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Colorectal Cancer Screening: What's the Evidence?

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Colorectal cancer screening saves lives. This fact is clear and unequivocal.

Yet it could be argued that no other preventive health measure raises as many questions or causes as much confusion for patients and for their doctors.

"Why do we have all these different tests? Just tell me which one is the best!"

"Aren't stool blood tests worthless? Shouldn't everybody just get a colonoscopy?"

"What about this 'virtual colonoscopy' I've been reading about?"

"Why can't the so-called 'experts' get their acts together and tell us what to do!"

The intent of this article is to cut through the confusion and misinformation surrounding colorectal cancer screening and to give primary care physicians the facts to help their patients make informed decisions and choose the test that's right for them.

—The Editor

Overview

Each year in the United States, more than 140,000 new cases of colorectal cancer are diagnosed, and more than 50,000 people die from this disease.[1] (*Note: Colon and rectal cancer are distinct diseases, particularly with regard to treatment and outcomes of advanced stage disease. Screening methods used for the diseases, however, are identical and salutary effects attainable through screening are similar. They thus will be addressed in a combined fashion in this article.*) Moreover, many who survive the disease must first face surgery, chemotherapy, and radiation treatments, resulting in significant morbidity and disruption not only of their lives, but of the lives of co-workers, friends, and family members. But there is unrealized potential; much of this death and suffering is avoidable simply by applying available knowledge and technology. Screening for colorectal cancer has been shown in randomized controlled trials to decrease death rates from the disease, and in some cases to actually prevent can-

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cer from occurring.[2,3] Unfortunately, this life-saving measure is, at present, markedly underutilized.

The unparalleled potential of screening to impact both the incidence and mortality of colorectal cancer is made possible by the pathogenesis and natural history of the disease.

Most colorectal cancers develop from polyps. Colorectal polyps occur primarily in two forms—*hyperplastic* and *adenomatous* (adenomas). It is widely accepted that hyperplastic polyps have limited potential for malignant transformation and that, therefore, the vast majority of colon cancers begin as adenomas.[4] The time for transition from benign polyp to cancer is highly variable, but in most instances appears to take anywhere from seven to 15 years.[5] In addition, adenoma size is closely associated with malignant potential; adenomas significantly smaller than 5 mm in diameter are believed to carry a low risk of malignant progression, those between 5 and 9 mm an intermediate risk, and adenomas greater than 10 mm to have the highest risk. Other features associated with an increased likelihood of malignant transformation include the presence of villous histology, or high-grade dysplasia in the adenoma.[4] Adenomas demonstrating any of these high risk features (greater than 10 mm, villous histology or high-grade dysplasia) commonly are grouped in studies of colorectal cancer under the general category of advanced adenomas.

These elements (an easily identified precursor lesion, coupled with a prolonged benign-to-malignant transformation period) make colorectal cancer ideally suited for intervention via screening. Treatment of the precursor lesion (i.e., adenoma removal) can prevent cancer. And even if cancer is present at the time of screening, individuals whose colon cancer is diagnosed and treated in its earliest stage (stage I) have a five year survival rate exceeding 90%. This is in sharp contrast to the 10% survival rates found in stage IV disease.[6] Unfortunately, only about one-third of colorectal cancers in the United States are diagnosed at this earliest, most treatable stage.[6] In addition to the clinical efficacy of colorectal cancer screening, it also has been shown to be cost-effective in a number of different analyses.[7,8].

Incidence and mortality rates from colorectal cancer have been declining since 1998. It is believed that this decline is a result of a combination of factors, including the growing use of colon endoscopy for both diagnostic and screening purposes.[9] However, considering the potential for cancer prevention and the above noted survival advantage of early detection, overall screening rates for colorectal cancer remain disturbingly low. Data from the Centers for Disease Control and Prevention's National Health Interview Survey show that in the year 2000, only 39.4% of age-eligible adults were up-to-date with screening based on widely accepted recommendations.[10] This contrasts with breast and cervical cancer screening rates of 70% and 82%, respectively. Indeed, rates of screening for prostate cancer (for which controversy exists and clear efficacy data are lacking) exceed documented colorectal cancer screening rates.

A number of reasons for the relatively low rates of colorectal cancer screening have been documented. These include barriers related to patient knowledge and beliefs, public policy and payer issues, and factors related to the organization and delivery of care.[11,12] However, the most important single factor associated with patient screening for cancer, including colorectal cancer, may be physician encouragement.[13-15] And while primary care physicians report high levels of awareness regarding the importance of screening their patients, studies show that a significant proportion of PCPs are not screening all of their at-risk patients, and that when screening is recommended it frequently is initiated at non-standard ages and recommended on a too-frequent basis.[16]

Risk Factors and Protective Measures

The efficacy of screening for any disease requires identification of a clearly defined at-risk population. There are a number of recognized risk factors for colorectal cancer, allowing for both identification of the at-risk population and stratification of this group into different risk categories. (*See Table 1.*)

A number of conditions (i.e., personal or family history of adenomas or colorectal cancer, personal history of inflammatory bowel disease of significant duration and severity, and gene-based familial syndromes including HNPCC and FAP) confer a significantly higher risk of developing colorectal cancer. Because of this increased risk, individuals with these conditions require individualized screening regimens, often starting at an early age (i.e., 20s to 40s).[17]

Fortunately, these conditions account for, at most, one-quarter of all cases of colorectal cancer diagnosed in the United States. The vast majority of colorectal cancers occur in individuals whose primary identified risk factor is simply being age 50 or older. In fact, more than 90% of new cases and deaths occur after the age of 50. For this reason, colorectal cancer screening should

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Table 1. Colorectal Cancer Risk Groups

AVERAGE RISK

Screen by any available options at standard recommended intervals

- Age ≥ 50 years;

INCREASED RISK

Screen by any available options at standard recommended intervals

- Race/ethnicity (African Americans, Ashkenazi Jewish descent)
- Diet high in animal fats, red meat, processed meats
- Obesity
- Tobacco use

HIGH RISK

Screen with colonoscopy; interval varies based on risk factor

- Personal history of colorectal cancer or adenomatous polyp
- Personal history of inflammatory bowel disease (Crohn's disease, ulcerative colitis after 8 years of pancolitis or 12-15 years after the onset of left-sided colitis)
- Family history of colorectal cancer or adenomatous polyp
- Familial syndromes (hereditary non-polyposis colon cancer, familial adenomatous polyposis)

be initiated for everyone beginning at age 50 (unless screening has been initiated before this age due to the presence of one of the risk conditions described in the preceding paragraph). Due to space limitations, this article will focus on screening recommendations for the average risk population.

In addition to fixed risk factors (i.e., age, family history, and personal medical history), there are a number of modifiable factors that have been shown to increase an individual's risk of developing colorectal cancer. These include dietary factors (especially consumption of processed meats and red meat), tobacco use, obesity, and excessive alcohol use.[18-20]

Factors also have been identified that offer protection against the development of colorectal cancer. These include lifestyle elements such as physical activity and a diet low in red meats and fat.[21,22] A variety of medications (such as aspirin and other non-steroidal anti-inflammatory drugs, exogenous estrogen, and HMG-CoA reductase inhibitors) have demonstrated a modest protective effect in clinical studies.[23-25] However, by far the most powerful intervention available today to decrease incidence and death from colorectal cancer is screening.

Screening recommendations for colorectal cancer first were issued by the American Cancer Society in 1980.[26] Since that time, a number of major medical organizations have recognized the value of screening. During the early and mid-1990s, the guidelines published by various organizations lacked consistency; however, subsequent updates and revisions of these various guidelines now have resulted in recommendations from a number of organizations which, aside from a few points of emphasis, have little substantive difference.[17,27,28] (*See Table 2.*)

Unlike Pap smears for cervical cancer screening, there is no unequivocal best test for colorectal cancer screening. For this reason, guidelines from all major organizations list a variety of screening options. There is evidence supporting the potential value of each of these recommended methods, and colorectal cancer screening using these testing approaches has been determined to be cost effective in a number of analyses.[7,8] The remainder of this article will focus on currently recommended screening options for colorectal cancer, discussing the evidence in support of their inclusion as well as the limitations of each method. New and emerging technologies for colorectal cancer screening also will be addressed.

Recommended Screening Methods

Fecal Occult Blood Tests. Fecal occult blood tests (FOBTs) are designed to detect hidden blood in the stool. This test is an effective method to screen for colorectal cancer because cancers (and, to a lesser extent, adenomas) often bleed.

FOBTs are of primarily two varieties—*guaiac* or *immunochemical*. Guaiac-based tests are by far the most commonly used in the United States, and are the type that were used in all of the colorectal mortality studies that will be discussed in this section. Sold under a variety of brand names (Hemoccult, Hemoccult II, Hemoccult Sensa, and others), this method utilizes a guiaic impregnated card onto which stool is smeared. The card is later activated by the addition of a few drops of a developer containing hydrogen peroxidase. If blood is present in the specimen, a reaction involving the heme portion of the hemoglobin molecule results in a color change. Test sensitivity may be enhanced by rehydration of stool specimens prior to application of the developing agent, however this increased sensitivity comes at the cost of increased false positive tests.[29]

Guaiac tests are not specific for colonic bleeding, and will be positive if bleeding occurs from any portion of the gastrointestinal (GI) tract. In addition to rehydration, a number of substances can cause false positive results, including ingested blood (i.e., from dietary red meats), foods with peroxidase-like activity (i.e., horseradish, cruciferous vegetables, and certain fruits), and medications (such as therapeutic iron, aspirin, and other non-steroidal anti-inflammatory drugs). False negative tests may be induced by patient ingestion of vitamin C in fruits or from vitamin supplements.[29]

An alternative to guaiac-based testing is provided by immunochemical stool tests. Immunochemical tests utilize antibodies directed against human globin, and because of this different target and mechanism of action, have the potential to circumvent many of the problems encountered with guaiac stool tests. Because they are specific for human globin, there is little danger of false positive results related to meat or vegetable intake. In addition, the globin portion of the the hemoglobin molecule is rapidly broken down during passage through the upper GI tract, thus globin from upper GI bleeding is not detected by immuno-

Table 2. Screening Guidelines of Major Medical Organizations

ORGANIZATION	YEAR REVIEWED	RECOMMENDATION
U.S. Multisociety Taskforce on Colorectal Cancer	2003	• FOBT • FSIG • FSIG + FOBT • Colonoscopy • DCBE
U.S. Preventive Services Task Force	2002	"A" recommendation good to fair evidence for: • FOBT • FSIG • FSIG + FOBT • Colonoscopy
American Cancer Society	2001	• FOBT • FSIG • FSIG + FOBT • Colonoscopy • DCBE
American College of Gastroenterology	2000	• Colonoscopy • FSIG and FOBT • DCBE (in select instances)
Institute for Clinical Systems Improvement	2000	• FSIG • FOBT • FSIG + FOBT • TCE
American Society of Colon and Rectal Surgeons	1999	• FSIG and FOBT • Colonoscopy • DCBE + FSIG

Key:
FOBT = fecal occult blood test; FSIG = flexible sigmoidoscopy; DCBE = double contrast barium enema; TCE = total colonic exam (i.e., BE or colonoscopy)

chemical tests. Therefore, a positive finding on an immunochemical stool blood test is more specific for a colonic bleeding source than a similar finding with guaiac-based testing. A growing body of evidence supports the ability of immunochemical tests to detect polyps and cancers.[30-32] At the present time their use by U.S. physicians remains very limited.

In the face of the rising use and availability of new technologies (particularly gastrointestinal endoscopy), some primary care physicians have expressed skepticism regarding the continued utility of FOBT as a screening modality. When considering this question, it is important to recognize that FOBTs are the only form of colorectal cancer screening for which randomized controlled trial data (often considered the gold standard) are available. Three published studies have documented decreases in colorectal cancer mortality ranging from 18% to 33% as a result of FOBT screening programs.[2,33,34] Although there is evidence supporting the use of each of the other currently recommended colorectal cancer screening methods, data on these tests come primarily from case control studies or are inferential in nature (i.e., come from studies demonstrating the validity of the technology on a non-screening basis).

Another point to keep in mind with regard to fecal blood testing (and indeed for all forms of screening) is the importance of a screening program. In nearly all instances, disease screening attains its primary value not from the one-time use of a screening test but from the repeated use of testing over time. Nowhere is this more evident than when considering FOBT. In optimal circumstances, a correctly performed fecal blood test has a sensitivity level ranging from 40-50% for cancers that are present at the time of testing, and only 20-35% for detection of adenomas.[29,35,36] These sensitivity levels appear unacceptably low unless one keeps in mind that no organization advocates the use of one-time fecal occult blood testing for colorectal cancer screening. All organizations that recommend FOBT stress the importance of annual testing. Taking advantage of the relatively slow progression period from adenoma to cancer, testing on an annual basis significantly improves the likelihood of lesion detection over time. Thus, the program sensitivity (based on years of annual testing) exceeds the one-time test sensitivity by a large margin.[37]

Despite its proven value in reducing colorectal cancer incidence and mortality, there are challenges to the integrity of FOBT screening as it currently is applied in clinical practice. To achieve the test and program sensitivity levels discussed above, it is imperative that fecal occult blood testing be performed correctly. Patients should be given three specimen collection cards to take home, and instructed to collect a small amount of stool from three different bowel movements, preferably on different days. This approach helps to address the intermittent pattern of bleeding demonstrated by many cancers and adenomas. Failure to collect and analyze multiple specimens markedly limits the effectiveness of FOBT. This was clearly illustrated by a recent study that compared the sensitivity of occult blood testing of a single sample of stool obtained during a digital rectal exam (DRE) with the findings from three specimens collected at home by the same patients. All patients subsequently underwent colonoscopy. The results of this study were startling. In patients in whom cancer or significant adenomas were found on colonoscopy, the sensitivity of occult blood testing of the single stool sample obtained at DRE was only

4.9%. This was in sharp contrast to the detection rate of 23.9% for all lesions (and 44% for cancers) of the recommended three-card take-home method of fecal occult blood testing.[36]

Not surprisingly, all of the previously discussed studies that demonstrated a mortality benefit from fecal occult blood testing were done using the three-card, take-home approach. But research tells us that FOBT screening in the United States is not always performed in this prescribed manner. Investigators from the National Cancer Institute and the Centers for Disease Control and Prevention recently surveyed nearly 1200 primary care physicians across the United States regarding their practices for colorectal cancer screening and follow-up.[38] Approximately one-third of respondents reported using occult blood testing of stool obtained during a rectal exam as their primary method of screening for colorectal cancer.

In addition to the high level of misuse of the in-office FOBT, this survey also uncovered concerns related to the follow-up of positive FOBTs. The guidelines of all major organizations recommend that all individuals found to have a positive FOBT undergo visualization of their entire colon (usually via colonoscopy). In spite of this clear and unequivocal guidance, 29.4% of responding physicians reported repeating FOBT as their initial approach to a positive stool blood test. Furthermore, those who order additional studies often recommend sigmoidoscopy rather than a total colonic examination to evaluate abnormal findings.

In the same paper, these investigators reported the results of a survey of more than 12,000 patients age 50 and older regarding the colorectal cancer practices of their treating physicians. Patient responses corroborated the findings of the physician report, with one-third of those who reported having a positive FOBT stating either that their doctor followed this positive only with a repeat FOBT, or that they had no diagnostic work-up whatsoever for this positive finding.

Screening tests alone cannot modify the course of any disease; decreases in morbidity and mortality are attained only when screen-detected abnormalities are assessed and managed appropriately. Based on the findings of these studies, it is clear that there is substantial room for improvement in both the utilization of FOBTs and the follow-up of abnormal findings from these tests.

Flexible Sigmoidoscopy. Flexible sigmoidoscopy is performed by inserting an endoscope equipped with a video system into the anus and directly viewing the lumen of the rectum and distal colon. In addition to directly visualizing the colon wall, lesions can be biopsied during the procedure. Flexible sigmoidoscopy is performed as an outpatient procedure, and is commonly done in a physician office. Preparation is simple, usually consisting of one or two enemas on the day of the procedure. Many primary care providers learn to perform this test during their residency training, and nearly one-quarter of flexible sigmoidoscopies performed in the United States are done by internists and family physicians.[39]

Due to the limited length of sigmoidoscopes (35-60 cm) only the distal one-third of the colon can be viewed during the procedure. If a suspicious lesion is found during sigmoidoscopy the entire colon lumen should be evaluated via colonoscopy. Studies suggest that more than 60% of cancers and significant adenomas either are located within reach of the sigmoidoscopy or have concurrent lesions in the distal colon that should trigger colonoscopic follow-up.[35,40] However, a recent report has raised the question as to whether there may be gender differences in the distribution of cancers and suspicious adenomas.[41] In this study of 1463 asymptomatic women who underwent colonoscopy, the investigators determined that if flexible sigmoidoscopy alone had been performed, significant pathology would have been missed in 64% of these women.

A case control study using data collected in the Kaiser Permanente health system suggested that sigmoidoscopy screening decreased colorectal cancer deaths by 59% for cancers in the rectum and distal colon. This study, however, found no improvement in mortality related to cancers in the more proximal sections of the colon that were out of reach of the sigmoidoscope.[42] Other published case control studies support this finding.[43,44] The National Cancer Institute is sponsoring a screening trial involving the use of flexible sigmoidoscopy,[45] and a similar study is underway in the United Kingdom.[46] Results are expected from both within the next few years.

Flexible sigmoidoscopy has a low rate of serious complications.[47,48] The most common complications of the procedure are patient discomfort, cramping, and bloating (related to insufflation of air during the procedure). Post-procedure bleeding may occur. Perforation of the bowel is, fortunately, a rare complication. A large health maintenance organization recently reported complications associated with flexible sigmoidoscopy in their colorectal cancer screening program.[48] At the time of the report more than 100,000 flexible sigmoidoscopies had been performed in this program, and 24 persons had been hospitalized for a GI complication (only two involving colon perforation). Other complications included two episodes of diverticulitis requiring surgery, two cases of bleeding requiring transfusion, and one episode of unexplained colitis.

The guidelines of most organizations that address periodicity recommend that screening flexible sigmoidoscopy be performed every five years. As already mentioned, any abnormal finding should be evaluated further with colonoscopy.

Flexible Sigmoidoscopy Combined with Fecal Occult Blood Testing. Due to the limited reach of the sigmoidoscope,\ and data suggesting the absence of a mortality benefit for proximal cancers with the procedure, an advantage has been postulated for the combination of flexible sigmoidoscopy supplemented by annual fecal occult blood testing. In theory, sigmoidoscopy will be more accurate than fecal occult blood testing alone in detecting cancers and adenomas in the rectum and distal colon, while the addition of annual fecal occult blood testing to the screening regimen will provide an opportunity to detect lesions that occur proximal to the reach of the scope. Data from one nonrandomized trial lend credence to the conceptual benefit of combining these screening methods.[49]

Colonoscopy. Like flexible sigmoidoscopy, colonoscopy is performed by inserting a flexible, fiberoptic scope into the anus

and visualizing the rectal and colon walls. The procedure requires more extensive patient preparation than sigmoidoscopy, usually involving 1-2 days of a low bulk or liquid diet, as well as cathartics. The primary difference in the two procedures is the length of the scope—a standard colonoscope is approximately three feet long—and the associated extent of colonic visualization. While flexible sigmoidoscopy will, at most, reach the splenic flexure (and often falls short of this target), a successful colonoscopy will view the entirety of the colon, ending with intubation of the cecum. Lesions found during colonoscopy can be biopsied or, in many instances, completely removed through the scope. In most cases, patients receive light anesthesia during the procedure. If no abnormalities are detected during a screening colonoscopy, the patient does not need repeat colorectal screening for 10 years.

Because of the increased complexity of colonoscopy, training for the procedure is much more extensive and time consuming than that required for flexible sigmoidoscopy. This increased complexity is accompanied by a higher risk of serious complications. For these reasons the vast majority of colonoscopies in the United States are performed by specialists, primarily gastroenterologists and surgeons.

There are no randomized controlled trial data demonstrating the efficacy of colonoscopy as a screening method for colorectal cancer. The ability of colonoscopy to decrease colorectal cancer incidence and mortality first was documented by the National Polyp Study.[50] This project was not a study of colonoscopy in a screening population, but was designed to confirm the benefit of colonoscopic polypectomy and post-polypectomy surveillance. This study found a reduction in the incidence of colorectal cancer of up to 90% with polypectomy intervention. In addition, it is widely accepted that the decreases in incidence and mortality seen in the fecal occult blood trials were due, in large part, to colonoscopic follow-up of positives. Due largely to the findings of these studies, colonoscopy is recommended for follow-up of abnormalities detected by any of the other colorectal cancer screening methods, as well as for on-going colorectal surveillance.

The direct visualization of the entire colon, the combined diagnostic and therapeutic capabilities, and the 10-year screening interval have led to the perception of colonoscopy as the gold standard approach to colorectal cancer screening. However, it often is not appreciated by physicians and patients that the sensitivity of colonoscopy is good, but not perfect. A number of trials have shown that even experienced colonoscopists fail to detect up to 10% of significant lesions.[51,52] In addition, colonoscopy is significantly more expensive (on a one-time basis) than other recommended screening methods.

Colonoscopy also has a significantly higher complication rate than that of other recommended colorectal cancer screening approaches. Complications may be confined to the colon (i.e., bleeding, infection, perforation), or may involve other systems (myocardial infarction, stroke). In even the most experienced hands, colon perforations or other serious complications occur in approximately 1 per 1000 to 1 per 3000 procedures.[53-55]

Keeping in mind that screening occurs, by definition, in asymptomatic individuals who are not suspected to have disease, the association of serious (and at times life-threatening) complications with colonoscopy is an important factor hindering colonoscopy from designation as the primary mode of colorectal cancer screening. The relatively high cost of the procedure and the absence of randomized controlled trial data in screening populations also play a role in the decision-making by guideline-issuing organizations. Colonoscopic capacity and access issues also must be taken into account. A recent survey by investigators at the Centers for Disease Control and Prevention suggests that sufficient capacity exists in the United States today to provide screening (using a mixed strategy combining primary FOBT, flexible sigmoidoscopy, and colonoscopy) and appropriate colonoscopic follow-up to all who currently are unscreened.[39] However, anecdotal reports by physicians and the general public speak to long appointment delays,[56,57] and other researchers have postulated capacity limits and a shortage of colonoscopists.[58]

If a capacity shortage exists, it clearly is exacerbated by inappropriate application of available colonoscopy resources. As was mentioned previously, colonoscopy is the recommended method for follow-up of abnormal screening studies, as well as for post-cancer resection and post-polypectomy surveillance. Guidelines for colonoscopic surveillance have been published by a number of organizations, and there are variations in recommended surveillance intervals for some conditions. Evidence suggests, however, that a significant proportion of surveillance colonoscopies are performed on individuals who do not require surveillance (i.e., following removal of small hyperplastic polyps) and, in those for whom surveillance is warranted, often are done more frequently than is recommended by any of the available guidelines.[59] Overuse of a limited (and relative expensive) resource places additional strain on an already challenged system. To address this concern, the American Cancer Society and the U.S. Multi-Society Taskforce (an organization representing the American College of Physicians and major GI organizations) have partnered in an effort to develop a single set of evidence-based guidelines that will be approved and promoted by all participating organizations.[60] Such consensus among specialty organizations should serve as a positive first step in decreasing inappropriate surveillance practices.

Double Contrast Barium Enema (DCBE). The DCBE is another option mentioned by a number of the existing colorectal cancer screening guidelines. DCBE allows examination of the entire colon and detection of lumen and wall abnormalities. The procedure consists of instilling a barium solution into the rectum through an anal tube, followed by insufflation of the colon with air. The patient then is rotated on the examining table and radiographic images are acquired in a number of positions.

Evidence for DCBE as a screening tool is limited. No studies have documented a decrease in colorectal cancer incidence or mortality with the use of screening barium enema. A number of studies have evaluated the accuracy of barium enema in diagnosing polyps or cancer.[61,62] Recent studies of DCBE demonstrated polyp detection rates of 53% for adenomas between 6 and 9 mm,

and 48% for lesions of 1 cm or greater.[61,63] The sensitivity of DCBE for cancer may be as high as 85%.[64] Based on available evidence, guidelines recommend that screening barium enema be repeated every five to 10 years.

Although many radiologists continue to view the DCBE as a useful method to screen for colorectal cancer, primary care physicians lack enthusiasm for the test. A recent survey by NCI investigators found that while 75% of surveyed radiologist believed DCBE to be "very effective" for screening, only 33% of primary care physicians shared this view.[65] In the same study radiologists were asked about the volume of DCBE in their practice. While 86% reported performing one or more of the procedures during a typical month, only one-quarter of the radiologists averaged 11 or more. Eighty-five percent of responding radiologists reported that their DCBE volume is either static or declining. In fact, if data from the Medicare population is at all reflective of population trends, the proportion of screening through DCBE is miniscule. While Medicare was billed for more than 3 million colonoscopies and 1.7 million FOBTs in 2002, the program paid for fewer than 200,000 barium enemas.[57]

Emerging Technologies

While all of the screening methods discussed in the preceding sections have evidence to support their value, none can be viewed as perfect, either in terms of test performance or patient acceptance. Indeed, there is evidence that the unpleasant characteristics of these tests (handling stool, enemas, tubes inserted into the rectum) and the perception by the public that these tests are painful and embarrassing contribute to the low rates of screening seen today.[66] A great deal of energy and effort are being applied to identifying new screening approaches that may be more attractive to the public than current options, and have similar or improved sensitivity and specificity.

Two such tests have advanced beyond the investigational stage and are being actively promoted to the public as alternatives to traditional screening methods. Readers are cautioned that while all of the screening methods discussed in the preceding portions of this paper are recommended as colorectal cancer screening options by a number of major medical organizations, the technologies addressed below have not yet achieved such endorsement.

Stool Screening for DNA Mutations. Advances in technology have allowed science to enter a new age of gene- and molecular-based diagnosis and treatment. A number of DNA mutations have been found in diseased tissue, including in adenomas and cancers of the colon and rectum. Recent improvements in collection and DNA magnification techniques now allow such altered DNA to be recognized not only from tissue sampling, but from DNA contained in exfoliated colonic cells in the stool.

In theory, DNA should be an excellent marker of colorectal disease. Unlike bleeding from cancers or adenomas that occurs intermittently, DNA is excreted continuously (albeit in small amounts). Early studies of stool DNA found it to be resistant to degradation as it passes through the GI tract and stable in the stool while awaiting analysis.[67] A number of DNA mutations have been identified, and the combination of certain mutations is highly suggestive of the presence of adenomas or colorectal cancer. Because altered DNA also is found in adenomas, screening with this approach can contribute to cancer prevention. One possible additional benefit of DNA stool screening relates to the prevalence of aerodigestive cancers. In addition to colorectal cancer, this category includes cancers of the lung, esophagus, stomach, pancreas, and other sites along the aerodigestive tract, which together account for more than half of all malignant deaths.[1] Each of these cancers excretes cells (and therefore DNA) into the GI tract. Once the unique patterns of DNA alteration for each of these is elucidated, stool screening could assist in early detection and intervention for this full range of cancers.

There is one published randomized controlled trial of stool DNA screening for colorectal cancer in an average risk population.[68] In this study, more than 4400 individuals underwent standard fecal occult blood testing, fecal DNA stool testing, and colonoscopy. In this study, DNA screening detected 51.6% of cancers found on subsequent colonoscopy, and 18.2% of advanced neoplasia. These values were significantly better than the sensitivities reported for stool hemoccult tests done in this study.

Recent reports appear to confirm the relatively low sensitivity of DNA testing for advanced adenomas, and raise questions about the sensitivity of this technology for cancer detection. In one study, fecal DNA was evaluated as a possible surveillance tool in patients with a history of prior adenoma removal. Stool was collected for DNA analysis prior to surveillance colonoscopy. No cancers were detected in the study; however, 60% of individuals had at least one adenoma. Sensitivity of fecal DNA testing for the presence of any adenoma was only 11%, and the technology detected 18% of advanced adenomas in this high-risk population.[69]

Researchers participating in a multicenter colorectal cancer screening study recently reported preliminary findings from their ongoing study.[70] An analysis of data from the trial's first 2500 participants found that the detection rate for all significant lesions (adenomas and cancers combined) was 20%. However, contrary to the 51.6% cancer detection rate reported in the earlier screening trial, in this study stool DNA screening detected lesions in only eight of the 23 patients with colonoscopy-proven cancer or high-grade neoplasia (35%). Standard fecal occult blood testing was slightly superior to DNA testing in this study, identifying nine of these lesions (39%).

While the potential value of stool DNA testing as a screening method for colorectal cancer is clear, there remain a number of questions and concerns. There currently are no studies or data that allow an evidence-based assessment of the frequency with which the test should be performed. This is a particularly important factor with regard to DNA stool screening; the test currently costs several hundred dollars,[71] as compared to $6 to $40 for fecal occult blood testing.[72] In addition, while a number of mutations have been shown to be associated with colorectal adenomas and cancers, the optimal combination of markers has not yet been determined. Stool specimens in the first screening trial discussed above used a fecal DNA panel consisting of 21 mutations, and it was this panel that was used in the initial commercial ver-

sion of the test. This panel has since been revised, and a study utilizing the new panel is under way.[69] Questions also have arisen regarding marker stability. Adenoma detection based on one of the markers in the original panel (long DNA) has been shown to fall to 0% for stools analyzed more than 35 hours after defecation.[70] If test panel and sensitivity issues are worked out, specimen collection also may pose a barrier to widespread adoption. Because of the relatively small amount of DNA extractable from stool specimens, the patient must collect an entire bowel movement for shipment to the laboratory.

Fecal DNA analysis has been evaluated by both the American Cancer Society and the U.S. Multisociety Task Force on Colorectal Cancer for potential inclusion in the colorectal cancer screening guidelines of each organization. Both groups viewed the technology as promising, but decided that the current level of evidence is not yet sufficient to support its adoption as a screening measure.[27,73]

Computed Tomographic Colonography (Virtual Colonoscopy). Computed tomographic colonography (also known as CT colonography or virtual colonoscopy) is a radiographic technique in which thin-slice CT images are acquired and, with the use of specialized computer software, are reconstructed into two-dimensional and three-dimensional images. Advanced software utilizing "pathfinding" technology (used commonly in video games) allows immediate cross-sectional 3-D reconstructions to be displayed on a computer terminal in interactive "fly through" views that simulate the appearance of the colon lumen seen during a traditional optical colonoscopy (thus the label virtual colonoscopy).

CT colonography offers the potential advantage of examining the entire colon in a non-invasive manner. Results from early studies of the technology in high-risk populations found this technology to have high sensitivity for cancers and large adenomas.[74,75]

Three recent studies of CT colonography in average-risk screening populations reported widely divergent findings.

By far the most impressive results of CT colonography screening have been reported by Pickhardt and colleagues.[52] In a study involving CT colonography of more than 1200 asymptomatic patients, these investigators found detection rates of approximately 90% for adenomatous polyps 6 mm or larger, essentially equal to the performance rates of optical colonoscopy in the same patients. CT colonography even detected two cancers that were missed on the first colonoscopy. These results, however, have not been replicated. Indeed, other researchers have found much lower rates of polyp and cancer detection. Rockey et al[76] compared CT colonography with both DCBE and optical colonoscopy. While CT colonography was clearly superior to DCBE, its accuracy for polyps 6-9 mm in size (51%) and greater than 10 mm (59%) was far short of that seen with colonoscopy (99% and 98%, respectively). Other investigators have found similar performance differences and colonoscopic superiority.[77]

A recent meta-analysis reviewed findings from 33 studies of CT colonography and attempted to explain the inconsistencies seen in these reports.[78] The researchers found that the sensitivity for polyps varied significantly across these studies, but improved with polyp size. On average, sensitivity for polyp detection was 48% for lesions smaller than 6 mm, 70% for 6-9 mm, and 85% for those larger than 9 mm. The heterogeneity in findings was judged to be due to a wide array of factors: patient characteristics (average-risk vs. high-risk study population); scanner characteristics (single-detector vs. multi-detector scanner, slice thickness); performance and interpretation technical issues (2-dimensional vs. 3-dimensional images for primary interpretation). Other elements that were not evaluated in this analysis but may contribute to the variation seen in these studies include limitations in technology and technique as well as the expertise of the radiologists reading the scans.

In addition to the inconsistencies in test performance described above, there are a number of other issues associated with the use of CT colonography that have contributed to slow the widespread uptake of the technology. One such issue relates to the experience of the patient undergoing the procedure. CT colonography often is promoted as allowing patients to avoid the perceived discomforts associated with optical colonoscopy, however this is a somewhat disingenuous argument. Studies have determined that most patients undergoing traditional colonoscopy have few complaints about the test itself, due in large part to the fact that the vast majority of patients are anesthetized. Complaints regarding colonoscopy relate primarily to the dietary restrictions and the cathartics used to prepare for the procedure. While there is hope that technology eventually may allow a prepless procedure, at the present time CT colonography usually requires a preparation similar to that used for colonoscopy. In published reports, patients who have undergone both CT colonography and conventional colonoscopy usually express minimal preference for one procedure over the other.[77,79]

Another factor to keep in mind when considering CT colonography is the fact that any significant abnormality seen on a CT exam must be assessed with colonoscopy. Abnormalities that definitely require colonoscopic follow-up (i.e. polyps greater than 10 mm in size) are identified in anywhere from 4% to 17% of patients in published trials. In addition to the increased costs associated with this second procedure, most non-research settings do not provide colonoscopy on the same day as the CT colonography, meaning that patients must return for the colonoscopy at a later date and undergo a second preparation prior to the procedure.

The need for colonoscopic follow-up also brings up the challenge of deciding what is a "significant" polyp. As discussed in the introductory section of this paper, polyps smaller than 5 mm are believed to have a very low likelihood of malignant progression. However, when these lesions are seen during a colonscopy they usually are removed. Because of this practice, there are limited data to support development of an evidence-based surveillance strategy for the follow-up of smaller polyps that are not removed. Some radiologists and gastroenterologists have recommended that small lesions seen on CT colonography safely can be ignored, thereby limiting the number of follow-up colonoscopies required.[80] However, there is no current agreement

among radiologists or gastroenterologists regarding this recommendation. Without such expert consensus, it seems unlikely that primary care physicians or patients will be comfortable simply leaving small polyps in place. As might be expected, the prevalence of lesions 5 mm or larger is much greater than the prevalence of lesions 10 mm or larger, and at this size threshold, the proportion of patients that would be referred for colonoscopy is quite substantial (possibly as high as 50%).[74]

One final complication encountered with CT colonography is the issue of extracolonic findings. While the focus of scans performed for these studies is on the colon, other intra-abdominal and pelvic organs routinely are visualized. Up to one-quarter of patients undergoing CT colonoscopy will be found to have abnormalities in one or more extracolonic sites.[81,82] Many of these abnormalities are of minimal significance; however, a number of these will require additional evaluation. This evaluation may consist simply of additional radiologic studies but may entail more invasive tests, including biopsy or surgical intervention. As with the small polyp, there are currently no clear guidelines or recommendations regarding which of these extracolonic lesions need addressing and which safely can be ignored.

No organization currently includes CT colonography among its recommended colorectal cancer screening measures. For now, this technology should be considered an exciting emerging tool that shows considerable promise but has not yet demonstrated consistent comparable performance or superiority to conventional, recommended screening methods in average-risk populations

Final Thoughts

As was stated in the introduction, the goal of this article is to clarify current recommendations regarding colorectal cancer screening. At this point, it should be clear that clarify is not synonymous with simplify. Colorectal cancer screening remains a complex topic, particularly for patients. For this and other reasons it is imperative that primary care physicians provide their patients with sound guidance regarding their screening options. The importance of physician encouragement in motivating patients to be screened for cancer cannot be overemphasized. Study after study has shown that physician endorsement is a key factor (possibly the determining factor) in whether patients are screened for cancer.

Based on available data, it appears that physicians recognize the importance of screening their patients for colorectal cancer, and most believe they are doing a good job in this realm. There appears to be a disconnect, however, between physician perception and the available data on screening. Surveys of primary care providers indicate that they believe 75% or more of their average-risk patients are screened for colorectal cancer.[16,83,84] Conversely, national data collected from patients consistently indicate much lower screening rates, and specify a lack of provider recommendation as a major cause of these low rates.[85]

Patients and their physicians often are focused on addressing acute or chronic illness during office visits. Scheduling well-patient visits specifically for addressing preventive health issues has been associated with increased rates of cancer screening.[86,87] So, too, have the incorporation of patient and physician reminders and other office interventions that involve nurses and other staff in educating and preparing patients for screening.[88,89] It also is imperative that physicians (or delegated staff) solicit a thorough patient and family history to assure that the individual is not at elevated risk of developing colorectal cancer and thus in need of earlier and/or more aggressive screening.[17]

Table 3. Recommended Colorectal Cancer Screening Options for Average Risk Individuals

TEST	INTERVAL
Flexible sigmoidoscopy	Every 5 years
Fecal occult blood test (FOBT)	Annually
FOBT and flexible sigmoidoscopy	FOBT annually and flexible sigmoidoscopy every 5 years
Colonoscopy	Every 10 years
Double contrast barium enema	Every 5 years

In addition to the overwhelming medical evidence supporting screening, a variety of other factors are at work that have the potential to dramatically improve screening rates. National public awareness campaigns by the American Cancer Society and the Centers for Disease Control and Prevention, as well as media events like the nationally televised colonoscopy of "Today Show" host Katie Couric have brought the disease to the attention of the public. Medicare added colorectal cancer screening as a covered benefit in 1999, and in 2001 expanded coverage to the full range of options, including screening colonoscopy. Many private insurers also pay for some or all screening options, and the National Committee for Quality Assurance has begun collecting data on colorectal cancer screening from thousands of health plans across the country; they will report this data annually as part of health plans' Health Employer Data and Information Set (HEDIS) scores.

All primary care physicians should be discussing the benefits of colorectal cancer screening with all of their patients older than age 50, and helping these patients to decide which of the currently recommended screening methods is best for them. (*See Table 3.*) Obviously, patient preference should be the key element in guiding this decision, but additional factors such as local availability of various testing methods and insurance coverage also may need to be considered. Remember, current evidence indicates that the best test for colorectal cancer is the one that the patient will take and can get; not screening is no longer an option.

Additional information and resources for physicians and patients are available from the American Cancer Society (www.cancer.org/colonmd), National Colorectal Cancer Roundtable (www.nccrt.org), Centers for Disease Control and Prevention (www.cdc.gov/cancer/colorctl/index.htm), and the National Cancer Institute (www.nci.nih.gov/cancertopics/types/colon-and-rectal).

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Physician CME Questions

58. Which of the following is a risk factor for colorectal cancer?
    A. Diet high in red meat
    B. Family history of colorectal polyps
    C. Tobacco use
    D. Physical inactivity
    E. All of the above

59. Which type or feature of colorectal polyps is *not* associated with increased malignant potential?
    A. Villous histology
    B. Hyperplastic polyp
    C. Size greater than 10 mm
    D. High-grade dysplasia

60. Screening for colorectal cancer should be initiated at which of the following ages in average-risk individuals?
    A. 40
    B. 45
    C. 50
    D. 60

61. Which of the following is *not* currently recommended by major medical organizations as a screening method for colorectal cancer?
    A. Fecal occult blood testing (FOBT)
    B. Flexible sigmoidoscopy (FSIG)
    C. Colonoscopy
    D. CT colonography (virtual colonoscopy)
    E. Barium enema (BE)

62. Fecal occult blood testing of a stool sample obtained during an office rectal exam is an effective method of screening for colorectal cancer.
    A. True
    B. False

63. Colonoscopy has been proven in randomized controlled trials to be the single best method to screen patients for colorectal cancer.
    A. True
    B. False

64. A positive fecal occult blood test always should be followed up with:
    A. repeat fecal occult blood testing to make sure the first was not a false positive.
    B. flexible sigmoidoscopy.
    C. CT colonography (virtual colonoscopy).
    D. colonoscopy.

CME Answer Key

58. E; 59. B; 60. C; 61. D; 62. B; 63. B; 64. D

In Future Issues:

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Primary Care Reports

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To help physicians:

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• describe the pros and cons of new testing procedures.