

# New fecal occult blood tests may improve adherence and mortality rates

## ABSTRACT

Several new fecal occult blood tests have advantages over older ones when used for colorectal cancer screening. Fecal immunochemical tests can detect antibodies to human globin in the stool and can be used without the dietary restrictions needed with traditional guaiac tests. Although colonoscopy is often considered the gold standard, we hope that these new tests will allow more people to be screened and more cases of colorectal cancer to be detected early.

## KEY POINTS

Hemoccult Sensa and several fecal immunochemical tests are more sensitive than Hemoccult and Hemoccult II for detecting colorectal cancer and advanced adenomas, with similar specificity.

In most screening studies, fecal immunochemical tests have been more sensitive than guaiac-based tests. In addition, rates of adherence were higher, likely because dietary and medication restrictions are not needed and fewer stool samples are required.

Better compliance should improve participation in colorectal cancer screening and reduce colorectal cancer mortality rates.

NEW FECAL OCCULT BLOOD TESTS hold promise for improving our detection of colorectal cancer and for lowering mortality rates. This is good news, because despite the proven benefit of being screened for colorectal cancer,<sup>1</sup> only an average of 62% of eligible adults are screened,<sup>2</sup> and colorectal cancer remains the third leading cause of cancer deaths in the United States.

Colonoscopy is often considered the gold-standard screening test for colorectal cancer. However, many patients do not undergo screening colonoscopy because it is invasive and uncomfortable, bowel preparation poses a challenge, the procedure has risks, and it is costly. Members of minority groups, people of lower socioeconomic status, and those who lack health insurance are less likely to undergo screening.

While fecal occult blood tests are cheaper and less invasive than colonoscopy, they do not allow us to prevent colorectal cancer by removing adenomatous polyps. Still, randomized controlled trials have proven that fecal occult blood testing is associated with a decrease in the rate of death from colorectal cancer,<sup>3</sup> and it has been shown to be cost-effective.

The challenge is that all guaiac-based tests (gFOBTs), even the newest one, require strict dietary and medication restrictions to be accurate, and the difficulty of collecting stool specimens often results in either false-positive results or failure to complete the test.

The newer tests—one guaiac-based test and several fecal immunochemical tests (FITs)—are more sensitive, and the FITs are more convenient for patients to use than the older guaiac-based tests, advantages that, we hope, will increase the rates of compliance with testing.

**TABLE 1**

**Recommendations for colorectal cancer screening**

TESTS	UNITED STATES MULTI-SOCIETY TASK FORCE <sup>4</sup>	UNITED STATES PREVENTIVE SERVICES TASK FORCE <sup>5</sup>	AMERICAN COLLEGE OF GASTROENTEROLOGY <sup>6</sup>
Colonoscopy	Every 10 years	Every 10 years	Every 10 years
Computed tomographic colonography	Every 5 years	Insufficient evidence to assess benefit or harm	Every 5 years
Flexible sigmoidoscopy	Every 5 years with or without fecal occult blood test	Every 5 years with fecal occult blood test every 3 years	Every 5–10 years
Double contrast barium enema	Every 5 years	Not specified	Replaced by computed tomographic colonography
Fecal occult blood testing*	Every year	Every year	Every year
Fecal DNA	Uncertain	Insufficient evidence to assess benefit or harm	Every 3 years

\*Fecal immunochemical test or high-sensitivity guaiac test

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**Patients undergoing guaiac testing should avoid NSAIDs, red meat, and vitamin C for 3 days before testing, and during testing**

The US Multi-society Task Force (USMTF),<sup>4</sup> the US Preventive Services Task Force (USPSTF),<sup>5</sup> and the American College of Gastroenterology (ACG)<sup>6</sup> endorse a variety of options for screening (TABLE 1), and each option has different levels of cost, risk, and effectiveness.<sup>4-7</sup> The USMTF and the ACG prefer cancer prevention rather than cancer detection tests,<sup>4,6</sup> but all three organizations agree that the newer, more sensitive fecal occult blood tests should replace the older, less sensitive ones.

**■ GUAIIAC-BASED TESTS**

Guaiac tests detect the peroxidase activity of hemoglobin. If hemoglobin is present in stool, it catalyzes the oxidation of the active compound in guaiac paper when a hydrogen peroxide developer is added. The resultant conjugated compound is blue.

The lower-sensitivity guaiac tests are commercially available as Hemoccult and Hemoccult II, and the higher-sensitivity guaiac test is Hemoccult Sensa, which has a lower threshold for detecting peroxidase. All are made by Beckman Coulter, Fullerton, CA.

**Disadvantages of guaiac tests.** Guaiac tests can give false-positive results by detecting pseudoperoxidases in fruits, vegetables, and nonhuman blood. In addition, they can give false-negative results in people who take excessive amounts of vitamin C, which can inhibit peroxidase activity. Therefore, patients need to follow certain dietary restrictions before testing.

Another disadvantage of guaiac tests is that they cannot differentiate between blood lost from the stomach, small bowel, or colon.

Moreover, the interpretation of guaiac tests is subject to observer variation.

Since testing involves dietary restrictions and obtaining two specimens each from three separate stools, patient compliance is poor.

**Patient instructions.** Patients undergoing guaiac-based fecal occult blood testing should not take nonsteroidal anti-inflammatory drugs (eg, > one adult aspirin per day) for 7 days before and during the stool collection period to avoid causing gastrointestinal bleeding. They should also not eat red meat or take vitamin C in excess of 250 mg/day for 3 days before testing and throughout the test period.

Two specimens are collected from three

different stools with a wooden stick and are smeared onto the stool test card, which is then closed and returned to the physician's office. The specimens must be collected before the stool comes into contact with the toilet water.

### Efficacy of guaiac testing

Randomized, controlled trials of guaiac-based fecal occult blood testing have shown a decrease in colorectal cancer incidence.<sup>8-11</sup>

A **Cochrane review**<sup>12</sup> involved more than 320,000 people in Denmark, Sweden, the United States, and the United Kingdom who underwent testing every year or every 2 years with Hemoccult or Hemoccult II. The primary analysis was by intention to treat, and it showed that participants allocated to screening had a 16% reduction in the relative risk of death from colorectal cancer, or 0.1 to 0.2 fewer colorectal cancer deaths per 1,000 patient-years. The secondary analysis was adjusted for whether the participants actually were screened; the risk reduction in death from colorectal cancer was 25% in participants who attended at least one round of screening.

## ■ FECAL IMMUNOCHEMICAL TESTS

Fecal immunochemical tests use monoclonal or polyclonal antibodies to human globin to detect human blood in stool.

**Advantages of fecal immunochemical testing.** The antibodies used do not cross-react with nonhuman globin or peroxidases from food sources. Therefore, these tests avoid the dietary and medication restrictions required for guaiac tests. In addition, the stool collection method is simpler, and only one stool specimen is needed instead of three. For these reasons, patient compliance may be better than with guaiac tests.

Additionally, because human globin does not survive passage through the upper gastrointestinal tract, fecal immunochemical testing is specific for bleeding from the colon and rectum.

Immunochemical tests can be read either visually or by machine. Automation allows the threshold for detection of globin to be modified to balance the test's sensitivity and specificity for the population being served. Most studies have used a threshold of 75

ng/mL, but other studies have assessed thresholds as low as 50 ng/mL and as high as 100 ng/mL. A lower threshold of detection has been shown to increase the sensitivity and yet retain a high specificity.

The immunochemical tests are slightly more expensive than the guaiac tests. However, they are covered by insurance, including Medicare.

**Disadvantages of fecal immunochemical testing.** A number of tests are available; they use different antibodies and therefore differ in their sensitivity. While most screening studies used automated interpretation of the tests, some studies used visual interpretation (but trained technicians were used to decrease potential interobserver variability). Therefore, the characteristics of fecal immunochemical tests are particular to the specific test kit used.

The antibodies and their epitopes used in some fecal immunochemical tests may be unstable, so that these tests may perform poorly without refrigeration in warm climates or if there are postal delays.

**Patient instructions.** In some of the tests, a special wand is inserted into six different places in the stool (before the stool is in contact with toilet bowl water) and then placed in the plastic container provided. Other tests use a brush for sample collection. The container may be sent to the laboratory for automated interpretation, or, if the interpretation is performed manually, the container is shaken and a few drops of the liquid in the specimen are added to the test cassette. The interpretation is made after 5 to 10 minutes.

## ■ GUAIAIC VS IMMUNOCHEMICAL TESTING IN SCREENING

Allison et al<sup>13</sup> performed one of the earliest studies to compare the different types of fecal occult blood tests as screening tests for colorectal cancer. More than 7,500 participants in the United States who were due for screening were advised to follow the dietary restrictions for guaiac tests mentioned above for 3 to 4 days before screening and were given three specially made test cards, each of which contained three tests: Hemoccult II, Hemoccult Sensa, and the fecal immunochemical test HemeSelect (SmithKline Diagnostics, San Jose,

**Different fecal immunochemical tests use different antibodies and cutoffs and have different performance characteristics**

CA), which was visually read. The authors evaluated the performance of the tests by identifying screened patients found to have colorectal cancer or an adenoma larger than 10 mm in the 2 years after screening.

Sensitivities for detecting colorectal cancer:

- 37% with Hemocult II
- 69% with HemeSelect
- 79% with Hemocult Sensa.

Specificities:

- 98% with Hemocult II
- 94% with HemeSelect
- 87% with Hemocult Sensa.

**Smith et al**<sup>14</sup> evaluated the performance of two tests in a mix of a screening population and a high-risk group. More than 2,300 Australians sampled two consecutive stools for an immunochemical test, InSure (Enterix, North Ryde, NSW, Australia), and three consecutive stools for Hemocult Sensa. They were advised to adhere to the dietary and medication restrictions listed in Beckman Coulter's instructions for the Hemocult Sensa test. Both tests were read visually. The sensitivity and specificity were calculated from results of colonoscopy performed in participants with a positive stool test.

InSure had a higher sensitivity than Hemocult Sensa for colorectal cancer (87.5% vs 54.2%) and for advanced adenomas (42.6% vs 23.0%). The false-positive rate for any neoplasia was slightly higher with InSure than with Hemocult Sensa (3.4% vs 2.5%).

**Guittet et al**<sup>15</sup> in a French study in more than 10,000 people at average risk, compared a low-sensitivity guaiac test (Hemocult II) and an immunochemical test, Immudia/RPHA (Fujirebio, Tokyo, Japan). No dietary restrictions were required. Three stool samples were taken for the Hemocult II and three for the immunochemical test, which was read by machine with three different thresholds for detection of globin: 20, 50, and 75 ng/mL. Positive results were followed up with colonoscopy.

The immunochemical test had a higher sensitivity for both colorectal cancer and advanced adenomas, regardless of the cutoff values of globin. At a cutoff value of 75 ng/mL, the positivity rate was similar to that of the low-sensitivity guaiac test (2.4%), and the im-

munochemical test offered a gain in sensitivity of 90% and a decrease in the false-positive rate of 33% for advanced neoplasia.

**van Rossum et al**<sup>16</sup> performed a randomized comparison of more than 10,993 tests of Hemocult II and the fecal immunochemical test OC-Sensor (Eiken Chemical Co., Ltd, Tokyo, Japan) in a screening population in the Netherlands. The participants were not required to follow dietary or medication restrictions. They were asked to send in cards with two samples each from three consecutive bowel movements for the Hemocult II test and a single sample for the OC-Sensor test, for which interpretation was automated and a cutoff of 100 ng/mL or higher was considered as positive. All participants who had a positive Hemocult II test or a positive OC-Sensor test with a globin cutoff of 50 ng/mL were advised to undergo colonoscopy.

The study found a 13% higher rate of screening participation with the immunochemical test than with the guaiac-based test, and the positivity rate was 3% higher in the immunochemical testing group (5.5%).<sup>16</sup> Cancer was found in 11 patients with the guaiac test and in 24 patients with the immunochemical test; advanced adenomas were found in 48 patients with the guaiac test and 121 patients with the immunochemical test. The guaiac test was more specific, but the participation and detection rates for advanced adenomas and cancer were significantly higher with immunochemical testing.

**Park et al**<sup>17</sup> performed a study in nearly 800 patients undergoing screening colonoscopy in South Korea. Three stool samples were collected for a low-sensitivity guaiac test (Hemocult II) and for a fecal immunochemical test (OC-Sensor) for detecting cancer and advanced neoplasms. No dietary changes were required. At all globin thresholds between 50 and 150 ng/mL, the immunochemical test was more sensitive than the guaiac-based test, with a similar specificity.

**Hundt et al**<sup>18</sup> obtained a single stool specimen from each of 1,319 German patients before they underwent scheduled screening colonoscopy. Each specimen was tested with six automated immunochemical tests with globin detection thresholds set at 10 to 50 ng/mL. In addition, participants prepared a

**In general, the fecal immunochemical tests were more sensitive than the guaiac-based tests**

single Hemoccult card from the same stool sample at home. They were not told to follow any dietary restrictions.

For Hemoccult, the sensitivity for advanced adenoma (1 cm or more in diameter, villous changes, or high-grade dysplasia) was 9%, and the specificity was 96%. For the immunochemical tests, the sensitivity for advanced adenoma varied from 25% to 72%, and the specificity from 70% to 97%.

The reason for the variation in performance of different fecal immunochemical tests is not clear. In some of these tests, the sensitivity can be adjusted when automated interpretation is used. It has been shown that different thresholds for the detection of globin partially explain this. Differences in collection methods also affect the result.

Itoh et al<sup>19</sup> reported the results of a screening study done at a large Japanese corporation using a fecal immunochemical test, OC-Hemodia (Eiken Chemical Co., LTD, Tokyo, Japan). A small sample of a single stool was placed in buffer and read by machine. At a cutoff of 200 µg/mL, the sensitivity was 77.5% and the specificity was 98.9%. At a cutoff of 50 ng/mL, the sensitivity was 86.5% and the specificity was 94.9%. In this study, positive tests were followed by colonoscopy, but false-negative tests were identified from insurance claims.

Cole et al<sup>20</sup> assessed the rates of participation in colorectal cancer screening in a study in Australia. Participants were randomized and received by mail either Hemoccult Sensa or one of two fecal immunochemical tests, FlexSure OBT (Beckman Coulter, Fullerton, CA) or InSure. The Hemoccult Sensa group was instructed to follow dietary and medication restrictions during stool collection, while the immunochemical test groups were not. Three

stool specimens were required for the Hemoccult Sensa and FlexSure tests, while two stools were required for InSure.

The participation rate was 23.4% in the Hemoccult Sensa group, 30.5% in the FlexSure OBT group, and 39.6% in the InSure group ( $P < .001$ ).

Hol et al<sup>21</sup> found that the participation rate was 50% in a group asked to undergo guaiac testing requiring three samples without diet restriction and 62% in a group asked to undergo fecal immunochemical testing (OC-Sensor) requiring a single stool sample without restrictions. Higher participation rates are seen with fecal immunochemical testing than with guaiac testing and are an advantage of immunochemical testing.

### ■ CLEVELAND CLINIC SWITCHES TO FECAL IMMUNOCHEMICAL TESTING FOR COLORECTAL CANCER SCREENING

Cleveland Clinic recently switched to fecal immunochemical testing in place of Hemoccult Sensa for colorectal cancer screening. The data on fecal occult blood tests show that the sensitivities of Hemoccult Sensa and the immunochemical tests are higher than those of Hemoccult and Hemoccult II for the detection of colorectal cancer and advanced adenomas, with similar specificity. Fecal immunochemical tests have an advantage over guaiac-based tests in most screening studies by showing a superior sensitivity for advanced adenomas and colorectal cancer, as well as an increase in test adherence, likely because of the lack of dietary and medication restrictions and the lower number of stool samples required. Increased compliance should improve participation in colorectal cancer screening and positively affect colorectal cancer mortality rates. ■

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