

## A COMPARISON OF FECAL OCCULT-BLOOD TESTS FOR COLORECTAL-CANCER SCREENING

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**Abstract Background.** Hemoccult II, a widely used guaiac test for fecal occult blood, has a low sensitivity for detecting colorectal neoplasms in asymptomatic patients at average risk. In such patients, the performance characteristics of screening tests developed to improve on Hemoccult II are not known.

**Methods.** A set of three fecal occult-blood tests — Hemoccult II; Hemoccult II Sensa, a more sensitive guaiac test; and HemeSelect, an immunochemical test for human hemoglobin — was mailed to all patients 50 years of age or older who were scheduled for personal health appraisals at the Kaiser Permanente Medical Center in Oakland, California. The performance of each test and of a combination test (HemeSelect to confirm positive Hemoccult II Sensa results) was evaluated by identifying screened patients who had colorectal neoplasms (carcinoma or a polyp  $\geq 1$  cm in diameter) in the two years after screening.

**Results.** Of the 10,702 eligible patients, 8104 (75.7 percent) had at least one interpretable sample and were screened on the basis of at least one test; 96 percent of these patients had complete two-year follow-up. The sen-

sitivity of the tests for detecting carcinoma was lowest with Hemoccult II (37.1 percent; 95 percent confidence interval, 19.7 to 54.6 percent), intermediate with the combination test (65.6 percent; 95 percent confidence interval, 47.6 to 83.6 percent) and with HemeSelect (68.8 percent; 95 percent confidence interval, 51.1 to 86.4 percent), and highest with Hemoccult II Sensa (79.4 percent; 95 percent confidence interval, 64.3 to 94.5 percent). The specificity for detecting carcinoma was 86.7 percent with Hemoccult II Sensa, 94.4 percent with HemeSelect, 97.3 percent with the combination test, and 97.7 percent with Hemoccult II. HemeSelect and the combination test detected more colorectal carcinomas and polyps than Hemoccult II, with only slight increases in the number of colonoscopies needed.

**Conclusions.** HemeSelect and a combination test in which HemeSelect is used to confirm positive Hemoccult II Sensa results improve on Hemoccult II in screening patients for colorectal carcinoma. (N Engl J Med 1996; 334:155-9.)

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**G**UAIAC tests for fecal occult blood detect the pseudoperoxidase activity of heme, either as intact hemoglobin or as free heme. Hemoccult II, a widely used guaiac test for fecal occult blood, has a low sensitivity for detecting colorectal neoplasms in asymptomatic patients at average risk.<sup>1,2</sup> Hemoccult II Sensa, another guaiac test that is more sensitive than Hemoccult II to peroxidase-like materials, and HemeSelect, an immunochemical test for human hemoglobin, were developed in an attempt to improve on the performance of Hemoccult II.

In a previous study,<sup>3</sup> Hemoccult II Sensa and HemeSelect had a high sensitivity for colorectal neoplasia (90 to 97 percent for colorectal cancer, and 60 to 76 percent for adenomas  $>10$  mm in diameter), but only 276 healthy subjects at average risk who were 50 years of age or older were studied. Most of the subjects had previously diagnosed colorectal cancer or adenoma, had a family history of colorectal cancer, or were asymptomatic and between the ages of 13 and 29. It was suggested<sup>4</sup> that the performance of fecal occult-blood tests be evaluated under actual screening conditions. We prospectively evaluated the sensitivity, specificity, and predictive value of Hemoccult II, Hemoccult II Sensa, HemeSelect,

and the combination of Hemoccult II Sensa and HemeSelect in a screening program for a large, racially diverse group of people at least 50 years old who had an average risk of colorectal cancer.<sup>5,6</sup>

### METHODS

At Kaiser Permanente Medical Center in Oakland, California, a personal health appraisal is available to members who are 15 years of age or older. The appraisal includes a questionnaire, a physical examination, and laboratory tests. After approval of our study protocol by the institutional review board, each patient 50 years of age or older who was scheduled for such an appraisal between October 3, 1990, and October 8, 1991, received a packet with a letter describing the rationale for colorectal-cancer screening; three specimen cards, each containing three fecal occult-blood tests (Hemoccult II, Hemoccult II Sensa, and HemeSelect; SmithKline Diagnostics, San Jose, Calif.); and detailed instructions on how to use the tests. Each of the fecal occult-blood tests is approved by the Food and Drug Administration for colorectal-cancer screening. The combination of Hemoccult II Sensa and HemeSelect is not commercially available.

For the week before the appraisal, patients were told to follow a diet that excluded red meat, turnips, horseradish, broccoli, radishes, cauliflower, cantaloupes and other melons, supplemental vitamin C, aspirin, and other nonsteroidal antiinflammatory drugs. Patients began collecting specimens three days before the scheduled appraisal, using paper collection devices (saddles) designed to allow the sampling of stool before it made contact with water in the toilet bowl. Three separate stool specimens were applied to each of the cards.

The completed cards, submitted on the day of the examination, were separated into component tests and developed without rehydration within 48 hours after receipt. Technicians developed the tests independently, without knowledge of the results of other tests. Hemoccult II tests were developed at Kaiser Permanente Medical Center in Oakland, and Hemoccult II Sensa and HemeSelect were developed at SmithKline Diagnostics. The performance of the technicians was monitored periodically by physician investigators, and the laboratory periodically checked the quality of the tests.

A positive Hemoccult II or Hemoccult II Sensa test was defined as one in which a blue color diffused into a 0.5-cm margin around the specimen within one minute after the application of the developer.

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Specimen cards with copious stool obscuring the reading margin were considered unsatisfactory and were not included in the analysis. The absence of a blue color was interpreted as a negative result.

HemeSelect is based on an antigen-antibody reaction involving fixed chicken erythrocytes coated with an anti-human-hemoglobin antibody. Disks containing fecal samples were placed in U-shaped wells in a microtiter plate. A diluent was added to extract the specimens from the disks. A portion of the extract was removed and diluted serially in the next three wells of the plate. Erythrocytes coated with anti-human-hemoglobin antibody were added to the last two wells, and the mixture was incubated at room temperature for 30 minutes. Samples showing agglutination (a ring of agglutinated cells with a larger diameter than that in a negative control) at a dilution of 1:8 were interpreted as positive. The absence of agglutination was interpreted as a negative result. An inconclusive test had only slight peripheral agglutination.

Because each specimen card contained a set of all three tests, we were able to evaluate the performance of a combination test using Hemocult II Sensa and HemeSelect. The result of the combination test was considered positive when a positive Hemocult II Sensa result was confirmed by a positive HemeSelect result. All other combinations of results were considered negative. If the Hemocult II Sensa result was negative, the combination result was negative, regardless of whether the HemeSelect result was positive or negative.

A patient was considered to have been screened by a specific test if at least one of the available specimen windows for the test contained an interpretable sample. The results were based only on interpretable samples. Therefore, the number of patients screened varied for each test.

The patients' doctors were notified of all positive results and encouraged to recommend further evaluation, preferably by colonoscopy. However, when we noted an unacceptably high number of patients whose only positive test was Hemocult II Sensa and whose colonoscopic evaluations had uncovered no colorectal carcinoma, we requested approval from the institutional review board to modify the recommended evaluation for this group. We suggested that such patients, after informed consent, undergo flexible sigmoidoscopy and repeated Hemocult II testing at 6 and 12 months. Colonoscopy was offered to anyone who was found to have a colorectal neoplasm on sigmoidoscopy, to anyone who later had a positive Hemocult II result, and to anyone wishing to undergo colonoscopy.

The performance of the tests was evaluated by identifying the screened patients found to have neoplasms (colorectal carcinoma or a polyp  $\geq 1$  cm in diameter) in the two years after screening. These neoplasms were assumed to have caused the positive results. It was also assumed that all polyps or carcinomas present at the time of a negative test became clinically apparent within two years through subsequent screening or the appearance of symptoms.

Patients with colorectal carcinoma were identified through a search of the computerized data bases at the Kaiser Permanente Northern California Regional Cancer Registry Project and the pathology departments at the Kaiser Permanente facilities in Oakland, Walnut Creek, and Hayward, California. Charts and pathology files were reviewed to identify patients with benign polyps. Four percent of the subjects could not be followed for two years of continuous health-plan membership or until the discovery of a colorectal neoplasm or death, whichever came first.

The medical records of all patients with positive tests were reviewed to obtain information on follow-up procedures and any colorectal neoplasms diagnosed after the screening test. A chart review was also performed, regardless of the test results, for all screened patients identified from the cancer-registry or pathology files as having colorectal carcinoma or polyps.

Each carcinoma was examined histopathologically by the same pathologist and classified according to Dukes' stage and location. Polyps were classified, on the basis of pathology reports, in terms of their histopathological characteristics, size, and location. We considered the left colon to consist of the rectum, the rectosigmoid colon, and the descending colon; the transverse colon to consist of the splenic and hepatic flexures as well as the transverse colon itself; and the right colon to consist of the cecum and the ascending colon.

The test results were classified as follows, depending on whether a

colorectal neoplasm was found within two years of the test: a positive result was a true positive if a neoplasm was found and a false positive if no neoplasm was found; a negative result was a false negative if a neoplasm was found and a true negative if no neoplasm was found. Sensitivity, specificity, and positive predictive value were all expressed as percentages defined in the standard manner.<sup>7,8</sup> Ninety-five percent confidence intervals were calculated by methods for proportions.<sup>9</sup>

Differences in rates of positive tests according to race and age were tested for statistical significance by the two-tailed chi-square test for independence. Tests for linear trend in positive tests and positive predictive value according to age were performed with three age categories: 50 to 59 years, 60 to 69 years, and 70 years or older. Logistic regression was used to test for associations of race with positive tests and with positive predictive values, with adjustment for age.

## RESULTS

During the one-year study period, 10,702 eligible persons had personal health appraisals. The study subjects were the 8104 (75.7 percent) who were screened with at least one fecal occult-blood test. Of these subjects, 8065 (99.5 percent) were screened by Hemocult II, 7904 (97.5 percent) by Hemocult II Sensa, 7493 (92.5 percent) by HemeSelect, and 7847 (96.8 percent) by the combination of Hemocult II Sensa and HemeSelect. Of the study subjects, 7575 (93.5 percent) prepared all three Hemocult II test cards satisfactorily or had at least one card with a positive result, as compared with 7409 (91.4 percent) for all three Hemocult II Sensa cards and 5044 (62.2 percent) for all three HemeSelect cards.

The subjects were distributed evenly among three age groups: 2450 (30.2 percent) were 50 to 59 years old, 3159 (39.0 percent) were 60 to 69 years old, and 2495 (30.8 percent) were 70 or older. A total of 4335 subjects (53.5 percent) were white, 2523 (31.1 percent) were black, 975 (12.0 percent) were Asian, and 271 (3.3 percent) were of other or unknown race. There were 4802 women (59.3 percent) and 3302 men (40.7 percent).

At least one fecal occult-blood test was positive in 1312 patients (16.2 percent). The rates of positive results were 2.5 percent with Hemocult II, 3.0 percent with the combination test, 5.9 percent with HemeSelect, and 13.6 percent with Hemocult II Sensa (Table 1). Fifty-seven percent of the patients with positive test results had positive results only with Hemocult II Sensa. The rates of positive results increased with age for all tests. The rates of positive results varied according to race only with Hemocult II Sensa ( $P < 0.001$ ), with the lowest rate among whites (10 percent) and similar rates in the other groups (blacks, 17 percent; Asians, 20 percent; and patients of other or unknown race, 16 percent). This variation remained after we controlled for age.

Colonoscopy was performed in 155 patients with a positive Hemocult II test (78.3 percent), 386 patients with a positive Hemocult II Sensa test (36.0 percent), 355 patients with a positive HemeSelect test (80.7 percent), and 197 patients with a positive combination test (84.5 percent). Neoplasms, as defined, were detected in 142 subjects: 35 had colorectal carcinoma,

Table 1. Comparison of Four Fecal Occult-Blood Tests in 8104 People.

TEST AND FINDING	NEOPLASMS DETECTED	TRUE POSITIVE TEST	FALSE POSITIVE TEST	TRUE NEGATIVE TEST	FALSE NEGATIVE TEST
	<i>no.</i>	<i>no. of patients (%)*</i>			
Hemoccult II (8065 screened, 198 [2.5%] positive)					
Carcinoma	35	13 (0.2)	185 (2.3)	7845 (97.3)	22 (0.3)
Polyp $\geq$ 1 cm	107	33 (0.4)	152 (1.9)	7771 (96.8)	74 (0.9)
Combined	142	46 (0.6)	152 (1.9)	7771 (96.4)	96 (1.2)
Hemoccult II Sensa (7904 screened, 1073 [13.6%] positive)					
Carcinoma	34	27 (0.3)	1046 (13.2)	6824 (86.3)	7 (0.1)
Polyp $\geq$ 1 cm	105	72 (0.9)	974 (12.4)	6791 (86.3)	33 (0.4)
Combined	139	99 (1.3)	974 (12.3)	6791 (85.9)	40 (0.5)
HemeSelect (7493 screened, 440 [5.9%] positive)					
Carcinoma	32	22 (0.3)	418 (5.6)	7043 (94.0)	10 (0.1)
Polyp $\geq$ 1 cm	102	68 (0.9)	350 (4.7)	7009 (93.9)	34 (0.5)
Combined	134	90 (1.2)	350 (4.7)	7009 (93.5)	44 (0.6)
Combination (Hemoccult II Sensa and HemeSelect) (7847 screened, 233 [3.0%] positive)					
Carcinoma	32	21 (0.3)	212 (2.7)	7603 (96.9)	11 (0.1)
Polyp $\geq$ 1 cm	102	51 (0.7)	161 (2.1)	7552 (96.6)	51 (0.7)
Combined	134	72 (0.9)	161 (2.1)	7552 (96.2)	62 (0.8)

\*For carcinoma the percentages are based on the number of patients screened. For polyps the percentages are based on the number of patients screened minus the number with carcinoma detected on colonoscopy.

and 107 had benign polyps. Of the cancers, 14 were Dukes' stage A, 11 Dukes' stage B, 4 Dukes' stage C, and 6 Dukes' stage D.

The sensitivity of screening in detecting carcinoma was 37.1 percent (95 percent confidence interval, 19.7 to 54.6 percent) with Hemoccult II, which was about half the sensitivity with Hemoccult II Sensa, HemeSelect, and the combination test (Table 2). The sensitivity for detecting polyps had a similar pattern. The sensitivity of all tests was similar for lesions proximal and distal to the splenic flexure.

Hemoccult II Sensa had the highest sensitivity for detecting neoplasms (71.2 percent; 95 percent confidence interval, 63.3 to 79.1 percent), and the lowest specificity (87.5 percent; 95 percent confidence interval, 86.7 to 88.2 percent). Hemoccult II and the combination test had the highest specificity (>97 percent). The specificity of HemeSelect was intermediate (95.2 percent; 95 percent confidence interval, 94.7 to 95.7 percent).

The positive predictive value for carcinoma was lowest with Hemoccult II Sensa and highest with the combination test (Table 2). The positive predictive value for polyps and for carcinoma and polyps combined had a similar pattern. We also calculated performance characteristics for each test by including only those subjects who had satisfactorily completed all three cards for that test or who had at least one test card with a positive result. The sensitivity, specificity, and predictive values were similar to those given above (data not shown).

Hemoccult II detected 1.6 colorectal carcinomas and 4.1 polyps per 1000 patients screened. Hemoccult II Sensa, HemeSelect, and the combination test all detected more colorectal carcinomas and more polyps than Hemoccult II. For every 1000 people screened, Hemoccult II Sensa would find 1.8 more colorectal carcinomas and 5.0 more polyps than Hemoccult II, and 111 more

colonoscopies would be needed; HemeSelect would find 1.3 more colorectal carcinomas and 5.0 more polyps, and 34 more colonoscopies would be needed; and the combination test would find 1.1 more colorectal carcinomas and 2.4 more polyps, and 5 more colonoscopies would be needed.

## DISCUSSION

Colorectal carcinoma has a relatively high prevalence and potential for detection in the curable, pre-clinical phase and for prevention by removal of pre-malignant polyps. An ideal screening test would be highly sensitive and specific, as well as effective in decreasing morbidity and mortality. Hemoccult II has several of these characteristics, but its sensitivity for detecting colorectal carcinoma and polyps is low.<sup>1,2</sup> Until recently,<sup>10-12</sup> there were no data showing that fecal occult-blood screening could decrease mortality from colorectal cancer. Mandel et al.<sup>12</sup> reported a 33 percent reduction in mortality with rehydrated Hemoccult II cards. Rehydration raises the sensitivity of the test but decreases its specificity and leads to a high false positive rate; colonoscopy was necessary in 38 percent of those screened.

We found that the sensitivity of the newer tests was better than that of Hemoccult II. The most accurate means of measuring sensitivity is to perform colonoscopies in all screened patients regardless of their test results. We used an alternative method, long-term follow-up, as suggested by Cole and Morrison.<sup>13</sup> Colonoscopies in all 8104 screened patients were not feasible, but two-year follow-up data were available for 96 percent of the patients.

The two-year period of follow-up for detecting all substantial colorectal neoplasms present at screening was chosen on the basis of the generally accepted direct relation between the size of a neoplasm and the likeli-

Table 2. Performance Characteristics of Fecal Occult-Blood Tests.

TEST AND FINDING*	SENSITIVITY	SPECIFICITY	POSITIVE PREDICTIVE VALUE
	percent (95% confidence interval)		
<b>Hemoccult II</b>			
Carcinoma	37.1 (19.7–54.6)	97.7 (97.3–98.0)	6.6 (3.7–11.2)
Polyp $\geq$ 1 cm	30.8 (21.6–40.1)	98.1 (97.7–98.4)	16.7 (11.9–22.8)
Combined	32.4 (24.3–40.4)	98.1 (97.7–98.4)	23.2 (17.7–29.9)
<b>Hemoccult II Sensa</b>			
Carcinoma	79.4 (64.3–94.5)	86.7 (85.9–87.4)	2.5 (1.7–3.7)
Polyp $\geq$ 1 cm	68.6 (59.2–77.9)	87.5 (86.7–88.2)	6.7 (5.3–8.4)
Combined	71.2 (63.3–79.1)	87.5 (86.7–88.2)	9.2 (7.6–11.2)
<b>HemeSelect</b>			
Carcinoma	68.8 (51.1–86.4)	94.4 (93.8–94.9)	5.0 (3.2–7.6)
Polyp $\geq$ 1 cm	66.7 (57.0–76.3)	95.2 (94.7–95.7)	15.5 (12.3–19.3)
Combined	67.2 (58.8–75.5)	95.2 (94.7–95.7)	20.5 (16.8–24.6)
<b>Combination</b>			
Carcinoma	65.6 (47.6–83.6)	97.3 (96.9–97.6)	9.0 (5.8–13.6)
Polyp $\geq$ 1 cm	50.0 (39.8–60.2)	97.9 (97.6–98.2)	21.9 (16.9–27.9)
Combined	53.7 (44.9–62.5)	97.9 (97.6–98.2)	30.9 (25.1–37.3)

\*The calculations for polyps did not include patients with carcinoma.

hood of bleeding,<sup>14,15</sup> and because of our health maintenance organization's aggressive promotion of fecal occult-blood testing and sigmoidoscopy for screening asymptomatic patients who are 50 or older. In evaluating test performance, we did not include adenomas under 1 cm in diameter that were detected on follow-up, because small adenomas rarely bleed, or bleed in amounts unlikely to be detected by testing<sup>16</sup> unless by chance.<sup>17</sup>

We included in our analysis the 4 percent of patients without complete two-year follow-up data, because we had data for at least one year of follow-up in 51 percent of this subgroup. Our estimates would be affected by any carcinomas that may have occurred in these subjects during the time lost to follow-up. On the basis of our experience, we estimate that one additional carcinoma may have occurred, which would make essentially no difference (<1 percent) in our estimates of specificity and positive predictive value and would change the estimates of sensitivity by, at most, 2 percent.

If colorectal carcinoma or polyps 1 cm or larger in diameter were not detected during screening and the two-year follow-up, our estimates of the sensitivity of the tests for detecting these lesions would be too high. Thirty-five carcinomas were found in the 8104 subjects screened, or 2.2 per 1000 subjects per year, which is similar to our previous finding of 2.0 per 1000 per year in a similarly screened group.<sup>1</sup> It is likely that we found nearly all the carcinomas expected and that our estimates of test sensitivity for carcinoma are accurate. The estimates for polyps are less certain, because two years may be insufficient for 1-to-2-cm polyps to start bleeding and become clinically evident.

Screening with Hemoccult II Sensa detected the largest number of colorectal neoplasms, but its specificity was poor and similar to that for rehydrated Hemoccult II samples.<sup>12</sup> Of the tests studied, Hemoccult II Sensa is the most likely to be influenced by diet,

because of its high sensitivity to peroxidase activity. Compliance with the dietary restrictions was not assessed. Nonetheless, the rates of positive results with Hemoccult II Sensa may have been higher because of poor compliance with the restrictions or consumption of peroxidase-rich foods not mentioned as prohibited. Without specific dietary data it is not possible to analyze the reasons for the lower rate of positive Hemoccult II Sensa results among whites as compared with other groups.

The specificity of HemeSelect and the combination test for detecting carcinoma was higher than that of Hemoccult II Sensa. The specificity of all the tests for detecting polyps was similar to that for detecting carcinoma (i.e., HemeSelect and the combination test detected 1.5 to 2 times as many lesions without increasing the need for colonoscopy as much as Hemoccult II Sensa).

We calculated performance characteristics of each test by recording only results from cards with interpretable specimens. We believe this is the fairest way to show how each test performs in clinical practice. Nevertheless, true sensitivity may be underestimated, because the subjects with uninterpretable test results were not retested.

HemeSelect requires a larger sample and more even spreading of the stool on the collection cards than the guaiac tests and is more expensive to manufacture and develop. There were many more unsatisfactorily prepared HemeSelect cards than cards for the other tests. Nevertheless, HemeSelect's performance characteristics were better than those of Hemoccult II.

We believe the combination test incorporates the best features of new tests for colorectal-cancer screening. A positive result on the HemeSelect test confirms that a positive Hemoccult II Sensa result is due to the presence of human hemoglobin, thus making use of Hemoccult II Sensa's increased sensitivity while improving its specificity. The combination test largely avoids the problem of missing HemeSelect results. A screening program using the combination test and following our recommendation to evaluate patients for whom only the Hemoccult II Sensa test is positive with flexible sigmoidoscopy and Hemoccult II testing at 6 and 12 months would detect most colon cancers and polyps.

We did not conduct a formal cost analysis of the screening strategies. The manufacturer's estimated costs for each test (packet of three, including test kits, ancillary materials, labor, and overhead) are \$3.31 for Hemoccult II, \$3.82 for Hemoccult II Sensa, and \$19.23 for HemeSelect (Baker J: personal communication). Because HemeSelect results would not be determined in the combination test if the Hemoccult II Sensa results were negative, for most patients the cost of a combination test would be less than the combined cost of the Hemoccult II Sensa and HemeSelect tests performed independently.

No matter what screening policy is adopted, some colorectal carcinomas and polyps 1 cm or more in diameter will not be detected. We believe flexible sigmoidoscopy<sup>18-20</sup> and the combination test are likely to

detect most substantial colorectal neoplasms in people at average risk of colorectal cancer.

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