CLINICAL PRACTICE

Screening for Colorectal Cancer

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A healthy 76-year-old woman presents as a new patient for primary care. She reports having one daily bowel movement and no rectal bleeding. She has no family history of colorectal cancer. She reports having negative stool card tests during gynecologic examinations, most recently at 65 years of age. Would you advise this patient to undergo colon-cancer screening, and if so, what test would you recommend?

THE CLINICAL PROBLEM

Colorectal cancer is the second leading cause of death from cancer in the United States. This year, it is estimated that there will be 147,000 newly diagnosed cases of colorectal cancer and nearly 50,000 deaths associated with this disease.[1] The age-adjusted incidence of colorectal cancer in the United States is 61.2 cases per 100,000 population among men and 44.8 per 100,000 population among women.[1] These rates have been slowly decreasing since 1985.

There is considerable evidence that screening of asymptomatic persons who are at average risk can detect cancers at an early and curable stage, resulting in a reduction in mortality.[2-4] Furthermore, some screening tests may also detect cancer-precursor lesions, which, if removed, may result in a reduced incidence of colorectal cancer.[5] There are several different screening tests, each with advantages and limitations (Table 1); differences among strategies in terms of the sensitivity and specificity of the tests, their complexity, and the associated risk complicate the process of informed decision making.

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N Engl J Med 2009;361:1179-87.

STRATEGIES AND EVIDENCE

IDENTIFICATION OF HIGH-RISK PERSONS

The most common indicator of high risk is a first-degree relative with colorectal cancer. If the first-degree relative had colorectal cancer before 50 years of age, there should be suspicion of hereditary syndromes such as familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer syndrome, and MutY homolog (*MUTYH*) polyposis. Such patients require special screening and should be referred to a specialist with expertise in these hereditary syndromes to obtain a complete family history, consider genetic counseling and testing, and determine appropriate timing for endoscopic surveillance. If a first-degree relative had colorectal cancer at 50 years of age or older, the lifetime risk of colorectal cancer nearly doubles among his or her family members. Colonoscopy is the preferred screening test in these persons, and screening should be initiated either when they are 40 years old or when they are 10 years younger than the age at which the family member received a diagnosis of colorectal cancer, whichever comes first.[9] Patients with chronic ulcerative colitis or colitis due to Crohn's disease are at increased risk for colorectal cancer and should undergo surveillance with colonoscopy, generally beginning 8 to 10 years after diagnosis.

An audio version of this article is available at NEJM.org

PREVENTION STRATEGIES FOR AVERAGE-RISK PERSONS

Factors associated with an increased risk of colorectal cancer include dietary factors (diets high in fat or low in fiber, calcium, or both), obesity, low levels of physical activity, tobacco smoking, and a high alcohol intake. Although lifestyle choices may contribute to the risk of colorectal cancer, there is little evidence that a modification of lifestyle in adults will reduce this risk.[10] The regular use of aspirin or nonsteroidal antiinflammatory drugs and the use of hormone-replacement therapy have reduced the risk of new adenomas or cancer.[11,12] However, these agents have potential adverse effects that may offset any potential benefit with respect to the prevention of colorectal cancer and are not recommended for this indication.[3]

SCREENING TESTS AND STRATEGIES

Fecal Screening Tests

Fecal screening tests can detect occult blood in small stool samples. These tests can be performed at home, are noninvasive, have a low initial cost, and require few specialized resources. There are

Table 1. Advantages, Limitations, and Uncertainties of Screening Tests to Detect Colorectal Cancer.

Test	Advantages	Limitations and Uncertainties
Sensitive guaiac fecal occult-blood test	Low initial cost; can be performed at home; requires few specialized resources	Not specific for human hemoglobin; one-time testing with three stool specimens has limited sensitivity for cancer, so repeat testing annually recommended; unknown adherence to repeat testing, if negative, and to colonoscopy, if positive; potential for cancer prevention limited because of poor sensitivity for advanced adenomas
Fecal immunochemical test	Specific for human hemoglobin; low initial cost; can be performed at home	Uncertain benefit, as compared with less costly sensitive guaiac fecal occult-blood test; adherence unknown and annual repeat testing recommended; performance of new versions of test uncertain; ideal number of stool samples uncertain; potential for cancer prevention limited because of poor sensitivity for advanced adenomas
Stool DNA	Detection of specific mutations may be more accurate than detection of blood; can be performed at home	Costly; performance of new versions of the test uncertain; appropriate intervals for repeat testing unknown; potential for cancer prevention limited because of poor sensitivity for advanced adenomas
CT colonography	High sensitivity for detection of lesions ≥10 mm in diameter; less invasive than endoscopy	No evidence of reduction of colorectal-cancer incidence or mortality; requires bowel preparation, special resources, and expertise; cost and risk depend on rate of referral for colonoscopy and frequency of evaluation for extracolonic findings; treatment of patients with polyps <6 mm in diameter uncertain; appropriate intervals for repeat testing unknown; detection of flat polyps uncertain; radiation exposure; sensitivity and specificity in clinical practice unknown
Sigmoidoscopy	Office-based; does not require sedation; case–control studies show 60% reduction in mortality from cancers of the distal colon	Does not detect isolated proximal colorectal cancer; may be less effective with increasing age and in women because of higher rates of proximal colorectal cancer; sensitivity and specificity in clinical practice unknown
Colonoscopy	90% sensitivity for lesions ≥10 mm in diameter; case–control studies show a 53–72% reduction in incidence of colorectal cancer* and 31% reduction in mortality from colorectal cancer†; detection and removal of lesions during one examination	Lack of randomized, controlled trials showing reduced incidence or mortality; requires bowel preparation, special resources, and expertise; high initial cost; invasive, with 3–5 serious adverse events per 1000 examinations; sensitivity and specificity in clinical practice unknown

* Data are from Müller and Sonnenberg[6] and Singh et al.[7]
† Data are from Baxter et al.[8]

two types of fecal occult-blood tests. The standard guaiac fecal occult-blood test detects peroxidase activity of heme and is not specific for human blood. One-time testing with a standard guaiac test has a sensitivity for detecting cancer of only 33 to 50%,[2] whereas a more sensitive guaiac test (Hemoccult SENSA, Beckman Coulter) has a sensitivity for detecting cancer of 50 to 75% (Table 2).[2,4,18] Three separate stool samples per test have superior sensitivity, as compared with one or two samples.

The second type of occult-blood test is the fecal immunochemical test, which uses antibodies that are specific for human hemoglobin, albumin, or other blood components and is more specific for human blood than the standard guaiac fecal occult-blood test. These one-time tests have a sensitivity for detecting cancer of 60 to 85% with the use of one to three stool samples (Table 2).[2,4] Recent studies have shown considerable variation in the performance of different fecal immunochemical tests; the optimal commercial test and the number of stool samples required are unknown.[29]

Clinical trials have shown that persons with positive occult-blood tests have a risk of cancer that is three to four times as high as that among persons with negative tests, and colonoscopy should be recommended for persons with these positive tests. Randomized, controlled trials in which standard guaiac tests were administered annually or biennially have shown that cancers are detected at an early and more curable stage in persons who undergo screening than in persons who are not screened; over a period of 10 to 13 years, this results in a reduction in mortality from colorectal cancer of 15 to 33%.[13-15]

Fecal occult-blood testing has important limitations. Because of the relatively poor sensitivity of one-time standard testing (Table 2), the U.S. guidelines (Table 3) recommend the use of a sensitive guaiac fecal occult-blood test, with repeat testing annually if the results are negative.[2,3] Adherence to repeat testing in clinical practice is uncertain, but in clinical trials, 25 to 40% of patients do not complete scheduled testing over a period of several years.[13-15] Surveys have shown that after a positive test, many physicians do not recommend colonoscopy or patients do not agree to undergo colonoscopy; this renders a screening program ineffective.[30] Fecal occult-blood testing also has a limited benefit for cancer prevention.[31] Most advanced adenomas (defined as ≥10 mm in diameter or with villous histologic features or high-grade dysplasia) are not detected by means of fecal occult-blood tests (Table 2).

Surveys reveal that many health care providers consider a fecal test performed during an office digital examination to be "opportunistic" screening and "better than nothing."[30] Such tests have low sensitivity for the detection of high-risk adenomas and cancer,[32] may provide false reassurance to patients, and are not recommended for screening.[2]

Although the initial cost of fecal occult-blood testing is low, an appropriate analysis of costs should include the costs of annual testing, reminder systems, colonoscopy in patients with positive tests, and treatment for detected cancers. When all these factors are considered, the costs of screening by means of fecal occult-blood tests are similar to those of screening by means of flexible sigmoidoscopy or colonoscopy.[33]

Another fecal test can detect abnormal DNA in stool samples. Stool DNA tests are based on the research findings that specific mutations are associated with colorectal cancer and that cellular DNA is excreted in stool and can be detected with the use of polymerase-chain-reaction methods. In a study involving an early version of this test in asymptomatic patients undergoing colonoscopy, 51% of cancers and 18% of advanced cancer-precursor lesions were detected by means of the test.[16] New versions of the test appear to have greater sensitivity[17,19] but have not yet been carefully evaluated in screening cohorts. Thus, the overall test performance remains uncertain, as does the appropriate treatment of patients with positive tests and negative colonoscopic findings, the appropriate screening interval, and the cost-effectiveness of this test.

Structural Examinations of the Colon

Structural examinations of the colon have been shown to be effective for the detection of both cancer-precursor lesions and early cancer (Table 2). These tests may prevent the development of cancer through the detection and removal of adenomas.[5]

Radiographic Studies

Barium enema examination accurately identifies late-stage cancer, but it is a poor test for important cancer-precursor lesions[34] and is rarely used for colorectal-cancer screening today. Imaging with

Table 2. Sensitivity of One-Time Colorectal-Cancer Screening Tests.

Test	Sensitivity		References
	Cancer	Advanced Adenomas*	
	percent		
Stool-based tests			
Standard guaiac fecal occult-blood test (three stool samples)	33–50	11	Mandel et al.,[13] Hardcastle et al.,[14] Kronborg et al.,[15] Imperiale et al.,[16] Ahlquist et al.[17]
Sensitive guaiac fecal occult-blood test (three stool samples)	50–75	20–25	Levin et al.,[2] Whitlock et al.,[4] Ahlquist et al.,[17] Allison et al.[18]
Immunochemical fecal occult-blood test (one–three stool samples)	60–85	20–50	Levin et al.,[2] Whitlock et al.[4]
Old stool DNA test (one stool sample)	51	18	Imperiale et al.[16]
New stool DNA test (one stool sample)	≥80	40	Allison et al.,[18] Itzkowitz et al.[19]
Structural examinations of the colon			
CT colonography	Uncertain; probably >90	90 (if ≥10 mm in diameter)	Johnson et al.[20]
Sigmoidoscopy	>95 (in the distal colon)	70†	Selby et al.,[21] Lieberman et al.[22]
Colonoscopy	>95	88–98	Lieberman et al.,[22] Imperiale et al.,[23] Schoenfeld et al.,[24] Lieberman et al.,[25] Pickhardt et al.,[26] Cotton et al.,[27] Rockey et al.[28]

* Advanced adenoma is defined as a tubular adenoma that is 10 mm or larger in diameter or an adenoma with villous histologic features or high-grade dysplasia.

† If an adenoma is detected in the distal colon, the patient would undergo complete colonoscopy, which would result in the detection of some proximal advanced adenomas.

computed tomographic (CT) colonography (Fig. 1) renders two-dimensional and three-dimensional images of the colon and requires complete bowel preparation.[26-28] In clinical studies involving expert radiologists, 90% of polyps 10 mm or larger in diameter were identified correctly, with a false positive rate of 14%.[20] The detection rate for polyps that are 6 mm or larger in diameter (the threshold for referring a patient for colonoscopy) is 78% (specificity, 88%).[2] With the use of this cutoff point, 15 to 25% of persons undergoing screening would be referred for colonoscopy.[27,28,35] The rate of referral for colonoscopy is an important element of program cost.

CT colonography is less sensitive and specific for polyps smaller than 6 mm in diameter than it is for larger polyps. However, the treatment plan for a patient in whom the largest polyp is smaller than 6 mm in diameter is controversial. Less than 2% of these patients will have adenomas with advanced features, and cancer is rare.[35,36] No studies have demonstrated the safety of following such patients with repeat CT colonography. There is also uncertainty about whether CT colonography can be used to identify flat polyps, some of which may harbor malignant cells.[37] Appropriate screening intervals after negative examinations or in cases of growths that are smaller than 6 mm in diameter and that may be polyps are uncertain. In addition, the sensitivity and specificity of CT colonography in routine clinical practice settings are unknown.

Several other areas of uncertainty are listed in Table 1. Radiation exposure associated with CT colonography could increase the risk of cancer.[38] Although low-dose regimens are used, there is concern about cumulative radiation exposure, and some countries will not allow imaging for screening purposes. The rate of extracolonic findings that require further evaluation is an important driver of cost. Studies show that 27 to 69% of persons who undergo screening with CT colonography have at least one finding outside the colon, requiring further evaluation in 5 to 16% of persons undergoing screening.[2,4]

Sigmoidoscopy

Case–control studies have shown significant associations between the use of sigmoidoscopy and reduced mortality from colorectal cancer in that

Table 3. U.S. Colorectal-Cancer Screening Guidelines, 2008.*

Screening Test	ACS–MSTF–ACR	USPSTF	Recommended Interval for Rescreening
Sensitive guaiac fecal occult-blood test	Recommended if >50% sensitivity for colorectal cancer	Recommended	1 yr
Fecal immunochemical test	Recommended if >50% sensitivity for colorectal cancer	Recommended; high-sensitivity test only	1 yr
Stool DNA test	Recommended if >50% sensitivity for colorectal cancer	Not recommended (insufficient evidence to assess sensitivity and specificity of fecal DNA)	Uncertain
Flexible sigmoidoscopy	Recommended if sigmoidoscope is inserted to 40 cm of the colon or to the splenic flexure	Recommended; with guaiac fecal occult-blood test every 3 yr	5 yr
Barium enema examination	Recommended, but only if other tests not available	Not recommended	5 yr
CT colonography	Recommended, with referral for colonoscopy if polyps ≥6 mm in diameter detected	Not recommended (insufficient evidence to determine risk–benefit ratio)	5 yr
Colonoscopy	Recommended	Recommended	10 yr

* Data are from Levin et al.,[2] Preventive Services Task Force,[3] and Whitlock et al.[4] ACS–MSTF–ACR denotes American Cancer Society, U.S. Multisociety Task Force on Colorectal Cancer, and American College of Radiology; and USPSTF U.S. Preventive Services Task Force.

portion of the colon which is examined.[21] In a large, randomized, controlled trial, there was no reduction in the incidence of colorectal cancer among subjects assigned to screening sigmoidoscopy, and in an intention-to-treat analysis, there was a nonsignificant reduction in mortality at 6 years among these subjects as compared with controls.[39] However, studies with the use of screening colonoscopy have shown that more than 30% of patients with advanced neoplasia have only proximal lesions that would not be identified with sigmoidoscopy[22,23]; this scenario is more common in women than in men and in patients older than 60 years of age than in younger patients.[22,24,25] The examination requires bowel preparation and an office visit and is usually associated with some discomfort. For many clinicians and patients, colonoscopy is more appealing than sigmoidoscopy because patients can be sedated and undergo a complete colon examination with polypectomy. Reimbursement for sigmoidoscopy is low, relative to the resources used. All these limitations have discouraged its use in the United States.

Colonoscopy

Colonoscopy is the final assessment step in every screening program for the detection of colorectal cancer. Several large cohort studies have shown the feasibility and safety of colonoscopy as a primary screening test.[22-24,40] These studies show that among patients at average risk who undergo screening colonoscopy, 0.5 to 1.0% have colon cancer and 5 to 10% have advanced neoplasia that can be removed.[22-25,40] In case–control studies, colonoscopy is associated with reductions in the incidence of and mortality from colorectal cancer.[6-8]

No randomized, controlled trials have compared the outcomes of colonoscopy with those of other forms of screening. Several studies have shown that among patients with an adenoma that is detected and removed at screening colonoscopy, colorectal cancer may develop in 0.3 to 0.9% within 3 to 5 years after screening. Missed lesions account for some of the cancers detected at subsequent colonoscopy. Lesions that are 10 mm or larger in diameter may be missed in 2 to 12% of patients.[26-28] The detection of flat adenomas may be especially difficult and may require special techniques.[37] Colonoscopy may not reduce the risk of proximal colon cancer unless the examination is complete and all polyps are removed.[8] These issues underscore the importance of monitoring and improving the quality of colonoscopy; tools for measuring quality are now available.[41] The recommended 10-year interval for repeat ex-

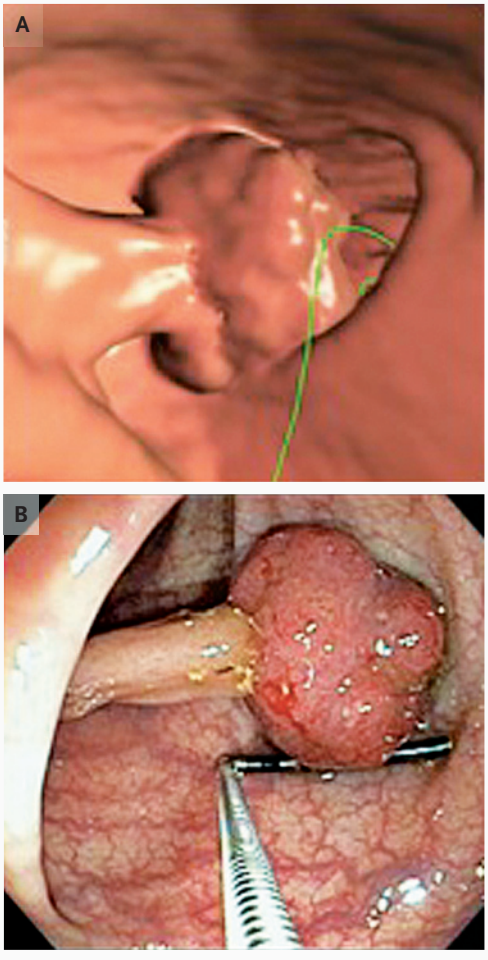

Figure 1. Pedunculated Polyp.

Panel A shows a pedunculated polyp detected by means of CT colonography. The green line indicates the center line for rendering the three-dimensional image. Panel B shows the same polyp at colonoscopy. (Images courtesy of Brooks Cash, M.D., National Naval Medical Center, Bethesda, MD.)

amination after negative colonoscopic findings is based largely on case–control studies. Two recent studies have shown a low rate of advanced neoplasia 5 years after negative colonoscopic findings.[42,43]

RISKS OF SCREENING

Although fecal testing does not cause direct harm, missed cancers and false reassurance may be unintended negative consequences. Sigmoidoscopy and CT colonography are very rarely complicated by perforations, but these procedures are sometimes uncomfortable. Since all screening programs lead to colonoscopy if initial test results are positive, the risks associated with colonoscopy affect every program.[44-52] When colonoscopy is performed by a properly trained endoscopist, the risk of serious adverse events is 3 to 5 events per 1000 colonoscopies (see the Table in the Supplementary Appendix, available with the full text of this article at NEJM.org). Few studies have been performed in diverse practice settings or have followed patients for 30 days to capture all hospitalizations and serious events. Perforation may occur with diagnostic or therapeutic procedures, whereas bleeding is primarily a concern with polypectomy. With advancing age and coexisting conditions, the risks associated with colonoscopy increase and the benefit diminishes because of a shorter life expectancy.[4,53]

AREAS OF UNCERTAINTY

Uncertainties associated with individual tests are summarized in Table 1. Screening recommendations do not currently vary according to age and race or ethnic group, but screening outcomes differ according to these characteristics. Age-adjusted rates of colorectal cancer[1] and advanced polyps[24,25] are lower among women than among men. The incidence of and mortality from colorectal cancer are higher among blacks than among whites.[1] Among persons who undergo screening with colonoscopy, rates of large polyps are higher among blacks, both men and women, than among whites.[54] Therefore, it may make sense for white women to delay screening and for black men and women to undergo the first screening before 50 years of age. The American College of Gastroenterology supports the initiation of screening in blacks at 45 years of age.[55] However, there are concerns that screening recommendations are already complex and that customization could paradoxically reduce screening rates.[2]

There are no data from randomized trials showing that a reduction in mortality from colorectal cancer is associated with the performance of colonoscopy or CT colonography. Large trials involving sigmoidoscopy are being conducted in the United States, the United Kingdom, and Italy.

The performance and quality of screening programs to detect colorectal cancer in diverse clinical practice settings remain uncertain. Further

Table 4. Considerations for Colorectal-Cancer Screening.

Screening Test and Expected Outcome	Follow-up	Likelihood of Negative Test	
		If Cancer Present	If Advanced Polyp Present
		percent	
Fecal test			
Negative in 90–98% of patients	Repeat at 1 yr	15–50	50–80
Positive in 2–10% of patients	Colonoscopy with bowel preparation	—	—
CT colonography			
No polyp or only polyps <6 mm in diameter in 75–85% of patients	Repeat; interval for repeat colonography unclear	—	10–20
Polyp or polyps >6 mm in diameter in 15–25% of patients	Colonoscopy with bowel preparation	—	—
Extracolonic findings that require evaluation in 5–16% of patients	Further tests, depending on finding	—	—
Sigmoidoscopy			
Negative in 75–93% of patients	Repeat at 5 yr	—	30–65
Positive in 7–25% of patients	Colonoscopy with bowel preparation	—	—
Colonoscopy*			
No adenomatous polyps in 50–80% of patients	Repeat at 10 yr	—	2–12
One or more polyps in 20–50% of patients	Colonoscopic surveillance; interval for repeat colonoscopy depends on pathological findings	—	—

* Colonoscopy is associated with a risk of 3 to 5 serious adverse events per 1000 procedures.[49-52]

study is needed to determine rates of adherence to recommended testing and of appropriate follow-up after initial testing, with attention to the effects of race or ethnic group and sex, to better inform patient and physician education regarding screening.

GUIDELINES

Two new sets of guidelines for colorectal-cancer screening in the United States (from the U.S. Preventive Services Task Force [USPSTF] and joint guidelines from the American Cancer Society, the U.S. Multisociety Task Force on Colorectal Cancer, and the American College of Radiology) were published in 2008 (Table 3).[2-4] The latter, joint guidelines recommend structural examinations of the colon that may lead to cancer prevention as the preferred test, if resources are available.[2] Both sets of guidelines recommend a sensitive guaiac test or fecal immunochemical test if fecal testing is required. Patients should be informed that colonoscopy is necessary if the test results are positive and that the test should be repeated annually if the results are negative. The USPSTF does not recommend CT colonography and stool DNA testing, which are new techniques that are associated with many uncertainties (Table 1).[3] Guidelines from the American College of Gastroenterology recommend colonoscopy as the preferred screening test.[55]

The USPSTF concludes that screening should not be routinely recommended in persons older than 75 years of age, and it should not be recommended at all in persons older than 85 years of age, even though the risk of colorectal cancer and advanced polyps continues to increase with age.[1,25] If persons between the ages of 75 and 85 years have never undergone screening, decisions about screening should be individualized according to health status.

Internationally, there is considerable variation among screening recommendations. Fecal occult-blood testing is recommended in Europe and

Canada. Alternatives to fecal occult-blood testing are sigmoidoscopy in the United Kingdom, Italy, and Norway and colonoscopy in Germany, Austria, Poland, and Italy.

CONCLUSIONS AND RECOMMENDATIONS

Colorectal-cancer screening should begin with a process of informed decision making (Table 4). Patients should be informed that there is strong evidence that screening persons who are at average risk is effective in reducing the risk of death from colorectal cancer, but that there is no perfect screening test and each program has advantages, limitations, and uncertainties (Table 1). Patients also should be informed about the "downstream" benefits and risks associated with the various screening tests, including the need for follow-up tests and the likelihood that the test will detect important pathologic findings, if present.

Although the USPSTF does not recommend routine screening in persons older than 75 years of age, the healthy 76-year-old woman in the vignette has never undergone proper screening and she should be offered it. Given that her sex and age are associated with an increased risk of neoplasia in the proximal colon, I would recommend colonoscopy. She should be referred to an endoscopist who monitors quality and meets benchmarks for colonoscopic examination. If this test is negative, she will not need any further screening in her lifetime. If she prefers fecal testing, she should understand the limitations of one-time testing for the detection of advanced polyps and cancer and the need for repeat testing over the next few years.

No potential conflict of interest relevant to this article was reported.

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