Published in final edited form as:

Med Care. 2008 September ; 46(9 Suppl 1): S138–S146. doi:10.1097/MLR.0b013e31818192ef.

Implications of New Colorectal Cancer Screening Technologies for Primary Care Practice

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Abstract

Colorectal cancer (CRC) screening reduces the risk of CRC mortality but is currently not well utilized, with adherence only 50% in the eligible U.S. population and rates that lag behind those for breast and cervical cancer. The primary care physician has the pivotal role of facilitating patient adherence to CRC screening by informed choice of the screening tests, follow up of positive tests, and coordination of medical resources when diagnostic intervention is required. Consequently, the primary care setting is where significant improvements can be made in CRC screening adherence. This article provides a summary of the newer CRC screening technologies that can be used by primary care physicians in shared decision making with their patients.

There are now multiple CRC screening tests which vary in their ability to detect the different stages in the adenoma to carcinoma sequence. Current guidelines of the Multi-Society (Gastroenterology) Task Force (1997, 2003, 2006, 2008), the American Cancer Society (2001, 2003, 2007, 2008), and the United States Preventive Services Task Force (2002) recommend a menu of CRC screening options, including fecal occult blood tests (FOBT) (Hemoccult II, Hemoccult SENSA, fecal immunochemical tests (FIT)), double contrast barium enema (DCBE), flexible sigmoidoscopy with or without annual FOBT's, and colonoscopy. In this report, we assess the options of fecal immunochemical tests, colonoscopy, CT-colonography (CTC or virtual colonoscopy), and fecal DNA tests. The tests are discussed with respect to the evidence in support of their use and within the context of how they could be managed and implemented in primary care practice. Primary care physicians will want to understand the tradeoffs among accuracy, costs, and patient preferences for the current and emerging CRC tests.

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INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer death in the US, and yet this mortality burden can be largely prevented with screening. Primary care practitioners are in a unique position to facilitate CRC screening but face at least three challenges because of dynamically evolving CRC screening technologies: facilitating informed patient choice among the various possible options for screening; enabling patient follow-through with the screening process; and ensuring coordination and communication between the patient and the various physicians and healthcare organizations involved in screening and diagnostic follow-up. There are now multiple CRC screening tests which vary in their ability to detect the different stages in the adenoma to carcinoma sequence. The original guaiac based CRC test (Hemoccult II) was used to detect CRC at an early stage. Most of the newer tests have at least some capacity to detect the larger adenomas and thus reduce CRC incidence as well as mortality. In this article, we discuss four CRC screening tests representing different stages of intervention, degree of invasiveness, frequency of repeat testing, and level of acceptance by patients.

Guidelines of the Multi-Society (Gastroenterology) Task Force (1–4) the American Cancer Society (4–7), and the United States Preventive Services Task Force (USPSTF) (8) recommend a menu of CRC screening options. The new 2008 guidelines by the Multi-Society Task Force (MSTF) for individuals at average risk are shown in Table 1 (4). These guidelines classify the screening tests as those tests which detect adenomatous polyps and CRC (structural examination tests) and those which primarily detect CRC (fecal tests). These guidelines make an important distinction between the sensitivity achieved in a single test at one point in time (test sensitivity) and the sensitivity of a test used serially over time in a program of repeat screening (programmatic sensitivity). The new guidelines require test sensitivity of 50% or higher for detection of CRC for that test to be included in the menu of recommended tests. Screening intervals and colonoscopic surveillance for those with adenomas or CRC detected have also been specified. Repeat screening for those with negative results and surveillance for those with adenomas detected are essential components to a program of CRC screening. In 2002 the USPSTF (8) stated that there was *sufficient* evidence to recommend CRC screening for average risk individuals beginning at age 50 but *insufficient* evidence to recommend one test over the other. Updated recommendations from the USPSTF are expected in 2008.

FOBT is the only CRC screening approach demonstrated to be effective in randomized controlled trials. Depending on whether the tests were done biennially or annually, and whether they were rehydrated or not, FOBT was associated with a 15 to 33% reduction in CRC mortality (9–12), and a 17–20% reduction in CRC incidence (13). The Hemoccult II test, which was used for these 3 randomized controlled trials, has high specificity (98%) but lower one-time test sensitivity (40%). However when Hemoccult II is used in a program of annual screening, the overall sensitivity for CRC for the multiple period testing (program sensitivity) is higher. Hemoccult II test sensitivity for the larger adenomas (≥1.0 cm) is markedly lower than for CRC. Consequently, the CRC mortality reduction observed in these 3 randomized controlled trials was mainly due to the detection of early curable cancer rather than prevention of CRC. The recent MSTF guidelines no longer recommend the Hemoccult

II test for CRC screening, because of its lower per test sensitivity for CRC but do recommend the more sensitive Hemoccult SENSA guaiac based test.(4) Quality control is required in developing the guaiac slide. (14–16)

In this article, we assess the options of fecal immunochemical tests, colonoscopy, CTC-colonography (virtual colonoscopy), and stool DNA tests as tools to increase the impact and participation in CRC screening. These tests are discussed within the context of how they could be managed and implemented within primary care practice. Fecal immunochemical tests (FIT) and colonoscopy have previously been placed in the recommended strategies. However CTC and stool DNA are newly included in the MSTF guidelines with caveats as these tests continue to evolve. (4)

In setting its initial guidelines in 1997 (1) the MSTF noted that new tests could be considered for inclusion without evidence from a randomized controlled trial demonstrating a CRC mortality reduction if the newer test had comparable or better test performance (sensitivity and specificity) in detecting CRC or adenomas as currently recommended tests; was equally or more acceptable to patients; and had comparable or lower complication rates and costs.

A summary of sensitivity, specificity, and payer costs for the CRC screening tests is given in Table 2.

FECAL IMMUNOCHEMICAL TESTS (FIT)

Origin

Since the publication of the landmark studies for the guaiac-based fecal occult blood test (GT), newer tests for fecal occult blood have been approved for clinical use in the US. CRC and some of the larger adenomas have a tendency to bleed sporadically. The guaiac tests use the peroxidase activity of heme or hemoglobin as an indicator of occult blood. The Hemoccult SENSA test was developed as a qualitative test to detect lower levels of peroxidase activity than Hemoccult II and has higher sensitivity but lower specificity than the Hemoccult II test given that peroxidase activity is found in plants and non-human blood such as in red meat. The fecal immunochemical test (FIT) is based on detection of human globin. These tests were developed as a quantitative test for occult blood in the stool that did not require the 3-day dietary restrictions of the Hemoccult II test. There is evidence that FITs are more sensitive then standard GTs, such as Hemoccult II (17). There is also mounting evidence that FITs may have better sensitivity than Hemoccult SENSA (18, 19), with comparable specificity.

Evidence based results

The standard hemoglobin concentration in most studies of FITs has been 100 ng of hemoglobin per mL of blood. At this concentration, results have varied somewhat between settings, by the number of samples, and the gold standard used to determine true prevalence of cancer and advanced adenomas. All studies have evaluated one-time testing of the FIT test (test sensitivity). In a preventive health HMO population, Allison used 3 samples of the HemeSelect FIT and reported a sensitivity for cancer of 68.8% (17), using 2-year follow-up

for clinical cancer incidence as a gold standard for the presence of cancer; the specificity for cancer was 94.4%. In a large screening colonoscopy cohort from Japan, Morikawa reported a sensitivity of 65.8% and specificity of 95.5%, using a single application of the Magstream 1000 test (20). The highest FIT cancer sensitivity reported to date by Allison, was 81.8% with a specificity of 98.1%, using the 3 samples of FlexSure OBT (now called Hemoccult ICT), and a combination of flexible sigmoidoscopy evaluation for left sided CRCs and 2 years of clinical follow-up for distal CRCs (19).

An explicit evaluation of varying the numbers of samples, and the target concentration of hemoglobin was performed by Levi in a high risk, colonoscopy population (21). They suggested using a two-sample test with a detection threshold of 75 ng Hgb/mL stool for this group.

Three studies have directly compared the sensitive GT (Hemoccult SENSA) to a FIT, in a population large enough to obtain relatively precise point estimates of sensitivity and specificity (Table 3) (17–19). In the one study in which a standard GT (Hemoccult II) was used, both the sensitive GT and the FIT showed improved sensitivity (37.1% vs. 68.8% vs 79.4%), but with a much lower specificity for the sensitive GT (17).

At the current time, due to heterogeneity in the evidence, it is difficult to say that one FIT is clearly superior. Sensitivity and specificity point estimates have varied across studies due to differences in populations and the criterion standard used to determine true incidence of cancer.

Practice implications

FOBT, while not as sensitive for colorectal adenomas as colonoscopy, CT colonography or flexible sigmoidoscopy, offers the advantage of being non-invasive, and convenient for individuals. Tests can be sent through the mail directly to individuals; samples are collected in the privacy of their homes, and can be returned by mail to a central processing laboratory. Patient acceptance is apt to be higher with FITs, due to the need for only 1 or 2 samples rather than 3 for the guaiac based tests. No dietary or medication restrictions are needed, because these tests are specific for human hemoglobin, and are specific for colonic bleeding. Selected FITs offer the option of automated test reading, which may result in improved precision and reliability of the interpretation, and the possibility of reporting a quantitative result, with resultant trade-offs in sensitivity and specificity (21). Given that the guaiac based FOBT has been found to be effective in randomized controlled trials (RCTs) and is considered a proven method for CRC screening by the USPSTF, the newer FOBT’s such as the FIT’s with increased sensitivity and roughly the same specificity as the original guaiac based FOBT, even at higher cost, are an increasingly used option for CRC screening.

Some patients and providers will opt for invasive endoscopic or CT colonographic screening, but there will be a limit on the population screening rate based on patient acceptance and available capacity (22). To achieve the goal of population screening, a non-invasive, efficient and scalable option will be needed. In these regards, the FIT is a promising alternative to conventional GT (Hemoccult II) and a promising complement to

colonoscopy. However patients must be aware that a positive FOBT must be followed up with colonoscopy for evaluation.

COLONOSCOPY

Origins

Colonoscopy was first introduced in the 1970's as a method to visualize the entire colon. In 1973 Wolf and Shinya demonstrated the feasibility of colonoscopic polypectomy (23) which initiated using colonoscopy as both a diagnostic and therapeutic tool. The ability of colonoscopy to visualize (i.e., optically) and remove polyps greatly enhanced the feasibility of FOBT and sigmoidoscopy screening programs, where colonoscopy could be used to evaluate positive FOBT or sigmoidoscopy findings.

Technical Evolution

Fiberoptic colonoscopes were replaced by digital video-endoscopy which enhanced visual detection of polyps and provided a record of the reach to the cecum, post-polypectomy site, and cleanliness of the bowel. Technical improvements have facilitated polyp removal and maneuverability within the colon and rectum.

Evidence Based Results

The National Polyp Study (NPS) was designed to assess how frequently a patient with an initial adenoma removed should be re-evaluated, given that the adenoma was the precursor lesion for CRC (24). The NPS required all participants to have a high quality colonoscopy which reached the cecum, with good bowel preparation, and all polyps removed. Thirteen percent of the adenoma patients enrolled had a repeat baseline colonoscopy to ensure a high quality examination with removal of all polyps. In an analysis using historical controls, NPS found that adenoma polypectomy was associated with a reduction in CRC incidence of 76% compared to the general population and 90% compared to a polyp bearing population without polypectomy over an average six year period following initial polypectomy (25). Although the NPS was not a screening population and did not have a concurrent control group for the adenoma patients, the results of high adherence and highly significant reduction in CRC with polypectomy were considered promising evidence for the use of colonoscopy as a primary screening tool. Further indirect evidence for the usefulness of colonoscopy came from the RCTs of FOBT (9–11), each of which had used colonoscopy to evaluate positive FOBT results. Colonoscopy provided the opportunity to intervene early in the adenoma-carcinoma sequence and to prevent CRC and its sequelae of surgical and chemotherapy treatment by removing adenomas, the precursor lesion.

The yield of clinically important lesions from colonoscopic screening has now been evaluated in studies in Veterans Administration patients (26), military women (27), Eli Lilly employees and retirees (28), and Poland (29). The VA study found a high yield of adenomas (38%) and advanced adenomas (18%) in its VA cohort which was partially enriched by those with positive family history (26). However the other colonoscopy studies have had a lower yield of neoplastic findings (27–29). Colonoscopic screening is invasive, requires a rigorous bowel cleansing, and sedation (in the United States) and is associated with risks of

perforation and bleeding, especially from the polypectomy.(30) Risks as well as benefits need to be considered in using colonoscopy as the primary screening test. Given that it is generally conducted with sedation, a second person is needed to provide transportation after the procedure.

Practice implications

Colonoscopy can be used as the primary screening tool or as the diagnostic and therapeutic tool after a positive FOBT, flexible sigmoidoscopy, or CTC test. In the two step procedure, colonoscopy is used for a higher risk population where the benefit of colonoscopic polypectomy would be greater than the possible harm associated with perforation or bleeding. Levin (31) and Imperiale (32) have suggested mixed modality screening of flexible sigmoidoscopy or FOBT at earlier ages and colonoscopy screening for older ages to identify the higher risk persons from within the average risk population.

Colonoscopy as a screening and therapeutic tool continues to improve technologically. However, of particular importance is the emphasis on continuous quality improvement in performance as stated in the Multi Society Guidelines (33, 34). The gastroenterology societies are working to provide tools for self-evaluation of endoscopic performance as a means to ensure high quality colonoscopies (35).

CT Colonography

Origins

The key conceptual basis for ‘CT Colonography’ (CTC) also called ‘Virtual Colonoscopy’ or VC arose over a decade ago when it was recognized that thin-slice contiguous abdominal CT images could be reconstructed in software to simulate visualization of the lumen of the colon and create a ‘fly-through’ display presenting polyps as prominent irregularities. It took a dozen years for this approach, combined with other improvements, to reach maturity.

Technical evolution

Between 2000 and 2002, commercial multi-row detector CT scanners advanced from 4-row detector devices to 64-row assemblies, enabling high-speed imaging of the total abdomen within a single breath-hold, thus nearly eliminating motion artifacts that had bedeviled earlier efforts. Hardware and software innovations also made possible multi-planar displays and visually-compelling 3D dynamic simulations. A last critical contribution was the development of bowel prep procedures that optimized polyp visualization.

Evidence-based results

The public health implication of CTC would be its utilization as an efficient screening filter for optical colonoscopy. Ideally, CTC might efficiently deflect from optical colonoscopy consideration many in the average risk population who do not harbor significant pre-malignant adenomas. This would lower the known colonoscopy risks of sedation and perforation.

Given the field's rapid technical and practice evolution determining how ready this approach is for public health deployment requires careful consideration of recent evidence. Highest quality evidence is best provided by prospectively designed large cohort multi-institutional trials using advanced (>16 detector array) CT scanners with visualization software and oral contrast colonic preps. In well designed screening trials of asymptomatic subjects, the CTC polyp findings on each individual should be validated for each subject by proceeding sequentially to colonoscopy to confirm the presence or absence of polyps. CTC must convincingly demonstrate that it has both high sensitivity and high specificity to minimize the number of subjects proceeding unnecessarily to optical colonoscopy. Two such reports exist. One three-site, 1233 subject trial was published in 2003 (36) reporting CTC sensitivity of 94% for polyps > 1 cm in size (specificity was 96%). The other is a national 15-institution prospective trial (ACRIN 6664: National CT Colonography Trial) which accrued 2531 subjects reporting a 90% sensitivity per patient for ≥1 cm polyps and an 86% specificity (37). For polyps as small as 7 mm, the latter trial reported sensitivities and specificities of 84% and 87% respectively.

Practice implications

Additional questions raised by the advent of this technology are now being addressed in the literature. These include:

- Current MSTF guidelines state that all patients with one or more polyps ≥ 6 mm detected by CTC should be referred for colonoscopy(4). Although there is clear consensus that patients with larger polyps (≥ 10 mm) or with 3 or more polyps with the largest 6 to 9 mm in size should be referred to colonoscopy, the management for patients with 1 or 2 polyps of size 6–9 mm is not well established. Under continued discussion is whether polyps less than 6 mm in size require accurate detection and removal or can they be adequately addressed by continued observation by CTC and at what intervals (4). Some have asked this same question about polyps 6–9 mm.
- Is CTC radiation dosage significant? Although CT scanning conveys a small degree of radiation risk, the lifetime cancer risk for individuals older than 50 is arguably minimal for CTC (38). The question remains as to whether overall CTC procedures significantly contributes to patients' exposure to ionizing radiation.
- What is the professional capacity for conducting CTC screening? CTC is operator dependent for high quality examinations.
- What are the clinical consequences of CTC discovered extra-colonic findings (e.g.: abdominal aneurysms, unexplained renal masses, etc.)?
- Can CTC detect flat and depressed lesions and what is the clinical consequence of missing such lesions (39)?
- Can innovative CTC contrast techniques achieve a less demanding bowel preparation?

Responsible incorporation of CTC into practice should logically encourage a single bowel prep strategy with the assumption that about 10% of individuals would be polyp positive and should proceed to a same-day optical colonoscopy exam. This would require coordination of

resources. Since CTC necessitates advanced technology and a properly skilled observer, it will benefit from 1) professional standards assuring appropriate CT scanner technology, 2) integrated visualization software, 3) verified qualifications for part image practitioners, 4) CT image archiving and auditability, 5) structured clinical reporting, 6) transparent recording of the clinical consequences of extra-colonic findings, and 7) meticulous record-keeping process that justifies confidence in any practice sensitivity and specificity claims.

The new 2008 MSTF guidelines (4) include CTC as a CRC screening test option, even though they state that additional research is needed to establish practice parameters for surveillance and repeat screening. However, insurance coverage for CTC is currently limited.

FECAL DNA TEST

Origin

Fecal DNA testing represents a new non-invasive approach to CRC screening. The approach has been made possible by elucidation, over the last 2 decades, of the molecular ‘pathway’ or changes that occur as colon mucosa progresses from normal tissue to adenoma and to CRC (40–44). These changes provide ‘targets’ that an assay can be designed to detect. Simultaneous technological advances have allowed human DNA to be separated and purified from stool and to be amplified and analyzed (43, 45, 46).

An approach that measures DNA in stool has at least a theoretical advantage over an approach that measures bleeding, like FOBT. The discriminatory ability of FOBT testing depends on two features of biology: first, the degree to which neoplasms bleed; second, how much does that rate of bleeding exceed normal blood loss. To the extent that neoplasms do not bleed (or do not bleed more than ‘normal’), they cannot be ‘detected’ by any FOBT, no matter how ‘sensitive’ an assay may be made. Similarly, for fecal DNA testing the rate-limiting step is whether neoplasms have DNA changes that are shed into stool and can be measured, and whether those changes ‘exceed’ those of a normal person. The possible theoretical advantage of stool DNA testing is that, because cancer is a disease of multiple mutations, a stool DNA assay might be made ‘sensitive enough’ if the right markers can be discovered and measured. These considerations are theoretical; how they actually play out quantitatively, for either approach, must be determined by empirical evidence from clinical research studies.

Technical evolution

While preliminary results have been reported for several methods of assessing alterations in stool DNA (47–53), only one major prospective blinded study has been done in a screening setting (54). The first-generation DNA assay that was tested included multiple mutations of the *APC, K-ras*, and *p53* genes that are in the ‘pathway’ described by Vogelstein and others (40–44), along with BAT-26, a marker of mismatch-repair-pathway tumors.

Evidenced-based results

Based on promising preliminary results (47, 55), a multi-center prospective study was planned so that patients received colonoscopy after stools had been collected. The assay consisted of 22 specific gene mutations and a 'DNA integrity assay' (DIA) (54) that measures the size of DNA fragments that are shed in stool; in those with CRC, the DNA in stool may be longer than in those who are normal. The panel consisting of these multiple markers was considered positive if any marker was positive. The first-generation panel had a 52% sensitivity for CRC and specificity of 94% (54). In contrast, guaiac-based FOBT (Hemoccult II) completed at home with office-based testing had a sensitivity of 13% and specificity of 95%. While these results represented an advance over FOBT, they were not as strong as in preliminary studies and were considered not sufficient to support a practical commercially available test (56).

A second-generation assay used improved DNA stabilization techniques (particularly important for the DNA integrity assay) and included a new promoter methylation marker. While methylation occurs in CRC (57–59), its role in carcinogenesis is not known. A study of a 'second-generation' assay compared stools from known CRC subjects to normals and showed that using just two markers resulted in an "optimal combination of vimentin methylation plus DIA... [with] 87.5% sensitivity and 82% specificity" (60). Further clinical confirmation of these second generation results is necessary in a general population asymptomatic screening population.

Practice implications

In the future, the potential usefulness of stool DNA testing may be affected by several developments. First, sensitivity and specificity might be further improved by combining (or replacing) current markers with other markers. However the current commercial cost (January 2008) is $800, although group practices or insurers may negotiate substantial discounts, and represents a significant financial barrier for some patients.

No version of the currently available stool DNA test has received FDA approval. FDA has determined that the only commercially available DNA-stool test, PreGen-Plus™, requires premarket review. Although CMS was asked to provide a national coverage determination for the stool DNA test, they will not consider expanding Medicare's CRC screening coverage to include the stool DNA test until a commercially available stool DNA test has been cleared or approved by the FDA. CMS also requested a decision analysis of the stool-DNA test based on microsimulation modeling of the currently available studies and with an estimated cost of $350 per test. The modeling group concluded that only if significant improvements in test characteristics or relative adherence with DNA stool testing compared with available options can be demonstrated, will stool DNA testing at the current costs of $350 be cost effective(61). The interval for retesting and the significance of false positive stool DNA tests are not currently known.

The MSTF now includes the stool DNA test in its recommended screening strategies but notes that stool DNA is an evolving test and cautions that new iterations of these tests must be carefully evaluated for acceptable test performance. This guideline group also noted that

there is insufficient evidence to establish a repeat screening interval for those with a negative stool DNA test.

DISCUSSION

Two main approaches to CRC screening are currently prevalent in the U.S. One is to use colonoscopy as the primary screening tool. The other is to use a less invasive initial screening test to triage those at higher risk for CRC or adenomas to colonoscopy. Candidates for this initial test include the stool based tests (guaiac-based Hemoccult SENSA, the new fecal immunochemical tests, or the fecal DNA test) or structural examinations (flexible sigmoidoscopy or CTC colonography).

Physician recommendation for CRC screening has an important impact on increasing adherence but also requires time and commitment from the primary care practitioners to explain the benefits and risks associated with CRC screening (62). With a decentralized system of health care delivery in the United States, primary care providers are central to implementing CRC screening guidelines. This is a challenging role because unlike screening for other cancers, there are multiple tests options which require explanation and discussion as to which test strategy to select for each patient. Schwartz (63) suggests that too much choice can lead to inaction or even bad decisions and recommends far fewer choices in medical decisions in which the patient is to have a major role. Also, CRC screening requires far more effort on the patient's part than for other preventive screening services. These challenges may contribute to CRC screening rates that are markedly lower than for breast or cervical cancer (64).

The challenge of implementing CRC screening in the average risk population in primary care practice could be managed with the use of the evidence based New Model of Primary Care Delivery (65) which uses 1. a team approach with responsibility for screening tasks shared among members of the practice to deliver the message for CRC screening and the logistics for screening; 2. information systems for identifying eligible patients and reminding them when screening is due; 3. involving patients in shared decision making about their preferences for screening; 4. information systems to target patients at increased risk because of family history or social disadvantage; 5. reimbursement for services outside the traditional provider-patient encounter, such as telephone or e-mail contacts to enhance screening adherence; and 6. provider training opportunities in communication, cultural competence, and use of information programs to facilitate CRC screening. The goal of the primary care physician is to educate and facilitate CRC screening by recommending CRC screening; discussing available screening options; performing the CRC screening test or referring to an appropriate specialist, and ensuring that all positive tests are evaluated with colonoscopy.

The currently available CRC screening tests will continue to improve with technology advances. Primary care physicians will need to be vigilant about keeping current with technology improvements and updated guidelines in this rapidly evolving field.

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TABLE 1

Colorectal Cancer Screening and Surveillance Strategies Recommended by American Cancer Society Colorectal Cancer Advisory Group, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology Colon Cancer Committee (MSTF).(4)*

Screening and Surveillance Strategies for Average Risk Patients	
Age to Begin Screening	50 years old‡
Recommended Screening Strategies	Tests which primarily detect colorectal cancer† • Hemoccult SENSA every year‡ • Immuunochemical Fecal Occult Blood Test (FIT) every year‡ • Stool-DNA test with unspecified interval Tests which detect adenomatous polyps and CRC • Double contrast barium enema every 5 years¶ • Flexible Sigmoidoscopy- every 5 years • Flexible Sigmoidoscopy (5-year) Plus FOBT** • CT Colonography - every 5 years • Colonoscopy – every 10 years
If negative CRC screening test then	Repeat per recommended interval (ie 1 year for FOBT, 5 year for flex sig or barium enema, 10 year for colonoscopy)
If positive CRC screening test then	Follow-up with Colonoscopy
If negative colonoscopy after positive CRC screening test then	Colonoscopy in 10 years
If colonoscopy detects hyperplastic polyps but no adenomas then	Repeat colonoscopy in 10 years (ie assume normal) • Small rectal hyperplastic polyps Intensive follow-up • Hyperplastic polyposis syndrome
If colonoscopy detects one or more adenomas then surveillance colonoscopy	Colonoscopy findings and next surveillance colonoscopy • 1 or 2 adenomas all <1.0 cm – Colonoscopy at 5–10 years • 3–10 adenomas or ≥ 1 cm – Colonoscopy at 3 years • > 10 adenomas at 1 colonoscopy– shorter interval for surveillance (< 3 years) and consider possibility of familial syndrome
If colorectal cancer detected	
If CRC detected, then surgical resection to remove the cancer and high quality perioperative clearing	Patients require high-quality perioperative clearing • Non-obstructing tumors by Preoperative colonoscopy • Obstructive tumors by CT-Colonography or DCBE
Colonoscopy at one year following resection	Patients with curative resection should have colonoscopy one year after the resection. This colonoscopy is in addition to the perioperative colonoscopy
If normal colonoscopy at one year	Next colonoscopy at 3 years If 3-year colonoscopy is normal, then next colonoscopy at 5 years
If findings at one year colonoscopy	Surveillance intervals can be shortened if there is evidence of HNPCC or if adenoma findings warrant earlier colonoscopy

Screening and Surveillance Strategies for Average Risk Patients	
If low-anterior resection of rectal cancer	Periodic examination of the rectum to detect local recurrence at 3 to 6 month intervals for the first 2 to 3 years

[*] United States Preventive Services Task Force recommendations are expected in 2008. See MSTF guidelines for more detailed explanation for screening and surveillance guidelines as presented here (4)

[+] American College of Gastroenterology advocates colonoscopy as the preferred screening strategy and to begin CRC screening at age 45 for African Americans (66) at www.acg.gi.org/physicians/clinicalupdates.asp#guidelines

[†] An annual Hemoccult II test had been included in previous guidelines but is not included in the current guidelines because its one time test sensitivity for CRC is less than 50%.

Neither digital rectal examination (DRE) nor the testing of a single stool specimen obtained during DRE is recommended as an adequate screening strategy for colorectal cancer.

[‡] Hemoccult SENSA test is based on a two samples from each of 3 separate bowel movements. FIT is based on 2 to 3 separate bowel movements with two samples per movement depending on the manufacturer.

[¶] Barium enema was part of the original guidelines with repeat testing at 5 years but its use as a primary screening tool has diminished because of its low sensitivity for detection of large adenomas.(67)

[**] For the combined strategy of Flex Sig and FOBT, the FOBT is done first and if negative then the flex sig is done.

TABLE 2

Sensitivity, Specificity, and Payer Costs for CRC screening tests.

Test	Sensitivity* by adenoma size or CRC (%)				Specificity (%)	Payer (CMS) costs(61)
	≤5 mm	6–9 mm	≥10 mm	CRC		
FOBT Hemoccult II+	*2.0*	*5.0*	12.0	40.0	98.0	$4.54
FOBT Hemoccult SENSA	*7.5*	*12.4*	24.0	70.0	92.5	$4.54
Immunochemical FOBT	*5.0*	*10.1*	22.0	70.0	95.0	$22.22
DNA stool test (v1.1)§	*4.0*	*12.0*	43.0	70.0	96.0	No CMS cost; insurance $350–$800
CTC Colonography**	11.0	85.0	90.0	90.0	89.0	No CMS cost; insurance approximately that of colonoscopy++
Colonoscopy	75.0	85.0	95.0	95.0	90.0††	$498/$649 ¶
Sigmoidoscopy‡	75.0	85.0	95.0	95.0	92.0††	$161/$348¶

*Sensitivity is provided per individual patient for stool-based tests and per lesion for endoscopy tests. We make the assumption that the FOBT tests cannot detect adenomas of size less than 1.0 cm and that detection of such adenomas would be due primarily to a false positive findings (denoted by italics for these size lesions)

+Hemoccult II is no longer recommended by the combined Multi-Society Task Force, ACS, and ACR guidelines (4).

†Immunochemical stool tests (FIT) currently available in the United States include 1) Hemoccult ICT from Beckman Coulter with Point of Care Test (3 samples) 2) InSure from Quest manually read in a central reference laboratory, 2 sample test and 3) OC Auto Micro 80, from Polymedco, with automated platform test, read in a central lab, 1 sample test. HemeSelect is expected to be available in the near future in the US.

§Results from a study of archived stool sample; a replication in a clinical study had specificity estimate of 89% (60)

**News report September 28, 2007 (37); publication of these results is expected

++D Vanness, personal communication

††The lack of specificity with colonoscopy and sigmoidoscopy screening reflects the detection of non-adenomatous lesions. With colonoscopy these non-adenomatous lesions are removed and therefore induce polypectomy costs. With sigmoidoscopy the presence of non-adenomatous lesions induces biopsy costs (in case of sigmoidoscopy with biopsy) or results in referral for diagnostic colonoscopy (in case of sigmoidoscopy without biopsy).

‡Test characteristics for sigmoidoscopy only apply to the distal colon and rectum.

¶with and without polypectomy; polypectomy has additional pathology review charges

TABLE 3

Studies Directly Comparing FITs to Guaiac Fecal Occult Blood Tests* (Hemoccult SENSA)

Study	FIT Test	Sensitivity for Cancer		Specificity	
		FIT	GT	FIT	GT
Allison (1996)(17)	Heme Select+	68.8%	79.4%	94.4%	86.7%
Smith (2006)(18)	InSure	87.5%	54.2%	96.6%	97.5%
Allison (2007)(19)	FlexSure OBT†	81.8%	64.3%	96.9%	90.1%

*GT: Hemoccult SENSA in all studies.

+HemeSelect is an earlier version of at FIT called Magstream 1000 HP which is widely used in Japan, Australia, and Europe and soon to be available in the US.

†FlexSure OBT has been renamed Hemoccult ICT by Beckman-Coulter.