Melvin Schapiro, M.D., Series Editor

The Role of Fecal Occult Blood Testing in Screening for Colorectal Cancer

James E. Allison

All of the most recent guidelines for colorectal cancer (CRC) screening recommend a menu of screening options (1–3), however; the lay press and many gastroenterology opinion leaders encourage Americans to have only one test—colonoscopy (4–10). It would not be surprising, therefore, if primary care physicians and their patients believed there is no role for FOBT testing in screening for colorectal cancer. This review will discuss the various FOBTs available and make the argument that FOBT screening is still relevant and important in population screening efforts.

THE AVAILABLE FECAL OCCULT BLOOD TESTS—THE GUAIAC TESTS (GT)

In 1985, Simon published an excellent review of FOBT testing for colorectal cancer (11). He stated that the concept of occult blood detection is generally credited to Van Deen, who in 1864 used gum guaiac, as an indicator reagent. Boas was the first to demonstrate its value for the detection of bowel malignancy (12) and Greegor was the first to stimulate interest in screening with the guaiac test (13).

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The guaiac FOBTs (GT) detect the peroxidase activity of 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. In screening for colorectal neoplasms a true positive GT is one which indicates bleeding from a colon cancer or polyp. All other positive results are considered to be false positive. 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. Some reports suggest that delaying development of GT cards for at least three days will decrease the number of false positives due to plant peroxidases and obviate the need for diet restriction of

fruits and vegetables (14,15). It isn't clear, however, that arranging such a processing delay is practical in most clinical settings or that these initial findings will be validated in future studies.

Although there are several available GTs only three, Hemoccult II, Hemoccult Sensa (Beckman Coulter Inc.; Primary Care Diagnostics, Los Angeles, CA), and hema-screen (Immunostics, Ocean, NJ), have been extensively evaluated in large screening populations. The Hemoccult test first became available around 1970 and was in use until modifications in 1977 led to the Hemoccult II test. Each Hemoccult II and Hemoccult Sensa slide has two windows of guaiac-impregnated paper, on which a small amount of stool is smeared (Figure 1). This is repeated with two subsequent bowel movements. The three-slide package is then returned to the laboratory or physician's office for development (Figure 2). It is important to remember that screening for colorectal cancer with FOBT should not be done with stool samples obtained at a digital rectal examination (DRE). FOBT results of a single stool sample obtained by DRE should be considered inadequate screening as there is a possibility of an increased false positivity rate and a decreased sensitivity when compared to the standard three specimen requirement (16,17).

Figure 1. Hemoccult Sensa cards each with two windows of guaiac impregnated paper. A wooden spatula is used to smear a small stool specimen onto each window.

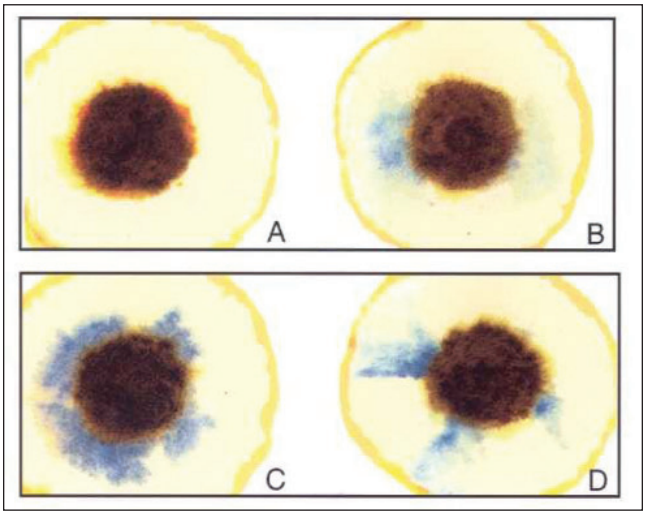

Figure 2. Guaiac test development showing one negative (A) and three positive test results (B,C,D). In the presence of heme and a hydrogen peroxide developer guaiac acid is oxidized producing a blue color. Accurate interpretation of results for GT require training and supervision especially when interpreting borderline results.

If one of the six smears is positive further investigation with colonoscopy is advised. Where colonoscopy resources are limited or the procedure is unacceptable to the patient, flexible sigmoidoscopy plus double contrast barium enema may be used for further evaluation. Repeating the test and only evaluating those patients with repeat positive results is not acceptable practice. Gastrointestinal neoplasms bleed intermittently and a negative test following a previously positive one may be a false negative.

The guaiac tests Hemoccult II and Hemoccult Sensa have several limitations as screening tests for colorectal cancer. Application sensitivity (one time testing only) for cancer and significant polyps (>1 cm) is low for

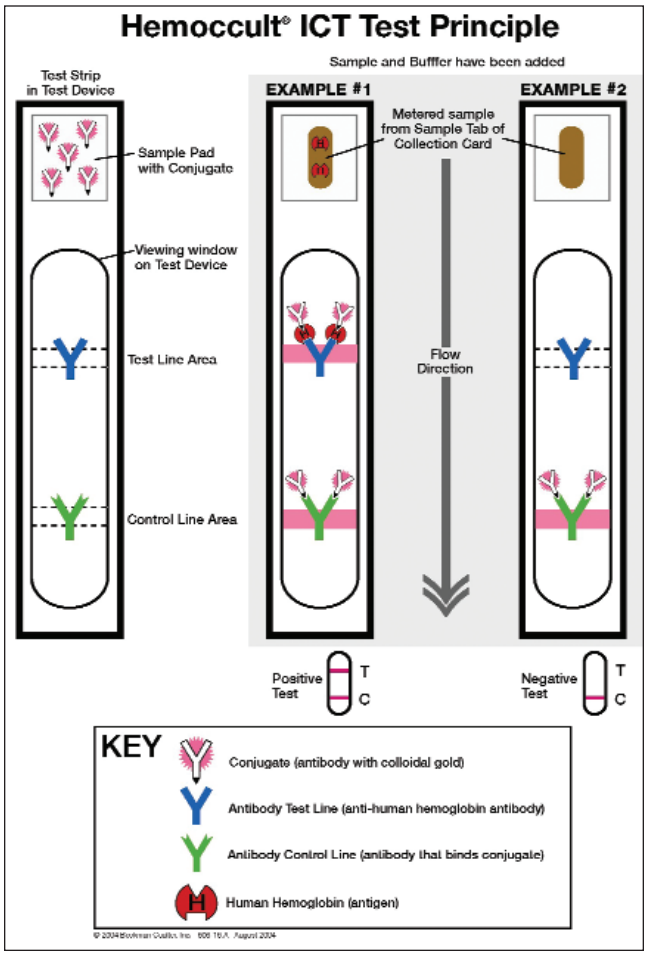

Figure 3. Cartoon illustrating principle of Hemoccult ICT FIT Method.

Hemoccult II and specificity is low for Hemoccult Sensa (18,19). Poor sensitivity limits effectiveness in decreasing colon cancer mortality and poor specificity increases the costs of screening because individuals with false positive results will undergo the discomfort, cost and risk of an unnecessary colonoscopy. Randomized controlled trials in the United Kingdom and Denmark using the unrehydrated Hemoccult II showed modest reduction of colorectal cancer mortality in the screened group. In the United Kingdom the mortality reduction for biennial screening was 15% and in Denmark it was 18% (20,21). The 33% mortality reduction in the Mandel Minnesota study was achieved with rehydrated Hemoccult tests (22). The rehydrated Hemoccult II test has never been standardized nor endorsed by its manufacturer. It is not recommended in the clinical guidelines of the U.S. Preventive Services Task Force or in the guidelines of the American Gastroenterological Association (2,3).

Accurate interpretation of results for Hemoccult II requires training and supervision especially when interpreting borderline results (23–25). Results are affected by vitamin C, which inhibits the guaiac reaction (26). The person screened is required to collect the stool sample in the dry state and to sample the feces with a wooden stick. These requirements limit patient acceptance. In a group of motivated volunteers in an Australian population where red meat consumption is relatively high a restrictive diet reduced participation by 13% (27).

THE AVAILABLE FECAL OCCULT BLOOD TESTS—THE IMMUNOCHEMICAL TESTS (FIT)

Recent data have shown that new FOBTs called fecal immunochemical tests (FIT) are superior to the more commonly used guaiac tests (GT). The operating and performance characteristics of the FITs address many of the weaknesses of the GT. They use specific antibodies to human hemoglobin, albumin, or other blood components. Some use monoclonal and polyclonal antibodies to detect the intact globin protein portion of human hemoglobin. The labeled antibody attaches to the antigens of any human globin present in the stool resulting in a positive test result (Figure 3). Globin does not survive passage through the upper gastrointestinal tract; therefore, FITs detecting globin are specific for occult bleeding from the large bowel. In addition, FITs do not react with nonhuman globin or with food such as uncooked fruits and vegetables that may contain peroxidase activity. Dietary restriction is therefore not necessary when screening with these tests. They are also unaffected by medicines such as nonsteroidal anti-inflammatory drugs or vitamin C. All these features may make use of FIT more acceptable to those screened than the GT.

All of the recommendations for an FOBT option in CRC screening guidelines were made on the basis of findings from randomized controlled trials using GT. If, as it appears, the FIT has better performance characteristics and acceptance than the GT, that is com-

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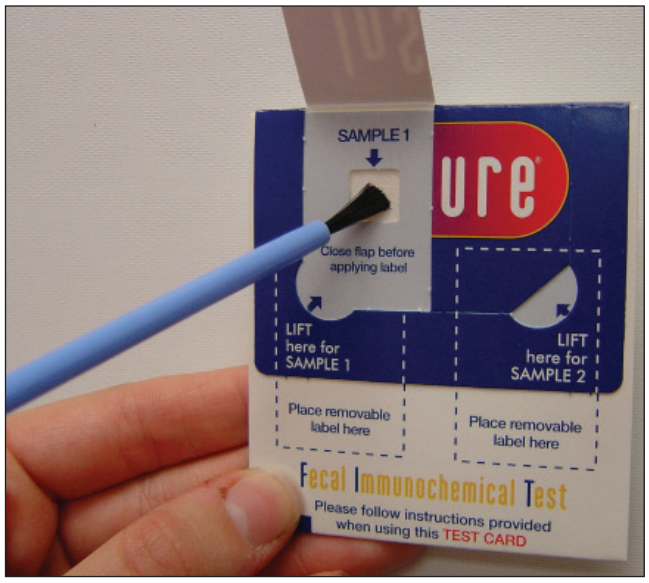

Figure 4. InSure FIT test card showing brush applicator.

pelling evidence for recommending its use as the FOBT of choice in CRC screening programs (28). In summary, the advantages of FIT over GT include the following:

1. FITs have superior sensitivity and specificity (19,29).
2. FITs use antibodies specific for human globin and are, unlike the GT, specific for colorectal bleeding and not affected by diet or medications.
3. Some FITs can be developed by automated developers and readers. This innovation allows for management of large numbers of tests in a standardized manner with excellent quality assurance.
4. There is evidence that FIT use improves patient participation in screening for CRC (30).
5. New technology for FITs allows them to quantify fecal hemoglobin so that sensitivity, specificity, and positivity rates can be adjusted in screening for colorectal neoplasia (31).
6. The developing instrument for some FITs has the ability to read a bar code on the test. This feature ensures accurate identification of the person screened and allows for a print-out of the result as well as a reminder print-out for future compliance.

When these innovations have been perfected and tested in large asymptomatic populations, government agencies or individual health plans will be able to decide what positivity rate their budget and human resources can accommodate and still have good sensitivity and specificity for advanced neoplasms in an annual screening program.

The new and improved FIT choices are now available and reimbursable by the US Center for Medicare and Medicaid Services (CMS) at $22 per test (including completed test card with two samples and analysis). In 2004 CMS concluded that adequate evidence exists to determine that the FIT is an appropriate and effective CRC screening test for detecting fecal occult blood in Medicare beneficiaries aged 50 years or older. The CMS reimbursement decision has led to the approval of several FITs by the US Food and Drug Administration (FDA) for marketing in the United States. These, include InSure (manufactured by Enterix Inc., a Quest Diagnostics company, Lyndhurst, NJ) (Figure 4), Hemoccult-ICT (Beckman Coulter, Inc., Primary Care Diagnostics, Los Angeles, CA) (Figure 5), Instant-View (Alpha Scientific Designs, Inc., Malvern, PA), immoCARE (Care Products, Inc., Waterbury, CT), MonoHaem (Chemicon International, Inc., Temecula, CA), Clearview Ultra-FOB (Wampole Laboratory, Princeton, NJ) and OC Auto Micro 80 (Polymedco, Cortland Manor NY). Magstream HemSp is the automated version of a test previously marketed by the name HemeSelect. The advances provided by the new version are machine reading of the test endpoint (to avoid problems related to human error), automation that allows a throughput of up to 1000 tests per hour for each auto-analyzer, and the ability to choose test performance characteristics rather than having to rely on the endpoint chosen by the manufacturer. Magstream 1000/Hem SP (Fujirebio Inc. Tokyo, Japan) is marketed in Australia and Europe by Bayer Diagnostics as Bayer Detect but it is not yet available in the United States.

Although it would be helpful to be able to recommend one or a few of these FIT choices as the best, there is, as yet, insufficient information to do so. Only FlexSure OBT (currently marketed as Hemoccult ICT), HemeSelect, (SmithKline Diagnostics, Palo Alto, CA), InSure, and now MagStream1000/Hem SP have been evaluated in large numbers (thousands) of average-risk patients with results published in US

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Figure 5. Hemoccult ICT test card showing stick applicator and positive test.

peer-reviewed journals (19,29,32). Head-to-head comparisons in large average-risk populations are not yet available. The methodology for stool handling and sampling differ among these tests regarding how (automated or by technician) and where (office or laboratory) the tests are developed. Because the immunochemistry appears to be similar for all of the tests, the advantages for one over another may be in sampling methods and development. The following sampling and development issues are important:

1. Is the sample representative of the whole stool specimen?
2. Are multiple stool specimens important given the known intermittent bleeding that occurs in colonic neoplasms? If so, how many is enough? One study suggests that at least 2 days of sampling is important (33).
3. What features of the FIT make it more suitable for maximum subject participation?
4. What is the stability of the collected sample, and how can it be transported to the laboratory?
5. What is the acceptability of the FIT for laboratory development—ease of development by technician or automation?
6. Is the test capable of quantifying the hemoglobin concentration and allowing for differentiation between significant and insignificant colorectal neoplasms and non-neoplastic bleeding lesions?

Representative information about a few of these tests is shown in Tables 1, 2, and 3.

Table 1
FIT sampling and testing

Fit	*Stool tested*	*Sampling method (per stool)*	*Test per stool*	*Sample stability*	*Safety and transport*
Clearview Instant View (Wampole Laboratory, Princeton, NJ)	One	Spike/pin into exposed surface	One test on one sample	Refrigerated as soon as possiple	Risk of spill, courier
InSure FIT (Produced by Enterix, Australia; Distributed by Quest Diagnostics, Lyndhurst, NJ)	Two	Brush, water around whole stool	One test on two samples	Dry, stable >14 days	Mail
Hemocult-ICT (Beckman Coulter, Inc., Primary Care Diagnostics, Los Angeles, CA)	Three	Stick, two smears of exposed surface	Three tests on three samples	Dry, stable >14 days	Mail

FIT = fecal immunochemical test.
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Allison JE and Lawson M, Screening Tests for Colorectal Cancer 2006
A Menu of Options Remains Relevant Current Oncology Reports 2006, 8:492-498

Table 2
Sampling and FIT performance

Sampling time	*Sensitivity, %*	*Specificity, %*
One day	67.9	97.5
Two days	88 (+20%)	95.6 (–1.9%)
Three days	90.8 (+2.8%)	92.1 (–3.5%)

FIT = fecal immunochemical test.
Data from Nakama, et al (33)
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FOBT (FIT OR GT) REMAIN AN IMPORTANT SCREENING OPTION FOR COLORECTAL CANCER

In 2000, 2001, and again in 2005, articles in *The New England Journal of Medicine* (34–37) demonstrated the superiority of colonoscopy over sigmoidoscopy alone and sigmoidoscopy plus fecal occult blood test (FOBT) in uncovering advanced proximal neoplasms. It was no surprise to the gastroenterology community that a one-time test—colonoscopy—would be better than a one-time sigmoidoscopy or one-time FOBT, but the press and public interpreted this information as "If a person is screened with a test other than colonoscopy there is a good chance he or she will die from a missed colorectal cancer." The evidence suggests, however, that if the other available screening tests are employed as recommended, the incremental benefit of colonoscopy in decreasing patient mortality from CRC is small. The concern about missed "advanced neoplasms" in once-only testing with methods other than colonoscopy may not be as important as it has been portrayed. Annual FOBT testing and flexible sigmoidoscopy every 5 years are the current recommendations, leaving the potential for discovery of a missed advanced neoplasm on subsequent screens before it has become malignant or lethal.

The fear engendered in non-specialist physicians and patients by the term "advanced neoplasms" is unnecessary and unhelpful for making rational decisions regarding screening test choices. Advanced colonic neoplasms consist of a range of lesions (from large tubular adenomas to early adenocarcinoma) that vary widely in terms of the risk of progression to fatal cancer. Large polyps (>1 cm) become colorectal cancers at a rate of roughly 1% per year (38). A large polyp, left in situ, has a cumulative risk of malignancy at 20 years of only 24% (39). The development of invasive cancer from a small (<10 mm) adenoma is extremely unlikely in less than five years (40). Since

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Table 3
FIT performance characteristics

FIT	*Sensitivity for CRCA, %*	*Sensitivity for polyps >1cm, %*	*Specificity for CRCA, %*	*Specificity for polyps >1cm, %*
HemeSelect (Fujirebio, Inc., Tokyo, Japan)	69	67	95	95
Hemoccult-ICT (Beckman Coulter, Inc., Primary Care Diagnostics, Los Angeles, CA)	82	30	97	97
Magstream (Tokyo, Japan)	66	20	95	95

CRCA = colerectal cancer lesions; FIT = fecal immunochemical test.
Data from Allison, et al (19,29) and Morikawa, et al (32)
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most polyps, even the "advanced" ones, do not directly lead to death from colon cancer, the most important value of one test over another is the incremental benefit of mortality reduction that test confers to the patient being screened. If screening tests other than colonoscopy are used as directed, that incremental benefit of colonoscopy is small.

The idea espoused by two gastroenterology specialty societies that colonoscopy is the preferred screening test (7,41) best fits the case-finding or individualistic approach to screening, in which what is considered best for the person drives the decision making. Population or mass screening is an organized and systematic approach aimed at maximum participation in screening within a population. Outcomes at the population level, such as acceptability, feasibility, and low initial cost, with proven cost-effectiveness are key issues. The arguments for caution when recommending colonoscopy as the preferred screening test for population screening are described below.

Evidence suggests that the resources necessary to provide a skilled colonoscopic examination for all eligible US citizens are inadequate (42,43). Ladabaum and Song (44) estimate that screening colonoscopy every 10 years would require 8.1 million colonoscopies per year, including surveillance, with other strategies requiring 17% to 58% as many colonoscopies. In a letter to the editor of *The New England Journal of Medicine,* a physician at Baylor College of Medicine estimated that screening their 62,000 out-patients aged 50 years and older by colonoscopy would take about 30 years (45). Unqualified examiners could absorb the overflow, and the increased inaccuracy and complications could undo the small incremental benefit that the test offers (46). The millions who undergo screening for no apparent gain are subject to harms that could cumulatively outweigh the benefits to the smaller group (those found to have advanced neoplasms), especially if the added benefit is not very great compared with that of other screening options (47). The serious complication rate in the Veterans' Administration (VA) study, in which the endoscopists were all very skilled, was 10 in 3000 or one in 300, including a cerebrovascular accident and a myocardial infarction (9).

The costs of population screening with colonoscopy are particularly worrisome at a time when the US federal deficit is projected to hit a record $477 billion, and other worthy causes (e.g., prescription drug benefits, screening for breast cancer, childhood vaccinations) are competing for health dollars. Policymakers in the UK have written that population screening by colonoscopy is a nonstarter for the foreseeable future (48). The UK has neither the resources nor the facilities to undertake such screening, and their experts estimate that the complication rate arising from screening 171,000 people aged 60 years using colonoscopy would be unacceptable (over 500 cases of severe hemorrhages, over 150 perforations, and 50 deaths each year). If history is any lesson, the current reimbursement for colonoscopy is unlikely to remain stable or to increase. For flexible sigmoidoscopy, the rate became too low to justify the required equipment, staff time, and dedicated space (49,50).

CONCLUSION

It is not realistic to believe that any CRC screening test will ever detect all advanced neoplasms. As Fletcher (51) has pointed out, clinicians should be prepared to miss some cancers because many other factors, such as complications, inconvenience, discomfort, cost-effectiveness, and the workforce needed to perform procedures, must also be balanced in decisions regarding which screening policies make the most sense. The best screening test is the one that gets done (52). The choice of screening tests should be suited to the screening situation. For the present and immediate future, the FOBT remains as one of several screening tests with an important role in colorectal cancer screening. ■

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