



J.J. Mahany, Jr. *Late Evening Mt. McKinley*, 2002. Photograph. Denali National Park, Alaska.

Advances in colorectal screening have led to the development of clinical practice guidelines to recommend appropriate screening techniques based on individual risk.

Current and Evolving Strategies for Colorectal Cancer Screening

James Helm, MD, PhD, Junsung Choi, MD, Rebecca Sutphen, MD, James S. Barthel, MD, Terrance L. Albrecht, PhD, and Thomas N. Chirikos, PhD

Background: *Colorectal cancer is a major cause of cancer mortality and morbidity. Screening can potentially prevent most colorectal cancers by detection and removal of precursor adenomas.*

Methods: *The literature and clinical practice guidelines are reviewed, with an emphasis on advances of the last 10 years and evolving screening methods.*

Results: *Colonoscopy has come to be used for screening in persons at average risk for colorectal cancer because of the comparative ineffectiveness of other methods, although these methods continue to be recommended. Virtual colonoscopy and fecal DNA testing are emerging technologies with promise to be more effective than fecal occult blood testing or sigmoidoscopy in selecting those persons who should undergo colonoscopy. Next to age, family history is the most common risk factor for colorectal cancer and one that warrants more aggressive screening and, in some instances, genetic counseling and testing. Hereditary nonpolyposis colorectal cancer accounts for as many as 1 in 20 colorectal cancers, but to take advantage of recent advances in genetic testing for this disorder, a high level of clinical suspicion must be maintained.*

Conclusions: *If we are to reduce mortality and morbidity from colorectal cancer, practicing clinicians need to be aware of current and evolving strategies for colorectal screening, and assertively recommend the appropriate strategy to their patients.*

From the Gastrointestinal Tumor (JH, JSB), Radiology (JC), Cancer Control (RS, TNC), and Medical Interaction Research Group (TLA) Programs at the H. Lee Moffitt Cancer Center & Research Institute, and the Departments of Interdisciplinary Oncology, Medicine, Epidemiology, and Radiology at the University of South Florida, Tampa, Florida.

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Address reprint requests to James Helm, MD, PhD, Gastrointestinal Tumor Program, H. Lee Moffitt Cancer Center & Research Institute, 12902 Magnolia Drive, Tampa, FL 33612. E-mail: helmj@hoffitt.usf.edu

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Introduction

Colorectal cancer is the third most commonly diagnosed cancer in both men and women, with nearly 150,000 new cases expected in 2003, and the second most common cause of death from cancer, with more than 55,000 deaths annually in the United States.¹ Significant morbidity results from colorectal cancer and its treatment by surgical resection, colostomy, radiation therapy, and chemotherapy.

Colorectal cancer screening has been shown to save lives by detection of cancer at an early asymptomatic stage with a better prognosis.^{2,5} The 5-year survival rate from colorectal cancer is 80% to 90% with local disease confined to the bowel wall, 40% to 60% with regional disease, and less than 5% with distant metastasis.⁵ Although detection at an early stage can save lives, prevention of colorectal cancer by screening has a far greater impact on mortality, morbidity, and the costs of cancer care. Screening potentially can prevent the great majority of colorectal cancers by detection and removal of the benign but potentially premalignant adenomatous polyps that are believed to be the precursors of most cancers.^{6,7} Hyperplastic polyps are of no significance because they are not premalignant, and their presence in the rectosigmoid colon is not predictive of adenomas or cancer in the more proximal colon.

Screening is the identification of individuals who are more likely to have unrecognized disease from among the apparently healthy, so as to select those who should undergo the more invasive and expensive but definitive diagnostic procedure. Fecal occult blood testing is a classic example of a screening procedure. The finding of occult blood in the stool is used to identify those who are more likely to have colorectal cancer, thereby selecting those who should undergo colonoscopy, the definitive diagnostic test. Many organizations and professional societies have published clinical practice guidelines recommending screening practices for colorectal cancer.⁸⁻¹¹ These recommendations for screening usually are based on the individual risk for colorectal cancer.

Screening Individuals at Average Risk

Individuals at average risk for colorectal cancer have no known risk factors other than age. Screening is advocated for those 50 years of age and older because the incidence of colorectal cancer begins to rise between 40 to 50 years of age.⁹ Since at least 75% of colorectal cancers occur in individuals at average risk,^{12,13} screening in this large group has the potential to substantially reduce the overall incidence and mortality from colorectal cancer.

Clinical practice guidelines for colorectal screening in those at average risk differ in specific details; however, the essentials are to recommend annual fecal occult blood testing, flexible sigmoidoscopy every 5 years, or both, in those 50 years of age and older. Colonoscopy at 10-year intervals is recommended as well, although the evidence for its effectiveness is less direct. Double-contrast barium enema is an accepted alternative for those in whom a complete colonoscopy cannot be done, although in practice it is seldom used for screening.

Benefits and Shortcomings of Recommended Methods for Screening

Fecal Occult Blood Testing: The strength of fecal occult blood testing lies in three randomized, controlled trials that offer convincing evidence that screening for occult blood in the stool saves lives.^{2,4} The major shortcomings of fecal occult blood testing lie in its ineffectiveness relative to other methods of screening (discussed elsewhere in this review) and the high false-positive rates.

A single screening for colorectal cancer consists of testing for occult blood in two specimens taken from each of three stools. The true sensitivity of a single fecal occult blood screening for detection of colorectal cancer is not easily determined from a clinical trial because individuals who test negative do not undergo further evaluation to establish whether the test was a true-negative result. Estimates of sensitivity biased in this way claim detection of as many as 92% of cancers by a single screen.^{4,14} However, more conservative estimates suggest that a single screening for fecal occult blood may detect as little as 30% of cancers.^{15,16} Although the intent of fecal occult blood testing is to detect cancers at an earlier stage with a better prognosis, screening for 10 years increases the proportion of early-stage cancers by no more than 10%.^{2,4} Furthermore, population-based, randomized, controlled trials have shown that fecal occult blood testing for 10 years reduces colorectal cancer mortality in the population by only 15% to 18%, with 60% of the population participating in screening.^{2,3} Such a participation rate is difficult to achieve in clinical practice.

With the exception of larger ones, benign adenomatous polyps would not be expected to bleed, and thus the great majority should not be detected by fecal occult blood testing. Evidence from one randomized, controlled clinical trial of fecal occult blood testing suggests that cancer can nevertheless be prevented by incidental removal of small precursor adenomas found as the result of a false-positive test.¹⁷ Approximately 30% of those undergoing screening tested false-positive for

colorectal cancer during the first 10 years of this trial. Although this trial did not show a reduction in the incidence of colorectal cancer during the initial 10 years of screening, an extended 18-year follow-up showed a late decrease in cancer incidence that may be attributed to incidental removal of adenomas early in the trial. Removal of small precursor adenomas early in the trial could be expected to prevent the cancers that would otherwise arise from these precursor adenomas many years later if they had not been detected and removed.

The major determinant of the cost of screening for occult blood is the number of participants who test positive and require diagnostic evaluation by colonoscopy.¹⁸ About 5% of those undergoing screening for 10 years will test positive for occult blood, but in 90% of these individuals the test will be a false-positive, leading to unnecessary and expensive diagnostic testing.^{2,3} If stool specimens are rehydrated before testing for occult blood in an attempt to increase test sensitivity, as was the case in one trial, the number testing positive over 10 years rises dramatically to 30% of those undergoing screening, but with no real improvement in cancer detection rate.⁴

Sigmoidoscopy: The best evidence that screening sigmoidoscopy is effective in saving lives comes from a high-quality, internally validated case-control study of rigid sigmoidoscopy.⁶ Internal validation refers to the fact that the protective effects demonstrated within reach of the sigmoidoscope were not observed in the colon beyond the reach of the instrument in the same participants. Specifically, the risk of death from cancer within reach of the 30-cm sigmoidoscope was reduced by approximately 60% among those individuals who had undergone sigmoidoscopy, whereas sigmoidoscopy was not protective against death from cancer arising beyond the reach of the instrument. This type of study is strong evidence that the protective effect of sigmoidoscopy is real. These findings are supported by two other case-control studies, one of which found that sigmoidoscopy was associated with an 80% reduction in mortality from rectosigmoid cancer, while the other reported a 60% decrease in cancer incidence.^{19,20}

The major shortcoming of flexible sigmoidoscopy is that it can detect no more than approximately 50% of cancers and polyps at best since no more than half of the colon is examined. Far less than half the colon is often examined due to examiner inexperience, inadequate preparation of the lower colon, and patient intolerance. Many primary care providers are not sufficiently experienced or trained to do sigmoidoscopy well, while a gastroenterologist's time is usually spent more productively in doing other procedures. Neither

group is reimbursed sufficiently to make it worth the practitioner's time.

Colonoscopy: Colonoscopy is recommended for screening even though the supporting evidence for its effectiveness in decreasing the incidence of colorectal cancer is not as strong as that for fecal occult blood testing. This recommendation arises largely from the observation that colonoscopy has the potential not only to detect all lesions, but also to remove the adenomas that are considered to be precursors of cancer. Evidence for the effectiveness of colonoscopy comes from two sources: a case-control study showing a 40% to 50% decrease in the incidence of colorectal cancer in those who have had colonoscopy¹⁹ and an uncontrolled observational study that found the incidence of colorectal cancer in patients who had colonoscopy to be 75% to 90% less than in historical controls.⁷ The use of historical controls, however, may overestimate cancer prevention. The previously cited studies of the effectiveness of screening sigmoidoscopy offer further evidence in support of recommending screening colonoscopy.^{6,19,20} Clinically significant lesions are missed infrequently by colonoscopy, as a prospective study of examinations done back-to-back found that colonoscopy detected 94% of polyps that were at least 10 mm in size and 87% that were 6 to 9 mm in size.²¹

Colonoscopy has disadvantages, some perhaps more critical than others. It is an invasive procedure, with a small but real risk of one to two serious complications per 2,000 procedures. Most patients either do not experience significant discomfort with colonoscopy or do not remember it because of the amnestic effects of medication used for conscious sedation. Nearly all patients, however, find preparation for colonoscopy to be far worse than the procedure itself because it requires complete evacuation of the colon. Finally, colonoscopy is a relatively costly procedure that would consume significant healthcare resources if used for unselected mass screening. Yet, preliminary economic analyses suggest that colonoscopy may be reasonably cost effective because it yields better outcomes commensurate with its higher cost.^{22,23} When its efficacy is more firmly defined by evidence from clinical trials, there is reason to suppose that its cost performance will improve. As screening colonoscopy becomes a more widely accepted standard of care, increasing numbers of third-party payers can be expected to join Medicare and the few others who currently offer reimbursement for the procedure.

Because other methods are comparatively ineffective, colonoscopy has come to be used for screening, but it is not a true screening tool. The purpose of screening should be to identify those individuals more

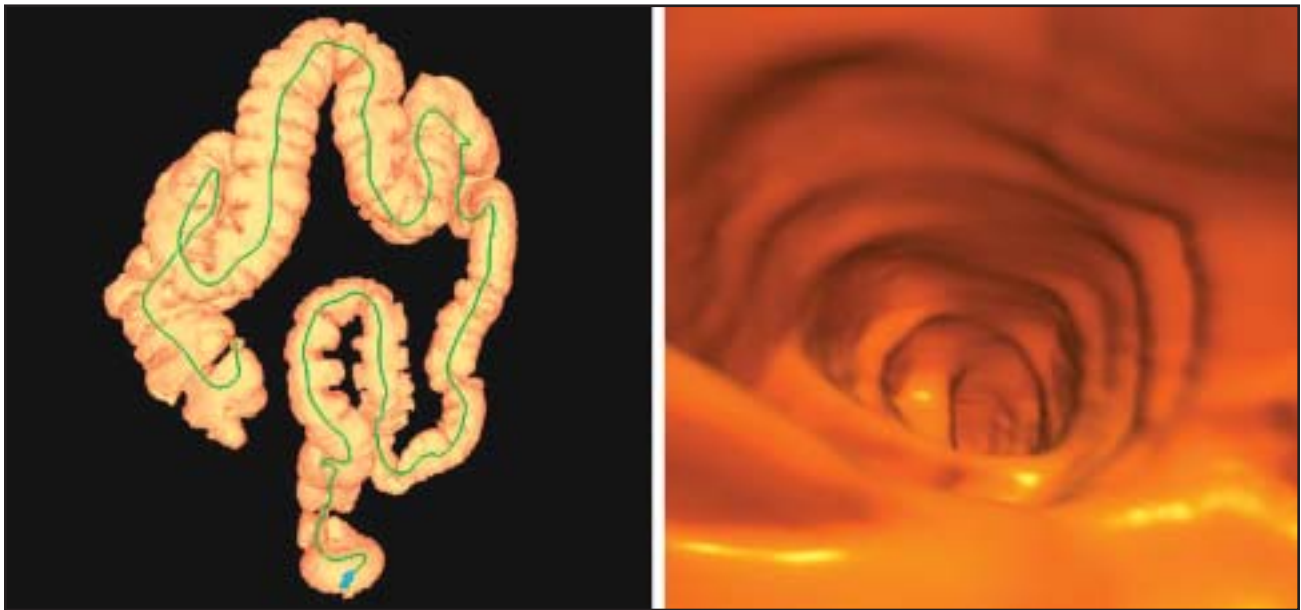


Fig 1. — Reconstruction of three-dimensional images from two-dimensional image data generated by a spiral computed tomography scanner. Entire colon is viewed from outside (left), or the colon is viewed from within the lumen, as seen by an endoscopist while advancing the endoscope (right). The green centerline on the image at left traces the path viewed in three-dimensions on “fly through” of the colon. Image courtesy of Viatronix Inc.

likely to have cancer or polyps who should then undergo colonoscopy, the definitive but more invasive and expensive diagnostic test. If screening tools were more effective, colonoscopy could be reserved for definitive diagnosis and the therapeutic removal of polyps detected by a screening test.

Virtual Colonoscopy

Virtual colonoscopy is an emerging screening technology that involves the reconstruction of three-dimensional images of the colon from the two-dimensional image data generated by a spiral computed tomography (CT) scanner. The resulting three-dimensional images can be displayed so that (1) the entire colon is seen from the outside at one time, similar to the image obtained with a double-contrast barium enema, or (2) the colon is viewed from within the lumen, just as the endoscopist sees the colon while advancing the endoscope (Figs 1 and 2). Bowel preparation is still necessary, and until recently, the required preparation has been the same complete evacuation of the colon that is needed for endoscopic colonoscopy. Immediately before the CT scan is performed, the colon is distended by insufflation with carbon dioxide, which serves as a contrast medium. Carbon dioxide is used in preference to room air because it is rapidly absorbed and exhaled, minimizing the time that colonic distension could cause discomfort. Patient control of carbon dioxide insufflation further limits discomfort but may compromise the adequacy of the examination if the colon is not distended sufficiently. After insufflation of the colon, scanning is done in the supine and prone positions. Sedation is

not required for virtual colonoscopy, thus eliminating the need for post-procedure recovery and a driver to provide transportation home.

Efficacy of Virtual Colonoscopy

Virtual and endoscopic colonoscopy can have similar efficacies for detection of polyps larger than 5 mm in size. A recent, frequently cited study demonstrated this potential in 100 patients at high risk for colorectal neoplasia who underwent virtual colonoscopy prior to undergoing endoscopic examination, with the radiologists blinded to the outcome of the endoscopy.²⁴ Virtual colonoscopy identified about 91% of polyps found at endoscopy that were 10 mm or more in size and 82% that were 6 to 9 mm in size. Endoscopic colonoscopy fares no better because, as we have already noted, endoscopy detects 94% of polyps 10 mm or more in size, and 87% of 6-9 mm polyps. Although endoscopists typically remove all polyps regardless of size, polyps less than 10 mm in diameter are regarded as having a low risk of being malignant or progressing to cancer. The false-positive rate reported for virtual colonoscopy was about 10% of “detected polyps” 10 mm or larger in size and 24% of 6-9 mm “polyps.” These values compare well with the 90% false-positive rate for fecal occult blood testing,^{2,3} which is the major determinant of cost for this mode of screening. Other studies have had similarly favorable outcomes.

It should be noted that virtual colonoscopy does not need to be the equal of endoscopic colonoscopy since it

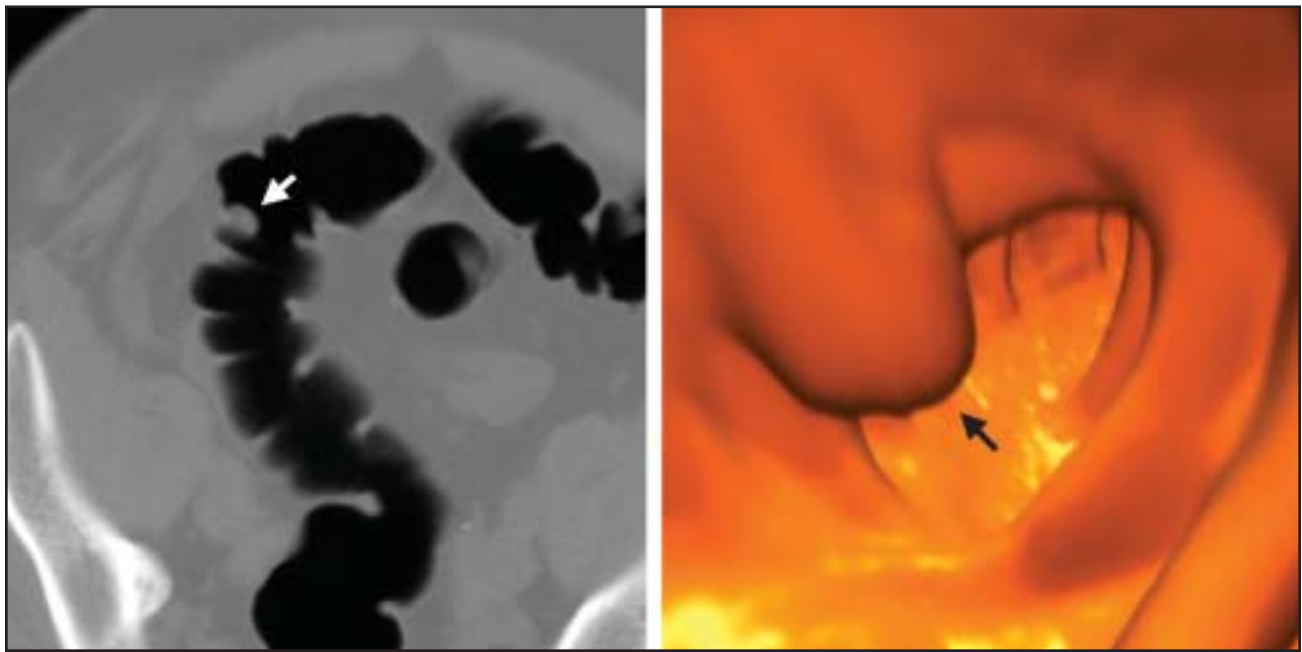


Fig 2. — Two-dimensional image (left) of a 10-mm colon polyp (arrow) generated by a spiral computed tomography scanner, and reconstruction of a three-dimensional image of the polyp (arrow) viewed from within the lumen (right). Image courtesy of Viatronix Inc.

is only a tool to screen for those at higher risk who should undergo a definitive endoscopic colonoscopy. It is expected that a screening tool will miss lesions, as is the case even with endoscopic screening. The study cited above used an earlier-generation single-slice CT scanner and less-advanced software than is available now, and complete evacuation of the colon was required in preparation for the examination. Results may be better with currently available technology.

Current Status of Screening by Virtual Colonoscopy

Three-dimensional imaging of scans is nearly as old as CT technology itself, but technological limitations prevented its use in clinical applications for some time. Recent events and technological advances, however, have made it practical to consider its use for screening the colon at this time:

- Substantial improvements in image resolution and speed with the advent of single-slice spiral CT first, and then multislice spiral CT, have improved the efficacy of scanning in detecting small lesions. Resolution of single-slice CT is limited by the 5-mm slice thickness, whereas multislice CT yields 1-mm slices in a single breath hold.

- Advances in software have reduced the time required for a radiologist to read the study, as well as the time required for computer reconstruction of three-dimensional images. Software advances may reduce the time required to read the study from over 1 hour to 15 minutes or less for a radiologist trained and

experienced in the technology, which makes reading a virtual colonoscopy more competitive with other demands on the radiologist's time.

- Development of an “electronic” bowel preparation to replace complete evacuation of the colon may improve polyp detection while reducing false-positive results and perhaps making the preparation more acceptable to patients (Fig 3). Electronic cleansing essentially requires that residual luminal contents only be liquefied and mixed with contrast, rather than all contents be completely evacuated. In constructing the images, computer software subtracts luminal contents identified by contrast. Although it can be less rigorous than for endoscopy, preparation for virtual colonoscopy is still sufficiently uncomfortable that work is ongoing in an attempt to develop the technology that would further reduce or eliminate the need for bowel preparation. A further disadvantage is that the patient found to have a lesion on virtual colonoscopy will usually need a second bowel preparation for endoscopic colonoscopy to evaluate the abnormality.

- Virtual colonoscopy has public appeal because of its minimally invasive, high-technological character. Celebrity endorsements and media attention have increased public awareness of virtual colonoscopy, as well as the need for colorectal screening in general.

Until relatively recently, virtual colonoscopy has been limited to low-volume use in a small number of academic centers with research interests in the technology. With technological advances and heightened

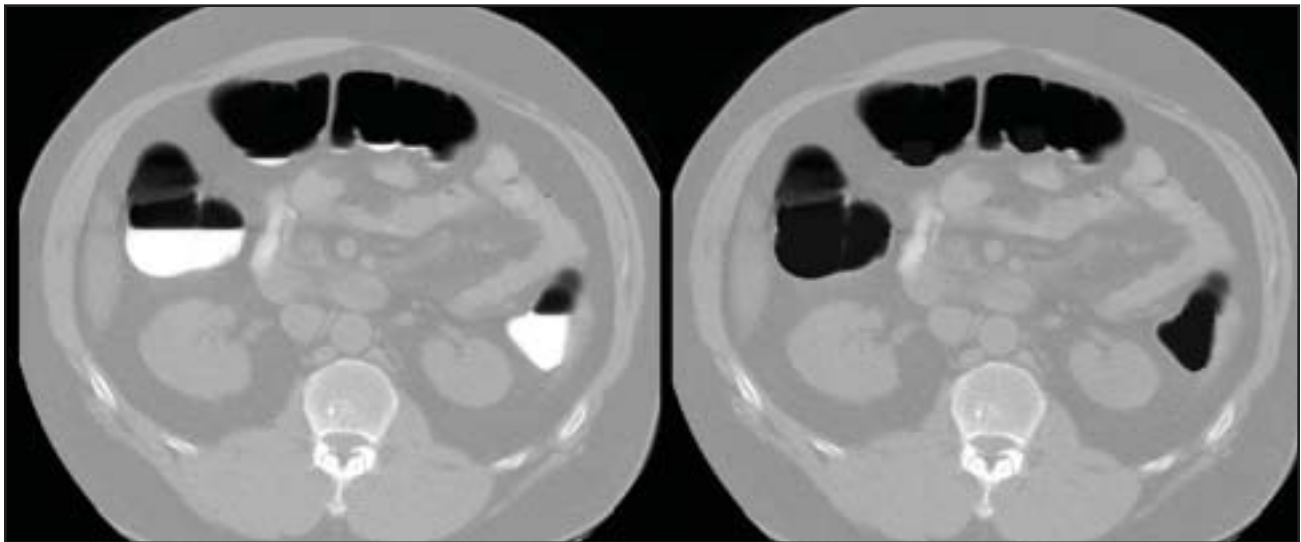


Fig 3. — “Electronic” bowel preparation results in residual luminal contents being liquefied and mixed with contrast (left). Computer software subtracts luminal contents identified by contrast in constructing the images (right). Image courtesy of Viatronix Inc.

interest, however, community hospitals and screening centers are beginning to offer screening by virtual colonoscopy to the public. Yet, few radiologists are adequately trained or experienced in interpreting virtual colonoscopic studies, and the learning curve is said to be steep. Standards for the use, performance, and reading of virtual colonoscopic studies have not been established, nor has the optimum technology been determined with certainty. Although virtual colonoscopy has demonstrated the potential to be an effective screening tool, the quality of such studies when performed in routine clinical practice is uncertain, particularly if performed outside the academic or research environment. None of the clinical practice guidelines or professional organizations and societies recommend virtual colonoscopy for colorectal screening at this time. Further work is needed if virtual colonoscopy is to make the transition from a screening tool with promise to one with a defined role in mass colorectal screening.

Fecal DNA Testing

Although not commercially available yet for screening individuals at average risk, fecal DNA testing is a promising new tool for colorectal cancer screening. For this test, a single stool is collected and screened for DNA markers originating from the cells of cancers and premalignant adenomas that are shed into the stool. DNA from neoplasms remains relatively stable in stool, whereas colonic cells shed from normal epithelium are broken down into short fragments by enzymes activated as a part of the normal process of epithelial cell death. Polymerase chain reaction is used to amplify fecal DNA by more than a billion-fold to yield a highly sensitive assay. DNA markers expressed in the neoplasm usually can be detected in the stool.

Colorectal cancers arise through multiple pathways of genetic alterations, each involving some combination of critical genes. Adenomatous polyposis coli (APC) and p53 are examples of genes targeted as DNA markers in stool testing because they are critical to the control of colorectal cell growth. Panels of multiple DNA markers are used to achieve a high sensitivity for detection of colorectal neoplasia. Early clinical studies have shown that multitarget DNA testing has a 71% to 91% sensitivity for detection of cancer^{25,27} and a 55% to 82% sensitivity for detecting adenomas 1 cm or larger.^{25,27} The specificity of multitarget DNA testing is estimated to be 93% to 100%.²⁵ In addition to high sensitivity and specificity, fecal DNA testing is noninvasive and requires no bowel preparation or restriction of medication or diet. With the appropriate panel of DNA markers, fecal DNA testing also has the potential to detect cancers in the aerodigestive tract proximal to the colon. Large, multicenter prospective trials of fecal DNA testing are underway and remain to be completed before this mode of screening can become available for routine clinical use.

Which Screening Method Should Be Recommended?

The US Preventive Services Task Force advises physicians to explain the benefits and risks of each test and then suggest the one preferred by the patient.¹⁰ The rationale for this advice presumably is that any screening test is preferable to none, because any of the screening tests can reduce colorectal cancer mortality by some clinically significant amount. However, shouldn't there be a preference among screening tests? Patients rely on recommendations of their physicians when making screening decisions. Many physicians, however, are unaware of the complex issues related to

the advantages and disadvantages of the various screening options. Full disclosure of benefits and risks to the patient is unlikely to occur, if only because of time limits on office visits. We favor clinical practice guidelines that give the physician realistic guidance as to preferred screening strategies.

Clinical practice guidelines strongly recommend colorectal screening but usually do not make recommendations as to the best method. Only recommendations from the American College of Gastroenterology specify colonoscopy as the strategy to be preferred whenever the needed expertise and resources are available.¹¹ We believe that physicians usually should not offer the comparatively ineffective strategies of fecal occult blood testing and sigmoidoscopy but rather should recommend colonoscopy whenever feasible (Table 1). Our recommendation of colonoscopy is based not only on evidence for its substantially greater effectiveness, but also on its potential to prevent the great majority of colorectal cancers by detection and removal of benign precursor adenomas. We believe that the effectiveness of colonoscopy far outweighs whatever disadvantages there may be. It is our observation that colonoscopy has come to be the screening strategy favored by gastroenterologists and the public, while primary care practitioners and clinical practice guidelines have lagged behind in this trend. At present, the emerging screening technologies either are unproven or have uncertain quality when performed in routine clinical practice, and none is as yet ready for widespread use outside the research setting or in selected centers.

Screening Individuals at High Risk

Individuals may be at increased risk for colorectal cancer because of their personal or family history. A personal history of adenomatous polyps, colorectal cancer, or inflammatory bowel disease requires surveillance colonoscopy because of the increased risk of colorectal cancer associated with these conditions. This review considers only those individuals at increased risk for colorectal cancer due to their family history. Recommended options for those at increased risk due to family history vary from simply starting to screen at an earlier age with the same tests as used for those at average risk, to more frequent screening with colonoscopy, and in some instances, genetic counseling and testing.

Common Familial Risk

Next to age, family history is the most common risk factor for colorectal cancer. About 10% to 30% of colorectal cancers are believed to arise in individuals with familial risk.^{12,13} Although the underlying basis

Table 1. — Colorectal Screening Strategy for Individuals at Average Risk: No Risk Factors Other Than Age \geq 50 Years

Preferred for effectiveness:	Colonoscopy every 10 years beginning at age 50
Accepted alternatives:	Annual fecal occult blood testing, flexible sigmoidoscopy every 5 yrs, or both, beginning at age 50

for common familial risk is usually unknown and multiple cancers may occur in some family members by chance, an inherited susceptibility to environmental exposures has been proposed. The inherited susceptibility factors in common familial risk are likely to be of low to moderate penetrance. For example, mutations of the mismatch repair gene MSH6 have been found in approximately 7% of patients with a family history of colon cancer.^{28,29} It has been suggested that mutations of this gene may be responsible for a significant number of familial colon cancers that occur at older ages and cannot be classified as hereditary non-polyposis colorectal cancer. It has also been shown that polymorphisms of certain genes involved in the metabolism of both harmful and protective environmental exposures have been associated with predisposition to colon cancer.³⁰

First-degree relatives (parents, siblings, children) of persons with colorectal cancer have a risk of developing this malignancy that is 2 to 3 times greater than the approximately 5% lifetime risk in the general US population.¹² The familial risk of colorectal cancer is related to the number of first-degree relatives with this cancer and to the age at cancer diagnosis. If two or more first-degree relatives had colorectal cancer or if the immediate relative was found to have colorectal cancer before about age 50, the risk may increase to approximately 3 to 4 times that in the general population. Colorectal cancer in a second-degree relative (grandparent, aunt, or uncle) or third-degree relative (great-grandparent or cousin) increases the risk of developing this disease by a factor of only about 1.5 times.^{12,31}

First-degree relatives of individuals with adenomas also have about a two-fold increased risk of developing colorectal cancer. The risk of colorectal cancer in siblings of an individual who was less than age 60 when the adenoma was found is about 2 to 3 times greater than if the adenoma was found at age 60 or older.^{12,32,33}

Screening Recommendations With Common Familial Risk

Recommendations for colorectal screening in individuals with common familial risk are empiric of

necessity. Ethical and practical considerations limit our ability to conduct the studies needed to determine the optimal screening strategies in persons known to be at increased risk due to family history. Recommended screening strategies in such persons are generally more aggressive and begin at a younger age than in individuals at average risk and are based on the risk increase associated with the specific family history.

The risk of colorectal cancer in the general population increases with age along a sigmoid-shaped curve that begins to rise between ages 40 and 50. The risk of colorectal cancer for first-degree relatives of persons with colorectal cancer parallels that of the sigmoid-shaped risk curve of the general population, but it is shifted to the left. As a result, the risk of colorectal cancer in persons with an affected first-degree relative is the same at age 40 as in the general population at age 50.³⁴ For this reason, it has been recommended that first-degree relatives of individuals with colorectal cancer or adenomatous polyps undergo the same colorectal screening as individuals at average risk, except that it begin at age 40.⁹ The American Cancer Society has further recommended complete colonoscopy every 5 years beginning at age 40 or at 10 years younger than the earliest diagnosis in the family, whichever comes first, if colorectal cancer or an adenomatous polyp were diagnosed in a first-degree relative younger than age 60 or if two or more first-degree relatives were found to have colorectal cancer at any age (Table 2).⁸ Second- or third-degree relatives of persons with colorectal cancer are advised to follow the same screening recommendations as those at average risk.

Inherited Colorectal Cancer Syndromes

Inherited colorectal cancer syndromes account for about 3% to 5% of all colorectal cancers at most.^{12,13,35}

Table 2. — Colorectal Screening Strategy With Common Familial Risk

Criterion:	Strategy:
One first-degree relative with colorectal cancer or adenoma diagnosed at age ≥ 60	Same as those at average risk, but beginning at age 40
One first-degree relative with colorectal cancer or adenoma diagnosed at age < 60 , or two first-degree relatives with colorectal cancer at any age	Colonoscopy every 5 yrs beginning at age 40 or 10 yrs younger than age at diagnosis, whichever comes first
Second- or third-degree relative with colorectal cancer	Same as for those at average risk
First-degree relative = parent, sibling, child Second-degree relative = grandparent, aunt, uncle	
American Cancer Society Guidelines. ⁸	

However, recognition of these syndromes is important because the underlying germline mutations confer a high lifetime risk of colorectal cancer in the carriers. The major inherited syndromes — familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer — are associated with development of adenomatous polyps. Other syndromes are characterized by the formation of hamartomatous polyps, and these include Peutz-Jeghers syndrome, juvenile polyposis, and Cowden syndrome. Only the syndromes associated with development of adenomatous polyps are considered in this review.

Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP), which accounts for less than 1% of colorectal cancers, results from autosomal dominant inheritance of a germline mutation in the adenomatous polyposis coli (APC) gene.^{12,36} The APC gene is a tumor suppressor gene that appears to be important in cell adhesion, signal transduction, and transcription activation. Mutation inactivates this gene and leads to a striking phenotype, the carpeting of the colon with hundreds to thousands of adenomas at a young age. Fifty percent of carriers develop adenomas by age 15 and 95% by age 35.³⁷⁻³⁹ Total colectomy with continent ileostomy or ileoanal pull-through with a pouch is recommended once polyps become evident, as development of colorectal cancer is inevitable (average age 35 to 43 years).^{37,40} Attenuated FAP is a variant syndrome characterized by fewer than 100 adenomas and a presentation with colorectal cancer that occurs, on average, 12 years later than typical FAP.³⁶

Patients with FAP may develop a number of benign extracolonic manifestations (Gardner's syndrome), including adenomas elsewhere in the gastrointestinal tract, osteomas, desmoid tumors, pigmented retinal lesions, dental abnormalities, and cutaneous lesions such as lipomas, fibromas and epidermoid cysts.^{12,36} Extracolonic malignancies that may develop include upper gastrointestinal adenocarcinoma and hepatoblastoma, as well as biliary, pancreatic, thyroid, and brain tumors. Turcot syndrome refers to typical FAP with malignancy of the central nervous system.

Genetic Testing and Screening in FAP

FAP has been associated with more than 300 different mutations of the APC gene.⁴¹ APC gene mutations can be detected in the peripheral blood of about 80% to 90% of families with FAP.⁴² Family members of the patient with the clinical syndrome of FAP should undergo genetic testing only if an APC gene mutation is found in the patient.^{12,36,43} Failure to find a mutation does not exclude FAP, however, and in these circum-

stances, all family members should undergo clinical screening. When a mutation is identified in a patient with FAP, clinical screening can be directed toward only those family members in whom this mutation is also found. Clinical screening of family members is done by annual sigmoidoscopy beginning at puberty, with the frequency to be decreased with increasing age by decade.³⁶ Screening by sigmoidoscopy should be sufficient, as adenomas arise throughout the colon. Following total colectomy in the patient with FAP, endoscopic surveillance of the upper gastrointestinal tract as well as the distal ileum is advised every 1 to 3 years.³⁶ Periampullary cancer is the most common FAP-associated malignancy that occurs after total colectomy.

Hereditary Nonpolyposis Colorectal Cancer

Hereditary nonpolyposis colorectal cancer (HNPCC) is by far the most common of the inherited colorectal cancer syndromes, and it may account for 2% to 3% of all colorectal cancers.^{12,35,36} HNPCC results from autosomal-dominant inheritance of a mutation in one of five mismatch repair genes, although mutations in two of them, MLH1 and MSH2, account for more than 95% of HNPCC families.^{36,44} Mismatch repair genes are responsible for fixing typographical errors in the DNA code that occur during replication. With mutation of mismatch repair genes, unrepaired DNA replication errors can accumulate in cells and ultimately lead to cancer. HNPCC gene mutation confers at least a 25% risk of developing colorectal cancer by age 50 and a 70% to 80% risk by age 70.^{35,45,46} It has been hypothesized that patients with HNPCC form adenomas at the same rate but at a younger age than the general population, while the proportion of adenomas that progress to cancer is clearly higher.³⁵

Unlike FAP, in which the colon is carpeted with adenomas, colorectal cancer in HNPCC usually arises from a single adenoma or from one of only a small number of adenomas. In HNPCC, cancers arise more often from the colon proximal to the splenic flexure (60% to 80%) and at a younger age (average 44 years) compared to sporadic colorectal cancer (23% to 32% proximal colon cancers and at an average age of about 70 years in the general population).⁴⁷ Precursor adenomas of HNPCC occasionally may appear more flat than polypoid.^{48,49} The histology of HNPCC cancers tends to be poorly differentiated and characterized by mucin-laden signet-ring cells and an abundance of extracellular mucin. Despite the greater incidence of an undifferentiated histology, HNPCC colon cancers have a better prognosis than sporadic colon cancers.⁵⁰ HNPCC patients have a 30% chance of developing a second colorectal cancer within 10 years and a 50% chance within 15 years.^{51,52}

Extracolonic Malignancies Associated With HNPCC

Mutations in the mismatch repair genes MLH1 and MSH2 are associated with an increased risk of cancer in the genitourinary tract, upper gastrointestinal tract, and brain.^{35,45,46} Of particular importance is the 20% risk of developing endometrial cancer by age 50, with the risk rising to 60% by age 70. Mismatch repair gene mutation is also associated with a 12% risk of ovarian cancer, a 13% risk of gastric cancer, and a 4% risk of brain and urinary tract cancer by age 70.

Diagnosis and Genetic Testing for the HNPCC Syndrome

HNPCC can be difficult to diagnose on clinical presentation alone due to the lack of a clear phenotype and because HNPCC cancers may resemble sporadic cancers in some instances. Similarly, nothing about the extracolonic cancers associated with HNPCC distinguishes them from sporadic tumors. Before the availability of genetic testing, the diagnosis of HNPCC was based on the Amsterdam clinical criteria alone (Table 3).⁵³ Among the concerns expressed with the Amsterdam criteria are its insensitivity in small families and the failure to consider other clinical features such as the proximal distribution of the cancers, the histologic characteristics of the tumor, and the association with extracolonic malignancies. The Amsterdam criteria have been expanded to address the concern that use of the original restrictive criteria to select those who should undergo confirmatory genetic testing would lead to missing many HNPCC families.⁵⁴ Even with modification to include extracolonic malignancies, the Amsterdam criteria exclude at least one third of families shown to have mutations in MLH1 and MSH2.⁵⁵ With modifications intended to increase sensitivity, however, comes an inevitable loss of specificity. The Bethesda criteria⁵⁶ (Table 3) have greater sensitivity for identifying individuals with MLH1 and MSH2 mutations (94% sensitivity), but these criteria have a specificity of only 25%.⁵⁷

Direct testing of peripheral blood for mismatch repair gene mutations is recommended for the colorectal cancer patient whose family meets any one of the first three modified Bethesda criteria.^{35,43} Genetic testing for HNPCC is not nearly as effective for detecting mutations as genetic testing is for FAP. Only about 50% to 60% of those individuals meeting the restrictive Amsterdam criteria will be found to have mismatch repair gene mutations associated with the disease.³⁶ The Amsterdam criteria are fairly specific, however, as not more than 10% of those who do not meet the criteria will test positive for mutations.⁵⁸ About 30% of

those meeting the less restrictive Bethesda criteria will be found to have MLH1 or MSH2 mutations.⁵⁹ If a mismatch repair gene mutation is found in the first family member tested, then other family members can be tested. Those family members testing positive for the mutation are advised to undergo surveillance colonoscopy every 1 to 2 years beginning at age 25 or at 10 years younger than the earliest colorectal cancer diagnosis in the family.^{35,36} Annual screening for endometrial cancer is recommended beginning at age 30 to 35 years, but no consensus exists as to the method of choice.^{35,36} Options for endometrial cancer screening include gynecologic examination, transvaginal ultrasonography, and tumor marker CA-125 testing. If a mismatch repair mutation is not found in the first family member tested, then all family members should undergo surveillance colonoscopy every 1 to 2 years.

Role of MSI Testing

As already noted, DNA replication errors can accumulate in cells when mismatch repair genes are mutated, as occurs in HNPCC. Unrepaired DNA replication errors

or mutations are most easily recognized in segments of DNA termed "microsatellites." Microsatellites are short, repeated nucleotide sequences located throughout the genome, whose length may change due to insertion or deletion mutations during DNA replication. When multiple microsatellite errors or mutations are detected in the tumor, the cancer is said to exhibit microsatellite instability (MSI). The significance of MSI is that it may be detected in more than 90% of HNPCC cases that fulfill the Amsterdam criteria,⁶⁰ whereas only approximately 15% of sporadic colorectal cancers exhibit MSI.^{61,62}

MSI testing has been recommended as a tool to screen for patients who should undergo genetic testing for mismatch repair gene mutations from among those patients who do not meet the Amsterdam criteria but are still suspected of having HNPCC.^{35,36} MSI testing is done on DNA extracted from the paraffin tumor block of the patient suspected of having HNPCC. The Bethesda criteria were developed to select patients for MSI testing, as well as to expand on the Amsterdam criteria, although patients meeting any of the first three modified Bethesda criteria may undergo direct genetic testing for mismatch repair gene mutations without MSI prescreening (Table 3). Finding MSI in the tumor usually leads to genetic testing, whereas a negative result is usually considered to exclude HNPCC in the absence of strong evidence to the contrary.

Table 3. — Hereditary Nonpolyposis Colorectal Cancer (HNPCC) Testing Recommendations

<p>Amsterdam Criteria⁵³</p> <p>Proceed directly to genetic testing if all satisfied:</p> <ul style="list-style-type: none"> • ≥3 relatives with colorectal cancer (1 of whom is the first-degree relative of the other 2) • ≥2 generations affected • ≥1 of those affected diagnosed at age <50 <p>Bethesda Criteria (modified)*</p> <p>Proceed directly to genetic testing if any satisfied:</p> <ul style="list-style-type: none"> • Amsterdam criteria satisfied • Individuals with 2 HNPCC-related cancers (synchronous or metachronous) • An individual with colorectal cancer and a first-degree relative with HNPCC-related cancer or colorectal adenoma (1 of the cancers diagnosed at age <50 and the adenoma at age <40) <p>Prescreen with MSI testing if any satisfied:</p> <ul style="list-style-type: none"> • Colorectal or endometrial cancer at age <50 • Right-sided colon cancer with undifferentiated histology at age <50 • Colorectal cancer with signet-ring histology at age <50 • Colorectal adenoma at age <40 <p>* Original Bethesda criteria⁵⁶ modified to reflect a cancer at age <50 rather than age <45.⁴³</p> <p>First-degree relative = parent, sibling, child</p> <p>HNPCC-related cancers = endometrial, ovarian, gastric, hepatobiliary, small bowel, and transitional cell carcinoma of the renal pelvis or ureter, as well as colorectal cancer</p> <p>American Gastroenterological Association Guidelines.⁴³</p>

Diagnosis of HNPCC

The decision to seriously consider the diagnosis of HNPCC in a given patient may not be an easy proposition for many clinicians, given the complexities of the various criteria. The most practical advice is to maintain a high level of suspicion in the individual found to have any of the following: colorectal or endometrial cancer arising before age 50, colorectal adenomas before age 40, synchronous or metachronous HNPCC-associated cancers (Table 3), or colorectal cancer and a first-degree relative with an HNPCC-associated cancer or colorectal adenoma (one of the cancers diagnosed at age <50 years or the adenoma at age <40 years). Any of these circumstances may warrant consideration of at least MSI testing of the patient's colorectal cancer. Strength of the family history remains the central consideration in determining who should be considered for direct genetic testing for mismatch repair gene mutations without MSI prescreening.

Genetic Counseling

Pre- and post-test counseling with written informed consent is a necessary part of any genetic testing. Genetic counseling should include education regarding the nature and basic genetics of the syn-

drome, assessment of the individual's hereditary cancer risk, potential benefits and disadvantages of genetic testing, and recommendations for screening and management. Due consideration must be given to psychosocial issues that may be raised by genetic testing, including the impact on other family members and the determination of who will be informed and when, survivor guilt in family members who test negative, anxiety associated with overestimation of risk by the patient, and concerns regarding insurability. Genetic counseling can be time-consuming and involve a complexity of issues that physicians are neither trained nor prepared to manage. Physicians would be advised to refer the patient and family to a regional center with genetics counselors, geneticists, and other knowledgeable health care professionals who can provide evaluation, counseling, and management recommendations.

Conclusions

Considering the various cancers for which we screen, the benefits of screening for colorectal cancer have been shown most convincingly and are the least controversial. While colorectal screening has been shown to reduce colorectal cancer mortality, the benefits of breast cancer screening have been questioned recently, and prostate cancer screening is controversial. Screening colonoscopy can potentially prevent the great majority of colorectal cancers by detection and removal of precursor adenomas. Awareness of family history and genetic testing can assist in targeting individuals for more intense screening efforts. However, to substantially reduce mortality and morbidity from colorectal cancer, practicing clinicians need to be aware of the advances in colorectal screening that have occurred in the last 5 to 10 years and assertively recommend the appropriate screening strategies to their patients.

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