure OBT; and 90.1% (95% CI = 89.3% to 90.8%) and 90.6% (95% CI = 89.8% to 91.4%), respectively, for the Hemoccult Sensa test. The Hemoccult Sensa had the lowest positive predictive value for distal colorectal carcinoma, and the combination test had the highest. The same relationship between the positive predictive values for these tests was found for colorectal adenomas and for carcinoma and adenomas combined. Likelihood ratio is a more accurate reflection than positive predictive value of how likely it is that persons with advanced

Table 3. Fecal occult blood test (Hemoccult Sensa), fecal immunochemical test (FlexSure OBT), and combination test performance characteristics in a population at average risk for colorectal cancer*

			Sensitivity		Specificity		Positive predictive value		Likelihood ratio (+)	
Finding per test	No of persons screened	No of neoplasms detected	No./ total	% (95% CI)	No./ total	% (95% CI)	No./ total	% (95% CI)	Ratio	(95% CI)
Distal cancer										
Hemoccult Sensa	5799	14	9/14	64.3 (35.6 to 86.0)	5210/5785	90.1 (89.3 to 90.8)	9/584	1.5 (0.8 to 3.0)	6.5	(4.3 to 9.6)
FlexSure OBT	5356	11	9/11	81.8 (47.8 to 96.8)	5181/5345	96.9 (96.4 to 97.4)	9/173	5.2 (2.6 to 10.0)	26.7	(19.4 to 36.6)
Hemoccult Sensa + FlexSure OBT	5819	14	9/14	64.3 (35.6 to 86.0)	5693/5805	98.1 (97.7 to 98.4)	9/121	7.4 (3.7 to 14.0)	33.3	(21.6 to 51.3)
Distal adenomas ≥1 cm										
Hemoccult Sensa	5799	126	52/126	41.3 (32.7 to 50.4)	5141/5673	90.6 (89.8 to 91.4)	52/584	8.9 (6.8 to 11.6)	4.4	(3.5 to 5.5)
FlexSure OBT	5356	112	33/112	29.5 (21.4 to 38.9)	5104/5244	97.3 (96.8 to 97.7)	33/173	19.1 (13.7 to 25.9)	11.0	(7.9 to 15.3)
Hemoccult Sensa + FlexSure OBT	5819	127	29/127	22.8 (16.1 to 31.3)	5600/5692	98.4 (98.0 to 98.7)	29/121	24.0 (16.9 to 32.7)	14.1	(9.7 to 20.6)
Distal advanced neoplasms										
Hemoccult Sensa	5799	137	59/137	43.1 (34.7 to 51.8)	5137/5662	90.7 (89.9 to 91.5)	59/584	10.1 (7.8 to 12.9)	4.6	(3.8 to 5.7)
FlexSure OBT	5356	121	40/121	33.1 (24.9 to 42.3)	5102/5235	97.5 (97.0 to 97.9)	40/173	23.1 (17.2 to 30.3)	13.0	(9.6 to 17.6)
Hemoccult Sensa + FlexSure OBT	5819	138	36/138	26.1 (19.2 to 34.4)	5596/5681	98.5 (98.1 to 98.8)	36/121	29.8 (22.0 to 38.9)	17.4	(12.3 to 24.8)

* Likelihood ratio (+) = sensitivity/(1 − specificity); CI = confidence interval.

colorectal neoplasia will test positive. The likelihood ratio showed that the FlexSure OBT and the combination test detected distal colorectal cancer more effectively than distal colorectal adenoma.

Discussion

We found that the sensitivity of FlexSure OBT for detecting left-sided colorectal cancer was 82%, substantially higher than that of the Hemoccult Sensa. The increase is important if the FIT (FlexSure OBT) has similar sensitivity for detecting right- and left-sided curable colorectal cancers. In addition, this sensitivity is higher than the 56%–66% that was reported for different FITs in two studies from Japan (31,32). Furthermore, the superior sensitivity for cancer demonstrated by an FIT has important implications for current and future screening program recommendations because a program of annual testing with the less sensitive GT and sigmoidoscopy every 5 years has been shown to be as effective—regardless of cost—as a program of colonoscopy screening at the individual patient level (4,5). Therefore, annual FOBT alone with an FIT that is as sensitive as FlexSure OBT might also be competitive with a colonoscopy screening program.

In the analyses of the Hemoccult Sensa and the combination test, we included 438 patients with test results recorded before our protocol changed from developing FlexSure OBTs only if the Hemoccult Sensa test was positive or inconclusive to developing the FlexSure OBT tests regardless of Hemoccult Sensa test results. As a consequence, we may have underestimated the sensitivity of the Hemoccult Sensa test and the combination test for advanced colorectal neoplasms by penalizing those tests for misses that FlexSure OBT may have also missed had it been done. Eliminating these 438 patients from our calculations led to an increase in sensitivity equally for Hemoccult Sensa and the combination test for left-sided colorectal cancer from 64% to 67%, which is still less impressive than the sensitivity of the FlexSure OBT (82%). Nevertheless, based on what is currently known from other studies about FIT performance (21,31,33–35), if the FlexSure OBT had been developed in these 438 patients it is likely that it would have performed as well or better than Hemoccult Sensa and the combination test in detecting advanced colorectal neoplasms.

Our findings are similar to those of previous studies of similar design examining the performance characteristics of other FITs. Screening 21 800 persons at average risk, Morikawa et al. (31) found that the sensitivity of the Magstream 1000/HemeSP test for detecting colorectal cancer was 66%. Although this estimate of sensitivity is lower than what we observed with FlexSure OBT, it was based on testing only one stool sample from each patient, whereas we tested three specimens for each patient screened. Nakama et al. (32) showed variable sensitivity of the Monohaem FIT (Nihon Pharmaceutical, Japan) for detecting colorectal cancer and colorectal polyps, depending on the number of stools tested. The sensitivity of the Monohaem FIT for detecting colon cancer was 90% when three tests were performed but only 57% when only one test was performed. The sensitivity for detecting advanced colorectal polyps was similar to that found by Morikawa et al. (31)—30% for one test, and 55% for three tests.

In both the Morikawa et al. and Nakama et al. studies (31,32), all participants received colonoscopy. Morikawa et al. (31) found a difference in sensitivity depending on the part of the colon where the advanced neoplasm was found. The sensitivity for cancer and for adenomas 10 mm in diameter and larger in the proximal colon was statistically significantly lower than that for these lesions in the distal colon, but the sensitivity did not differ by site for Dukes' A and B cancers or for adenomas with high-grade dysplasia. Differences in sensitivity for right- and left-sided advanced neoplasms were not reported by Nakama et al. (32).

Based on the results of Morikawa et al. (31), it seems likely that the sensitivity of our tests for detecting Dukes' A and B cancers are accurate for right- and left-sided curable cancers but that our sensitivity estimates for Dukes' C and D lesions and polyps at least 1 cm in diameter could be overestimated when applied to the whole colon. Another possible explanation, however, is that Morikawa et al. (31) used a different FIT and tested only one stool sample. Greater mixing of blood with stool, different neoplasia growth rates, and different tumor biology are possible reasons why performance characteristics of an FOBT might differ between distal and proximal colorectal lesions, but sensitivity estimates of FITs for cancer in two previous studies (36,37) in which three stool samples were tested showed no difference for proximal and distal neoplasia. Taken together, these data suggest that our results may be accurate for both right- and left-sided advanced colorectal neoplasms.

The more modest application (single testing) sensitivity of the FIT (FlexSure OBT) for detecting advanced colorectal polyps than cancers raises the question of the potential harm from missed advanced polyps. Invasive cancer is very unlikely to develop from a small (<10 mm in diameter) colorectal adenoma within 5 years, and large polyps (>1 cm) become colorectal cancers at a rate of roughly 1% per year (38,39). A screening program such as annual FOBT takes advantage of programmatic sensitivity (i.e., repeated testing). Multiple chances to detect an existing lesion are likely to detect many of the lesions missed on initial screens before they become fatal.

The strengths of our study include endoscopic examination in all study subjects, regardless of FOBT result, and its conduct in a real-world setting. Additional strengths are follow-up of test-negative patients, large sample size, minimal loss to follow-up, and administration of multiple tests in all subjects.

A limitation of this study is that we did not address the performance characteristics of the new FOBTs for detecting right-sided colorectal lesions. In the Kaiser Permanente Northern California health care system, sigmoidoscopy has been the screening test recommended for individuals at average risk of colorectal cancer, so we did not offer colonoscopy to all participants. Because all study participants with negative FOBT results were offered sigmoidoscopy, our analysis could address only detection of advanced neoplasia in the left colon. Among patients who had colonoscopy, several had advanced neoplasia on the right (but not the left) side of the colon. For such persons who tested positive on any FOBT, their test result was defined as a false positive in our analysis and thus led us to slightly underestimate test sensitivity.

The potential role of FOBT in colorectal cancer screening needs to be further addressed by clinicians and policymakers. Endoscopy is generally very thorough at a single examination but can miss some advanced colorectal neoplasms (40–46).

Furthermore, a 10-year interval between colonoscopy examinations might miss important (i.e., fast-growing) lesions (4,5,47). The findings from these studies (40–46,48) raise concern that the current recommended 10-year screening interval after a negative screening colonoscopy may be too long. Shortening the colonoscopy interval, however, increases cumulative procedure risks and raises costs. Some (49) have suggested that FIT could have a possible role as an interval screening test and that, if its performance characteristics are suitable, FIT might prove to be attractive and highly competitive with colonoscopy as a primary screening test.

Our study did not directly compare the performance characteristics of new FOBTs with the standard (and most commonly used) GT, Hemoccult II. However, comparisons have shown superiority of the FIT over Hemoccult II (21,37,50). In a recent Israeli study comparing an FIT with a sensitive GT (51), the sensitivities for clinically significant colorectal neoplasms were found to be similar; however, the FIT had better specificity and resulting positive predictive value.

Because screening decreases both the incidence of and mortality from colorectal cancer (6,7,8,9), it has become both widely recommended and increasingly practiced. FOBT has historically been the most commonly used test, although its usefulness has been questioned recently (52). The continued inclusion of FOBT in colorectal cancer screening programs is supported by the United States Preventive Services Task Force and the National Cancer Institute/Institute of Medicine analyses (53), which concluded that, regardless of cost, a program of annual GT FOBT and sigmoidoscopy every 5 years is as effective as a program of colonoscopy screening. The estimated sensitivity of the GT for early cancer ranged from 13% to 60% in the five economic models of colon cancer screening reviewed for the Institute of Medicine and National Research Council Workshop on the Economic Models of Colorectal Cancer Screening in Average-Risk Adults (4); the lowest estimate came from a study design that might best represent testing in the real world as opposed to a scientific study setting (54).

In our study, the FIT showed better sensitivity and specificity for detecting colorectal cancer than the sensitive GT, although the sensitive GT was more sensitive for detecting large polyps. One possible explanation for this result is that the peroxidase sensitivity of the sensitive GT is set so high that the test detects lower levels of bleeding than do the FITs. Some newer FITs can be set to detect very low levels of hemoglobin, but such alterations will probably increase the number of positive tests and decrease specificity. Although there were differences in results (sensitivity for cancer ranged from 66% to 89%), the sensitivities of FITs and sensitive GT were—in many published studies (21,33–35)—much higher than results reported for Hemoccult II, suggesting that they would all show improved performance over Hemoccult II in colorectal cancer screening programs.

The suggestion that FOBT has a useful role in colon cancer screening is further strengthened by data suggesting that newer FOBTs are substantially more sensitive than the older ones on which past recommendations were based. Although efficacy of FITs in decreasing colon cancer mortality and incidence has not been directly studied in randomized controlled trials, other researchers (55) have suggested that the relationship between test effectiveness and outcome of colorectal cancer mortality may not need to be studied because the efficacy of other FOBTs has already been demonstrated.

The potential usefulness of FIT compared with GT is being considered by several organizations. The American Cancer Society's recommendations for colon cancer screening now state that "in comparison with guaiac-based tests for the detection of occult blood, immunochemical tests are more patient-friendly and are likely to be equal or better in sensitivity and specificity" (56). The World Health Organization and the World Organization for Digestive Endoscopy have also endorsed the use of an FIT in instances where colonoscopy is readily available but where populations cannot be relied on to comply with the dietary and drug restrictions necessary for GTs (57). In the future, the advantages and disadvantages of such a program are likely to be clarified by quantitative analyses such as those produced by the United States Preventive Services Task Force. An improved FOBT would provide increased attractiveness of including FOBTs in the armamentarium of tests and programs that may be used for colorectal cancer screening (58).

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Funding

National Cancer Institute (1R01CA074562-01); American Digestive Health Foundation Outcomes Research Training Award (to T. R. L.); Kaiser Foundation Health Plan Community Benefit Program; The Permanente Medical Group Innovation Program; Beckman Coulter, Inc (formerly SmithKline Diagnostics) (to J. E. A.); Enterix Corporation (to J. E. A., T. R. L.).

Notes

Present address: Kaiser Permanente Vallejo Medical Center, Vallejo, CA (T. Cuff); Berkeley, CA (I. S. Tekawa).

Elaine Chung assisted with patient accession and project coordination, Soora Wi with study concept and design and data acquisition, and Carol Conell with data analysis. Editorial assistance was provided by the Medical Editing Service of The Permanente Medical Group Physician Education and Development Department. Dr J. E. Allison is on the Scientific Advisory Board of Beckman Coulter, Inc, but has not received compensation. Beckman Coulter, Inc (formerly SmithKline Diagnostics) provided the FOBT cards without charge. The sponsors had no role in the analysis of the data, interpretation of the findings, or the decision to submit the manuscript for publication.

Manuscript received January 31, 2007; revised July 9, 2007; accepted August 8, 2007.