A Comparison of Three Stool Tests for Colorectal Cancer Screening

Beverly Greenwald

Colorectal cancer (CRC) death rates continue to decrease in both men and women, yet the disease ranks third for estimated new cancer cases and third for estimated cancer deaths in both men and women. The American Cancer Society (ACS) predicts 149,280 new CRC cases and 56,910 CRC deaths in the United States in 2005. Few CRC cases are diagnosed at a localized stage (39%), when the survival rate is 90%. Most CRC cases are diagnosed at either a regional stage or distant stage, with resultant less-desirable survival rates of 67% and 10% respectively (Jemal et al., 2005).

ACS Screening Guidelines

The ACS recommends five screening regimens for CRC (Smith et al., 2005) because screening enables early detection and a reduced mortality rate (Levin, Brooks, Smith, & Stone, 2003). Three noninvasive stool tests are available for CRC screening: the guaiac fecal occult blood test (gFOBT), the immunochemical fecal occult blood test (iFOBT), and the stool deoxyribonucleic acid (DNA) test. The annual FOBT (either guaiac or immunochemical) is one regimen recommended by the ACS (Smith et al., 2005). The stool DNA test is considered a promising new technology, but there is insufficient evidence to support its use as a routine CRC screening method (Smith et al., 2003). Medical-surgical nurses need an awareness of the numerous advantages and disadvantages of each stool test to help patients decide which CRC screening test is right for them. Table 1 shows a comparison of the three noninvasive stool tests for CRC.

Stool Test Costs and Medicare Coverage

At $4.50, the annual gFOBT is the least expensive of all five screening regimens recommended by the ACS (van Ballegooijen, Habbema, Boer, Zauber, & Brown, 2003). The iFOBT costs $95 (Personal communication, Enterix, Inc. Customer Service, April 15, 2004). Medicare covers the cost of either of these tests. Medicare recipients can elect one to three simultaneous determinations of the iFOBT annually (“National,” 2003). The ACS determined in April 2002 the extra cost of the iFOBT is justified by the reduction of false positives and the diminished expense of unnecessary follow-up testing (“Medicare,” 2003; Smith et al., 2003). The stool DNA test, at $795 is less economical, but automation of testing may reduce the cost in the future.

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# Table 1.
## A Comparison of Three Noninvasive Stool Tests for Colorectal Cancer

<table>
<thead>
<tr>
<th>Substance detected</th>
<th>gFOBT</th>
<th>iFOBT</th>
<th>Stool DNA test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peroxidase activity of heme in blood and other peroxidases in stool (Cole et al., 2003)</td>
<td>Intact globin protein from human hemoglobin (Levin et al., 2003)</td>
<td>DNA markers in stool from cells of pre-malignant adenomas and tumors (Helm et al., 2003).</td>
<td></td>
</tr>
<tr>
<td>Special benefits</td>
<td>The least expensive and simplest CRC screening method (Wong et al., 2003)</td>
<td>The use of fewer samples and a lack of dietary and medication restrictions may help increase compliance.</td>
<td>Entire stool specimen is used and requires less handling by patient and physician (Deenadayalu &amp; Rex, 2004). Cancer cells continuously released DNA markers, while blood released from polyps or tumors is intermittent (Ahlquist, 2002).</td>
</tr>
<tr>
<td>Products available</td>
<td>Hemoccult II is the most widely used (Tagore et al., 2003) and most extensively studied test (Bleiberg, 2002; Crespi &amp; List, 2002).</td>
<td>PreGen-Plus is a stool DNA test which became available August 14, 2003 (Barkley, 2003). The PreGen-Plus is the only stool-based DNA CRC screening test available in the United States (B. Mitchell, personal communication, May 10, 2004).</td>
<td></td>
</tr>
<tr>
<td>Medicare coverage</td>
<td>Yes, annually (“National,” 2003)</td>
<td>Yes, one to three simultaneous determinations annually, effective January 1, 2004 (“National,” 2003).</td>
<td>No, more testing will be required (“National,” 2003). Adoption by the ACS as a recommended screening test may facilitate reimbursement in the future.</td>
</tr>
<tr>
<td>ACS recommendation</td>
<td>Yes (Smith et al., 2005)</td>
<td>Yes, as of April 2002 (Smith et al., 2003). The cost is justified because there will be fewer false positives, thus avoiding the cost of unnecessary follow-up testing (“Medicare,” 2003).</td>
<td>No, but this test has been identified as a promising new technology by the ACS Colorectal Cancer Advisory Group (Smith et al., 2003).</td>
</tr>
<tr>
<td>Dietary restrictions</td>
<td>Peroxidases in some foods can result in false-positive results (Cole et al., 2003). Alcohol in excess can cause false-positive results. Vitamin C-rich foods can result in false-negative results (Beckman Coulter, Inc., 2002).</td>
<td>None. Because this test is specific for human hemoglobin, peroxidases in foods do not affect the results (Levin et al., 2003). The lack of dietary restrictions makes this a more patient-friendly test than the gFOBT (Smith et al., 2003).</td>
<td>None. This test is specific for DNA tumor markers (Ahlquist, 2002; Ahlquist &amp; Shuber, 2002; Helm et al., 2003).</td>
</tr>
</tbody>
</table>
The stool DNA test currently is not covered by Medicare ("National," 2003), but the ACS Colorectal Cancer Advisory Group did identify this test as a promising new technology (Smith et al., 2003). EXACT Sciences Corp. (Maynard, MA), manufacturers of the stool DNA test, is completing the required testing to facilitate future recommendation of this test by the ACS and Medicare reimbursement. Although not yet prescribed, the stool DNA test may have the advantage of a longer screening interval than the FOBT (Tagore et al., 2003) because both tumors and precursor adenomas can be detected (Ahlquist, 2002; Ahlquist & Shuber, 2002). Therefore, the cost might be divided over multiple years.

### Substances Detected by Stool Tests

All three stool tests differ in the substances detected. The gFOBT detects the peroxidase activity of heme in blood and other peroxidases in stool (Cole, Young, Esterman, Cadd, & Morcom, 2003), while the iFOBT detects human hemoglobin’s intact globin protein (Levin et al., 2003). The stool DNA test is not blood-based; rather, this test detects DNA markers in stool from cells of premalignant adenomas and tumors (Helm et al., 2003).

### Stool Tests Available

The iFOBT and stool DNA tests are relatively new technology, while the gFOBT was first described in 1864, developed in 1967, and marketed since 1970. The convenience of point-of-care testing and the Clinical Laboratory Improvement Act of 1988 (CLIA88) waiver (Fleisher & Schoengold, 2003) has made gFOBT the most commonly used CRC screening test in Western countries (Nakama, Fattah, Zhang, Uehara, & Wang, 2000). Of

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### Table 1. (continued)

A Comparison of Three Noninvasive Stool Tests for Colorectal Cancer

<table>
<thead>
<tr>
<th>Test Interpretation Method</th>
<th>gFOBT</th>
<th>iFOBT</th>
<th>Stool DNA Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specimen Requirements</td>
<td>Pea-size amounts (x2) are collected with sticks from three consecutive stools (Fleisher &amp; Shoengold, 2003).</td>
<td>The brush provided dislodges blood from the surface of stool into the surrounding toilet bowl water. The water is placed on a test card (&quot;InSure,&quot; 2003).</td>
<td>The entire bowel movement is mailed in pre-paid packaging to LabCorp (&quot;PreGen-Plus fact,&quot; 2003).</td>
</tr>
<tr>
<td>Medication Restrictions</td>
<td>Some medications may result in GI blood loss (Fleisher &amp; Schoengold, 2003) so should be held for 7 days before stool collection (Cole et al., 2003).</td>
<td>Medications that cause gastric bleeding do not affect the results. This test will not detect blood that has passed through the upper GI tract because the globin protein will not be intact (&quot;InSure,&quot; 2003).</td>
<td>None (Ahlquist, 2002; Ahlquist &amp; Shuber, 2002; Helm et al., 2003).</td>
</tr>
<tr>
<td>Number of Specimens Collected</td>
<td>Six samples for three consecutive, spontaneously passed stools (Sharma et al., 2000).</td>
<td>Two samples from two successive bowel movements (&quot;InSure,&quot; 2003).</td>
<td>One entire bowel movement (30g minimum) (&quot;PreGen-Plus colorectal,&quot; 2003).</td>
</tr>
</tbody>
</table>

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(Deenadayalu & Rex, 2004; Levin et al., 2003). The stool DNA test currently is not covered by Medicare (“National,” 2003), but the ACS Colorectal Cancer Advisory Group did identify this test as a promising new technology (Smith et al., 2003). EXACT Sciences Corp. (Maynard, MA), manufacturers of the stool DNA test, is completing the required testing to facilitate future recommendation of this test by the ACS and Medicare reimbursement. Although not yet prescribed, the stool DNA test may have the advantage of a longer screening interval than the FOBT (Tagore et al., 2003) because both tumors and precursor adenomas can be detected (Ahlquist, 2002; Ahlquist & Shuber, 2002). Therefore, the cost might be divided over multiple years.
these, the Hemoccult II (Beckman Coulter, Inc., Fullerton, CA) is the most widely used (Tagore et al., 2003) and most extensively studied (Bleiberg, 2002; Crespi & Lisi, 2002). Beckman Coulter, Inc. introduced Homoccult ICT on August 15, 2005. The iFOBT is the most commonly used FOBT in Japan (Saito, 1996), but InSure (Enterix Inc., Falmouth, ME) only received U.S. Food and Drug Administration (FDA) clearance in February 2001 (“Enterix’s,” 2001). InSure has been marketed and distributed by Enterix and Quest Diagnostics since May 2003 (Enterix, 2003). The PreGen-Plus (EXACT Sciences Corp., Maynard, MA) is the only stool-based DNA CRC screening test available in the United States (B. Mitchell, personal communication, May 10, 2004), and is also newly marketed, available since August 14, 2003 (Barkley, 2003).

**Stool Collection and Test Development**

The gFOBT is the most convenient method because the visual interpretation of color change can be done in-office (Wong et al., 2003) and in less than 2 minutes as a point-of-care test (Fleisher & Schoengold, 2003). It requires six samples from three consecutive, spontaneously passed stools (Sharma et al., 2000). These samples are pea-size amounts (x2) collected with wooden sticks from three consecutive stools (Fleisher & Schoengold, 2003). The gFOBT has multiple dietary restrictions because peroxidases in some foods can result in false-positive results (Cole et al., 2003). A 72-hour dietary restriction is necessary before stool collection. No red meat (lamb, beef, liver), horseradish, radishes, lightly cooked or uncooked turnips, broccoli, cauliflower, cantaloupe (Cole et al., 2003), spinach (Crespi & Lisi, 2002) banana, tomato, or parsnips (Robinson, Pye, Thomas, Hardcastle, & Mangham, 1994) should be consumed. These false-positives can be reduced by a 3-day delay in test development, which allows for the degradation of food peroxidase activity (Fleisher & Schoengold, 2003). In excess, alcohol can cause false-positive results. Vitamin C-rich foods can result in false negatives (Beckman Coulter, Inc., 2002). Because medications such as corticosteroids, chemotherapeutics, aspirin, and other nonsteroidal anti-inflammatory drugs may result in gastrointestinal (GI) blood loss (Fleisher & Schoengold, 2003), they should be held for 7 days before stool collection (Cole et al., 2003).

The iFOBT does have several advantages over the gFOBT. The iFOBT requires only two samples from two successive bowel movements (“InSure,” 2003). Instead of using wooden sticks, the patient uses the long-handled brush provided to dislodge blood from the surface of stool into the surrounding toilet bowl water. The water is then placed on a test card (“InSure,” 2003) and mailed to a lab for a visual interpretation of color change (Levin et al., 2003). While lab development does delay interpretation of results, an advantage is a less subjective interpretation than at point-of-care (Wong et al., 2003). The iFOBT also does not require dietary or medication restrictions. It is specific for human hemoglobin, so peroxidases in foods do not affect the results (Levin et al., 2003). The lack of dietary restrictions makes this a more patient-friendly test than the gFOBT (Smith et al., 2003). Medications that cause gastric bleeding do not affect the results. The iFOBT will not detect blood that has passed though the upper GI tract because the globin protein will not be intact (“InSure,” 2003).

Specimen collection is entirely different for the stool DNA test. One entire bowel movement (30 g minimum) (“PreGen-Plus colorectal,” 2003) is mailed in pre-paid packaging to LabCorp (“PreGen-Plus fact,” 2003). The PreGen-Plus is actually a panel of 23 individual tests. In the LabCorp laboratory, the human DNA is extracted from the stool sample and analyzed for tumor markers (Ahlquist, 2002; Ahlquist & Shuber, 2002; Helm et al., 2003). The ordering physician receives the results in 2-3 weeks (“PreGen-Plus fact,” 2003). The specificity for DNA tumor markers eliminates the dietary and medication restrictions of the gFOBT (Ahlquist, 2002; Ahlquist & Shuber, 2002; Helm et al., 2003).

**Stool Test Specificities and Sensitivities**

Specificity and sensitivity are important factors that should be used by medical-surgical nurses to help patients choose a CRC screening test. A test with high specificity is negative in the absence of an adenomatous poly or cancer, and a test with high sensitivity is positive when an adenomatous poly or cancer is present (Ahlquist, 2002). Tests with low specificity are more likely to produce false positives and result in unnecessary, costly follow-up testing. These costs include time, patient anxiety, use of limited endoscopy resources, and money. Tests with low sensitivity are more likely to result in false negatives, or a missed diagnosis of an adenomatous poly or cancer. Early diagnosis and treatment are necessary for optimal survival rates (Jemal et al., 2005).

All three stool tests are highly specific for CRC. The greatest variation is in sensitivity for CRC, or the ability to not miss an adenomatous poly or cancer when
present. The gFOBT has a specificity for cancers of 96.8% to 98.9% and a wide range of reported sensitivities for cancers at 11% to 80.8% (“Medicare,” 2003). This blood-based test has a sensitivity for hemoglobin of 0.3 mg hemoglobin per gram of stool (Fleisher & Schoengold, 2003). The colon does have a small amount of normal blood loss, but 2 to 3 ml/day is considered the lower limit of GI tract pathology. Virtually all gFOBT will be positive with a blood loss of 10 ml/day (Beckman Coulter, 2002). Testing of three consecutive stools is important because tumors may bleed in small amounts, intermittently, or not at all (Ahlquist, 2002; Bleiberg, 2002; Crespi & Lisi, 2002; Fleisher & Schoengold, 2003; Helm et al., 2003; Levin et al., 2003). The gFOBT has a 30% false-negative rate (Helm et al., 2003), or the chance of a missed adenomatous polyp or cancer when present. A 3-5 minute wait between application of the sample and development allows the sample to penetrate the paper to lower the false-negative rate (Fleisher & Schoengold, 2003).

While a 30% false-negative rate for gFOBT may seem alarming, it is important to note colonoscopy, the “gold standard,” is not a perfect test either. Colonoscopy has been shown to have a 24% miss rate for adenomas in same day, back-to-back colonoscopies (Rex, Cutler et al., 1997). In another study, 5% of patients diagnosed with CRC had a negative colonoscopy in the previous 3 years (Rex, Rahmani et al., 1997). Yet, colonoscopy remains the best CRC screening test available.

The gFOBT has a 30% false-positive rate, which may be due to bleeding from the upper GI tract (van Ballegooijen et al., 2003), colonic angiodysplasias, or hemorrhoids (Ransohoff & Lang, 1996). A thick sample also may cause a false-positive gFOBT. As many as 50 people undergo colonoscopy due to a false-positive gFOBT for each CRC case diagnosed (Crespi & Lisi, 2002).

Compared to the gFOBT, the iFOBT has a similar specificity for cancers (86.2%-97.8%) and a higher sensitivity for cancers (62%-100%) (“Medicare,” 2003). The iFOBT’s sensitivity for hemoglobin is also much greater at 0.05 mg hemoglobin per gram of stool (“Fecal,” 2004). The increased sensitivity of the iFOBT makes intermittent tumor bleeding a less significant issue than with the gFOBT (Levin et al., 2003). An additional advantage is the iFOBT has fewer false positives than the gFOBT because the globin protein is denatured in the upper GI tract. The iFOBT therefore is specific for bleeding in the lower GI tract (“Final,” 2002; Levin et al., 2003).

The stool DNA test has the highest specificity for cancers (93%-100%), and sensitivities for cancers (71%-91%) and adenomas (55%-82%) (Helm et al., 2003). The stool DNA test does have false negatives, because tumors are genetically heterogenous and no DNA mutation is consistent among all colorectal tumors. For this reason, the panel of 23 individual tests targets multiple DNA alterations (Ahlquist & Shuber, 2002). The detection of stool DNA markers, which are released continuously, does provide a more reliable target than the intermittent bleeding from polyps or tumors (Ahlquist, 2002; Ahlquist & Shuber, 2002).

The stool DNA test may show false positives for CRC because DNA from any aerodigestive cancer (pancreatic, gastric, esophageal, and lung) can cause a positive test (Ahlquist, 2002). A great deal of research remains to be done on the stool DNA test, but it is hoped this test may be used eventually to screen for aerodigestive cancers. Large, multicenter studies are currently in progress to determine the performance of this test for this purpose (Ahlquist, 2002). So far, the sensitivities for aerodigestive cancers are comparable to those for CRC, and may be used to screen for them in the future (Ahlquist, 2000). However, it is not clear if screening for extra-colonic malignancies will be a proven advantage of the stool DNA test (Deenadayalu & Rex, 2004). It also is hoped the stool DNA test eventually may help differentiate which polyps may progress to CRC, allow selective removal of these polyps, and save resources (Ahlquist, 2002). The stool DNA test may help extend the 10-year interval between screening colonoscopies, or be an adjunct to once-in-a-lifetime screening colonoscopy (Tagore et al., 2003). The stool DNA test may be an acceptable option for patients who do not want to use the other screening methods (Deenadayalu & Rex, 2004).

The Digital Rectal Exam (DRE)

The challenge of patient compliance with CRC screening has prompted many physicians to use the in-office DRE gFOBT (Collins et al., 2005; Hawley, Vernon, Levin, & Vallejo, 2004; Nadel et al., 2005; Sharma et al., 2000). Tadikonda (“Digital,” 2001) proposes the DRE as one way to improve compliance. One study showed the DRE gFOBT does not increase false positives (“Testing,” 2000), while another study showed DRE gFOBT may be as effective as testing spontaneous-ly passed stools to detect CRC (Burke, Tadikonda, & Machicao, 2001; “Digital,” 2001). DRE gFOBT therefore may be better than no screening for noncompliant pa-
tients. However, DRE iFOBT specimen results are not as predictive of CRC as results from a spontaneously passed stool (Smith et al., 2004), so DRE iFOBT is not recommended. The stool DNA test has a 30 g minimum quantity, so a DRE quantity is insufficient.

Patient Compliance with Stool CRC Screening

The ACS guidelines recommend people over age 50 be screened for CRC, but about half of this group remains unscreened (Smith et al., 2004). The iFOBT has had a 30% increase in compliance over the gFOBT due to the better sampling method (Cole et al., 2003). Compliance with the stool DNA test has been described as “excellent” (Tagore et al., 2003). The stool DNA test also evokes increased confidence of physicians and patients due to fewer false positives (compared to FOBT), and may therefore improve compliance (Ahlquist & Shuber, 2002).

The ACS screening guidelines are for patients who are asymptomatic (Smith et al., 2005). Patients with symptoms, such as bleeding hemorrhoids, should not use either FOBT. The iFOBT is less sensitive for rectal cancers (Nakama et al., 1996). The stool DNA test is not recommended for patients with a known aerodigestive cancer (pancreatic, gastric, esophageal, or lung) because these patients may have a positive stool DNA test indiscernible from CRC (Ahlquist, 2002).

Morbidity and Mortality Reduction

Early detection of CRC enables a cure rate of over 90%, whereas diagnosis at the later stages allows a 5-year survival rate of only about 10% (Jemal et al., 2005). Compliance with the ACS CRC screening guidelines allows the early detection of CRC. Screening with the gFOBT reduces morbidity by 20% (Mandel et al., 2000) and mortality by 33% (Mandel et al., 1993). Screening with the iFOBT reduces mortality up to 60% (Saito, 2000). The stool DNA test might be used eventually to screen for aerodigestive cancers, which account for over half of all cancer deaths (Ahlquist, 2002).

Recommended Follow Up for Positive Stool Tests

Any positive stool test should lead to further evaluation (Deenadayalu & Rex, 2004; Fleisher & Schoengold, 2003). The preferred method of follow-up is a colonoscopy, which allows diagnosis and possibly treatment by polypectomy. A colonoscopy is generally a safe procedure but is accompanied by both a small risk of perforation and complications from intravenous sedation. Additionally, pelvic scarring may make intubation of the colon difficult, or co-morbidities may preclude sedation. For these reasons, a flexible sigmoidoscopy and double-contrast barium enema may be preferred (Ransohoff & Lang, 1997).

Conclusion

Each of the three stool tests for CRC screening has numerous advantages and disadvantages. Medical-surgical nurses should be knowledgeable about these three CRC screening tests to help patients decide which is right for them. Many Web resources are available for nurse and patient use (see Table 2). Medical-surgical nurses can have great impact on patient compliance with screening via patient education about CRC screening tests. Thompson et al. (2000) found nurse order entry an effective way to triple patient orders for the gFOBT. The ACS does not recommend one regimen over another (Smith et al., 2004); rather, the best CRC screening test for any patient is the one that the patient has available and will complete (Brooks, 2004).

<table>
<thead>
<tr>
<th>CRC Screening Test</th>
<th>Web sites</th>
</tr>
</thead>
</table>
| gFOBT             | http://www.beckman.com/products/RapidTestKits/hemoccult.asp  
|                    | http://www.beckman.com/customersupport/trainingeducation/pcdvideos.asp  
|                    | http://content.nejm.org/cgi/content/abstract/334/3/155 |
| iFOBT             | http://www.insuretest.com/  
|                    | http://www.insurefobt.com/kitrequest.html  
|                    | http://www.caonline.amcancersoc.org/cgi/reprint/53/1/44.pdf |
| Stool DNA test    | http://www.labcorp.com/services/hcp/colorectal_cancer/  
|                    | http://www.exactscience.com/consumers/faqs.html  
|                    | http://www.exactsciences.com/ |
References


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