A 79-year-old woman visits your office for routine health maintenance. She has normal daily bowel movements without rectal bleeding. Her medical history is notable for osteoarthritis but no other medical conditions. She takes nonsteroidal anti-inflammatory medication and multivitamins. Her maternal uncle received a diagnosis of colorectal cancer at 65 years of age, but she has never undergone screening for colorectal cancer. Would you advise this patient to undergo screening for colorectal cancer, and if so, which screening strategy would you recommend?

**THE CLINICAL PROBLEM**

Colorectal cancer is the third most commonly diagnosed cancer and cause of death from cancer in the United States; however, it can be detected in asymptomatic patients at a curable stage, and several randomized, controlled trials have shown lower mortality among patients who undergo screening than among those who do not. Screening can also detect precancerous polyps that can be removed during colonoscopy, thereby reducing the incidence of cancer. This review focuses on screening patients at average risk for the development of colorectal cancer.

**SCREENING OPTIONS**

Multiple strategies are available to screen patients who are at average risk for the development of colorectal cancer, including fecal occult blood testing (with the use of guaiac-based or immunochemical tests) alone or in combination with stool DNA examination, endoscopy (flexible sigmoidoscopy or colonoscopy), radiologic examination (computed tomographic [CT] colonography), and testing for blood-based molecular markers, such as circulating methylated septin 9 gene (SEPT9) DNA. Each strategy has differing characteristics with respect to accuracy, invasiveness, interval, costs, and quality of evidence supporting its use. The advantages and disadvantages associated with each screening strategy are summarized in Table 1. Colorectal cancer screening involves not only the one-time use of a screening test, but also repeated testing over a person's lifetime (programmatic screening). In addition, if colonoscopy is not performed as the primary screening test, all other screening strategies require colonoscopy as follow-up to a positive test.
Fecal screening tests can be divided into two broad categories: those that detect blood from ulcerated colonic mucosa resulting from cancer or large polyps and those that detect molecular markers that are shed from cancerous epithelial cells. Fecal occult blood tests include guaiac-based tests and immunochemical tests that use antibodies to detect human blood. The fecal immunochemical test (FIT) has the advantage of not requiring dietary restrictions; such restrictions are necessary with guaiac-based tests because they may be falsely positive in the presence of blood from red meat or food that reacts with the guaiac (e.g., raw horseradish, turnips, or broccoli). FIT should be performed at home on successive bowel movements; digital rectal examination in the clinic does not provide an adequate stool sample for testing. One-time FIT has been reported to have a sensitivity of 79% (95% confidence interval [CI], 69 to 86) and a specificity of 94% (95% CI, 92 to 95) for detection of cancer, and two or three samples do not significantly increase the accuracy over a single sample. However, many types of immunochemical tests are available, and their test characteristics vary widely.

High-quality evidence supports a strategy of fecal occult blood testing every year or every 2 years to screen for colorectal cancer, with colonoscopy used as follow-up to a positive test. Several randomized, controlled trials have shown up to 32% lower mortality from colorectal cancer with this strategy than with no screening, with up to 30 years of follow-up (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Although these studies used guaiac-based testing, almost all current population-based screening programs use immunochemical tests because their accuracy is greater and dietary restrictions are not required.

Molecular markers including abnormal DNA from cancerous cells can be detected in stool. FIT combined with a stool DNA test (FIT-DNA) has been approved by the Food and Drug Administration (FDA) for colorectal cancer screening. One study showed that one-time FIT-DNA had a higher sensitivity for detection of colorectal cancer than one-time FIT alone (92.3% vs. 73.8%), but specificity was lower (86.6% vs. 94.9%). The screening interval differs between FIT (annual) and FIT-DNA (interval unknown, although the U.S. Preventive Services Task Force recommends 1 or 3 years), which makes a comparison of the effectiveness of programmatic screening difficult. Data from studies evaluating the colorectal cancer mortality benefit of screening FIT-DNA are lacking.

Endoscopic Screening
Flexible Sigmoidoscopy
Randomized trials have shown that screening with flexible sigmoidoscopy, followed by colonoscopy if precancerous polyps are detected, reduces colorectal cancer mortality. Although not all trials have shown a significant benefit with respect to reducing mortality (mortality benefit), the intention-to-treat analyses in several large, randomized, controlled trials have confirmed the effectiveness of one-time and periodic (every 3 to 5 years) sigmoidoscopy, with a 26 to 31% lower mortality from colorectal cancer among patients who underwent flexible sigmoidoscopy screening than among those who underwent no screening.

Key Clinical Points

**Colorectal Cancer Screening**
- Patients at average risk for the development of colorectal cancer should begin screening at 50 years of age. Screening between 76 and 85 years of age should be tailored, and screening should stop after 85 years of age.
- There is no “best” strategy for colorectal cancer screening; therefore, the most effective strategy is the one that a patient can adhere to consistently.
- Screening strategies for colorectal cancer among patients at average risk include annual fecal occult blood testing (with the use of highly sensitive guaiac-based or immunochemical tests) or colonoscopy every 10 years. If these strategies are declined, other screening options may include flexible sigmoidoscopy, computed tomographic colonography, or blood or stool DNA testing.
- Although the harms of specific tests vary greatly, the overall risks of complications from screening are related mainly to colonoscopies (performed up front or as follow-up to other positive screening tests) and polypectomies; these risks are low and similar among all strategies.
## Table 1. Comparison of Key Features of Screening Strategies.

<table>
<thead>
<tr>
<th>Strategy and Effect on Cancer Mortality†</th>
<th>Quality of Evidence</th>
<th>Interval</th>
<th>Cost-Effectiveness‡</th>
<th>Convenience and Requirements</th>
<th>Detection of Precancerous Neoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guaiac FOBT and FIT: 32% lower mortality</td>
<td>Multiple RCTs have shown a mortality benefit (reduction in mortality) for guaiac FOBT; although FIT is more accurate than guaiac FOBT, RCTs evaluating FIT are lacking</td>
<td>Annual</td>
<td>May be more effective and less expensive than no screening; total costs lower than no screening, because of the high expense of late-stage cancer treatment with biologic agents</td>
<td>Performed at home</td>
<td>Does not reliably detect precancerous neoplasia</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy: 27% lower mortality</td>
<td>RCTs have shown a mortality benefit</td>
<td>Every 5 yr</td>
<td>Cost-effective as compared with no screening and other strategies</td>
<td>Limited bowel preparation as compared with colonoscopy</td>
<td>Can detect precancerous neoplasia</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy plus FIT: 38% lower mortality</td>
<td>A single RCT showed that flexible sigmoidoscopy plus FIT reduces cancer mortality more than sigmoidoscopy alone</td>
<td>Annual (FIT) and every 10 yr (sigmoidoscopy)</td>
<td>Cost-effective as compared with no screening and other strategies</td>
<td>Strategy that combines endoscopic and stool testing</td>
<td>Can detect precancerous neoplasia</td>
</tr>
<tr>
<td>FIT-DNA: unknown effect on mortality</td>
<td>Data from studies showing a mortality benefit are lacking; studies were limited to the detection of cancer and precancerous polyps by FIT-DNA as compared with colonoscopy</td>
<td>Every 1 or 3 yr</td>
<td>Less effective and more costly than FOBT, FIT, or colonoscopy</td>
<td>Performed at home</td>
<td>Does not reliably detect precancerous neoplasia</td>
</tr>
<tr>
<td>Colonoscopy: 68% lower mortality</td>
<td>A prospective cohort study showed a mortality benefit</td>
<td>Every 10 yr</td>
<td>Cost-effective as compared with no screening and other strategies</td>
<td>Requires full bowel preparation; usually requires sedation and an escort</td>
<td>Can detect precancerous neoplasia</td>
</tr>
<tr>
<td>CT colonography: unknown effect on mortality</td>
<td>Data from studies showing a mortality benefit are lacking; studies were limited to the detection of cancer by CT colonography as compared with colonoscopy</td>
<td>Every 5 yr</td>
<td>Less effective and more costly than FOBT, FIT, or colonoscopy</td>
<td>No sedation required but requires bowel preparation</td>
<td>Can detect precancerous neoplasia</td>
</tr>
<tr>
<td>Circulating methylated SEPT9 DNA: unknown effect on mortality</td>
<td>Data from studies showing a mortality benefit are lacking; studies were limited to the detection of cancer by circulating methylated SEPT9 DNA as compared with colonoscopy</td>
<td>Unknown</td>
<td>Unknown</td>
<td>A blood test may be associated with greater adherence than that with other screening tests</td>
<td>Does not reliably detect precancerous neoplasia</td>
</tr>
</tbody>
</table>

* CT denotes computed tomography, FIT fecal immunochemical test, FIT-DNA fecal immunochemical test combined with stool DNA test, FOBT fecal occult blood test, and RCT randomized, controlled trial.
† The effect on mortality represents a comparison of the strategy with either no screening or other strategies.
‡ Cost-effectiveness was determined as the cost per quality-adjusted life-year gained.
(Table S1 in the Supplementary Appendix).\textsuperscript{8-10,13,17} However, the benefit of sigmoidoscopy is limited to cancer in the distal colon (rectum, sigmoid, and descending colon), for which the reduction in mortality was reported to be 46%\textsuperscript{17}.

**Colonoscopy**

Case-control and prospective cohort studies have estimated cancer mortality to be 68 to 88% lower among persons who undergo screening colonoscopy than among those who do not (Table S1 in the Supplementary Appendix).\textsuperscript{12,17-19} A meta-analysis of observational studies showed that despite a 68% lower mortality overall, no significant mortality benefit from colonoscopy was seen with respect to cancer in the proximal colon.\textsuperscript{17} This discrepancy may be explained by the quality of colonoscopy (i.e., incomplete colonoscopy, poorer bowel preparation, or more difficult polyp removal in the proximal colon) or differences in the biologic characteristics of proximal and distal colorectal cancer. The mechanism underlying the majority of colorectal cancers is chromosomal instability with early mutations in APC followed by KRAS and late mutations in P53.\textsuperscript{20} Sessile serrated polyps are more commonly associated with early KRAS or BRAF mutations that may lead to chromosomal or microsatellite instability than are adenomatous polyps.\textsuperscript{21} Sessile serrated polyps are often flat or minimally raised, making them more difficult than other polyps to detect by colonoscopy, and are more common in the proximal colon, which may contribute to the higher risk of proximal cancer than distal cancer after colonoscopy.\textsuperscript{22}

**Radiographic Tests**

Published data from studies evaluating the effect of CT colonography on colorectal cancer incidence and mortality are lacking. The reported sensitivity and specificity of CT colonography to detect adenomas 1 cm in diameter or larger have ranged from 66.7 to 93.5% and from 86.0 to 97.9%, respectively.\textsuperscript{13} Because sessile serrated polyps are flat, CT colonography is inferior to colonoscopy for detection of these polyps.\textsuperscript{22} A polyp 6 mm in diameter or larger typically prompts a referral for optical colonoscopy, although the most useful size cutoff is controversial. Disadvantages of CT colonography include exposure to radiation and associated concerns regarding radiation-induced cancers and the potential need for additional testing and care for lesions outside the colon that were discovered incidentally.

**Blood-Based Tests**

The FDA has approved a blood-based colorectal cancer screening test that detects circulating methylated SEPT9 DNA. Data from studies evaluating the colorectal cancer mortality benefit of blood-based screening are lacking. In a prospective study conducted in a screening population, in which colonoscopy was used as the reference standard, the presence of circulating methylated SEPT9 DNA was shown to have a sensitivity of 48.2% (95% CI, 32.4 to 63.6), a specificity of 91.5% (95% CI, 89.7 to 93.1), a positive predictive value of 5.2% (95% CI, 3.5 to 7.5), and a negative predictive value of 99.5% (95% CI, 99.2 to 99.6) for detection of colorectal cancer.\textsuperscript{14}

**WHEN TO START AND STOP SCREENING**

The U.S. Preventive Services Task Force used comparative effectiveness modeling to examine different ages at which to initiate screening. Starting screening at 45 years of age instead of 50 years could increase life-years and reduce cancer mortality but could also increase the potential harms due to the increased burden of colonoscopy; for this reason, the recommendations are to begin screening at 50 years of age in patients at average risk for colorectal cancer.\textsuperscript{21} Although the risk of colorectal cancer increases with age, the competing risk of death from other diseases and the risk of serious complications from colonoscopy also increase with age.\textsuperscript{24,25} Several national organizations recommend that screening for patients between 76 and 85 years of age should be tailored on the basis of the presence of coexisting illnesses and that screening should be stopped after patients reach 85 years of age.\textsuperscript{23,26} A microsimulation model suggested that the intensity of prior screening and the individual risk of colorectal cancer should also be considered in determining the age at which to stop screening. Patients without a notable coexisting illness who are at average or higher risk for colorectal cancer and have had no prior screening would be expected to benefit from screening into their 80s.\textsuperscript{27}

**ADHERENCE**

The percentage of U.S. residents with up-to-date screening for colorectal cancer has not increased
Costs remain a barrier despite the perceived lack of importance or fear of screening. Barriers to screening include costs, lack of knowledge of colorectal cancer and screening, underappreciation of the effect or severity of colorectal cancer, fatalism, and a perceived lack of importance or fear of screening tests. Costs remain a barrier despite the mandate in the Affordable Care Act that health plans cover colorectal cancer screening with no patient cost-sharing, because Medicare and other insurers impose a cost-sharing requirement when a colonoscopy is performed to evaluate a positive screening test or when a screening colonoscopy becomes a therapeutic procedure with the inclusion of polypectomy.

Various interventions used in randomized, controlled trials have been shown to increase patient participation in screening; such interventions include sending patients invitations from their primary care provider, sending reminder letters and making telephone calls, and mailing fecal occult blood test kits to patients’ homes. The most successful programs use patient navigators to reduce logistic barriers, address cultural issues, and encourage participants to undergo screening; the use of patient navigators is especially important in underserved populations.

The National Colorectal Cancer Roundtable has established a goal of 80% adherence to colorectal cancer screening by the year 2018. Kaiser Permanente has implemented a comprehensive strategy focused on FIT screening, with colonoscopy performed as follow-up to a positive test, and has reached and maintained the goal of 80% adherence through four rounds of screening. Adherence to screening tests varies among strategies, and preference of strategy varies by race and ethnic group; white participants more commonly prefer colonoscopy, and nonwhite participants tend to prefer fecal testing. To achieve the highest level of adherence to colorectal cancer screening, it may be best to provide participants a choice, because the “best” strategy is the one that they will adhere to consistently.

**QUALITY OF SCREENING**

Maximizing the benefit of colorectal cancer screening requires a programmatic approach to implementing screening strategies. The quality of a screening program should be measured by its ability to identify patients who are due for screening, provide access to screening, assess adherence to the screening test and to follow-up colonoscopy if a noncolonoscopy screening test is positive, document test outcomes and disseminate accurate follow-up recommendations, identify patients with a negative test to follow them for repeat screening at the appropriate intervals, and provide timely surgery for cancers. The rate of adenoma detection (the percentage of patients in whom precancerous polyps are detected during screening colonoscopy) differs substantially among endoscopists and may be used as a measure of the ability of screening to prevent colorectal cancer. A retrospective study showed that for every 1% increase in the rate of adenoma detection, there is a 3% decrease in the rate of cancer developing after colonoscopy.

**HARMS AND COST-EFFECTIVENESS**

The harms of noncolonoscopy screening tests are low; however, all strategies require colonoscopy as follow-up to a positive test. As a result, the programmatic harms of screening are proportional to the number of colonoscopies and in particular polypectomies that are performed over the lifetime of the screened population. The technical report from the Cancer Intervention and Surveillance Modeling Network (CISNET) Colorectal Cancer Working Group estimated the number of complications (perforations, gastrointestinal bleeding, nausea and vomiting, ileus, dehydration, abdominal pain, myocardial infarction, angina, arrhythmias, congestive heart failure, respiratory arrest, syncope, hypotension, or shock) in a population of 1000 persons screened between 50 and 75 years of age to be 14 to 15 with colonoscopy at 10-year intervals, 9 to 12 with flexible sigmoidoscopy at 5-year intervals, 9 to 10 with FIT-DNA at 3-year intervals, and 10 to 11 with annual FIT.

Cost-effectiveness models more than a decade ago suggested that programmatic screening with fecal occult blood testing, flexible sigmoidoscopy, or colonoscopy reduced colorectal cancer mortality at a cost society was willing to pay. Findings from a more recent analysis suggest that given the high expense of late-stage cancer treatment with biologic agents, FIT screening may be cost-saving, with reductions in both cancer mor-
tality and overall costs — even if one includes program support costs to increase screening uptake. Moreover, screening with colonoscopy or FIT is more effective in reducing cancer mortality and less expensive than screening with FIT-DNA or CT colonography. From an economic perspective, FIT-DNA or CT colonography should not be recommended unless screening with FIT, sigmoidoscopy, or colonoscopy has been declined.

### Areas of Uncertainty

Data from completed randomized, controlled trials of screening colonoscopy are lacking, although several studies are under way. The Colonoscopy versus Fecal Immunochemical Test in Reducing Mortality from Colorectal Cancer (CONFIRM) trial (ClinicalTrials.gov number, NCT01239082) is a randomized comparison of one-time colonoscopy with annual FIT plus colonoscopy as follow-up to a positive test, to examine colorectal cancer incidence and mortality over 10 years. A similar trial comparing colonoscopy with FIT is being conducted in Spain (COLONPREV). Two additional European studies are comparing screening colonoscopy with no screening (the Nordic-European Initiative on Colorectal Cancer [NordICC]) or with FIT or no screening (Screening of Swedish Colons [SCREESCO], NCT02078804) with respect to mortality from colorectal cancer.

### Patients at Elevated Risk for Colorectal Cancer

Earlier and more frequent screening is recommended for patients at higher risk (Table S2 in the Supplementary Appendix). Patients with a first-degree relative in whom colorectal cancer developed before 60 years of age should undergo colonoscopy at 40 years of age or an age 10 years younger than the relative's age when cancer developed, whichever is earlier.
Additional factors that might influence colorectal screening strategies include race, lifestyle factors, or aspirin use. For example, among black men and women, the rates of death from colorectal cancer are 28.4 and 18.9 per 100,000 population, respectively; among white men and women, the corresponding rates are 18.7 and 13.2 per 100,000 population. Obesity, tobacco smoking, low physical activity, high intake of alcohol, high intake of red or processed meat, and low intake of fruits and vegetables are associated with increased risk of colorectal cancer, and regular use of aspirin has been associated with reduced risk. However, none of these factors are currently used to differentiate screening strategy, age of screening initiation, or surveillance intervals.

**GUIDELINES**

Several national organizations have published guidelines on strategies to reduce colorectal cancer mortality, including the National Comprehensive Cancer Network,43 the U.S. Multi-Society Task Force,50 and the American College of Gastroenterology.51 Whereas these organizations recommend certain screening strategies over others (Table 2), the 2016 U.S. Preventive Services Task Force recommendations do not support any specific testing strategy or strategies over others, but rather highlight the importance of screening patients at average risk for colorectal cancer between 50 and 75 years of age, with tailored screening for those between 76 and 85 years of age.31

**CONCLUSIONS AND RECOMMENDATIONS**

Although the patient described in the vignette is 79 years of age, she has not previously undergone screening for colorectal cancer. Because of her limited coexisting illnesses, she is expected to derive an overall benefit from a first screening for colorectal cancer, and thus I would recommend screening for this patient. I would explore her reasons for not previously pursuing screening and review with her the benefits and harms of different strategies. Because it is not feasible to summarize the entire menu of options during the span of a routine health maintenance visit, I would initially focus the discussion on colonoscopy or on annual FIT, followed by colonoscopy if the test was positive, and engage the patient in shared decision making. If she declined colonoscopy and FIT, I would discuss additional screening options, with the understanding that insurance coverage, cost-sharing, and other barriers may affect the feasibility of some options.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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