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# Colorectal cancer screening: Choosing the right test

## ABSTRACT

Colorectal cancer, the second most common type of cancer and cause of cancer-related deaths in the United States, can largely be prevented by screening. The 2 most used methods in the United States are colonoscopy and fecal immunochemical testing (FIT). FIT is noninvasive but must be done yearly for optimal performance and, if positive, must be followed by colonoscopy. Colonoscopy is invasive, operator-dependent, and more expensive, but it can detect and remove polyps during the same procedure. The choice of test depends on patient preference, family history, and the likelihood of compliance.

## KEY POINTS

Colorectal cancer rates are increasing in young individuals, with 10,000 new cases reported in 2017 in people ages 20 to 49. The evidence to support screening at ages 45 to 50 is not well established.

FIT is noninvasive but requires high patient adherence and the ability to follow a multistep process. Preliminary results from one trial showed it inferior to colonoscopy for detecting colorectal cancer precursors.

Colonoscopy allows visualization and removal of precursor lesions. A positive FIT result requires follow-up colonoscopy within 10 months.

**S**CREENING can help prevent colorectal cancer. The United States has seen a steady decline in colorectal cancer incidence and mortality, thanks in large part to screening. Screening rates can be increased with good patient-physician dialogue and by choosing a method the patient prefers and is most likely to complete.

In this article, we review a general approach to screening, focusing on the most commonly used methods in the United States, ie, the guaiac-based fecal occult blood test (FOBT), the fecal immunochemical test (FIT), and colonoscopy. We discuss current colorectal cancer incidence rates, screening recommendations, and how to choose the appropriate screening test.

This article does not discuss patients at high risk of polyps or cancer due to hereditary colon cancer syndromes, a personal history of colorectal neoplasia, inflammatory bowel disease, or primary sclerosing cholangitis.

## TRENDS IN INCIDENCE

Colorectal cancer is the second most common type of cancer and cause of cancer-related deaths in the United States, responsible for an estimated 50,000 deaths in 2017. The lifetime risk of its occurrence is estimated to be 1 in 21 men and 1 in 23 women.<sup>1</sup> Encouragingly, the incidence has declined by 24% over the last 30 years,<sup>2</sup> and by 3% per year from 2004 to 2013.<sup>1</sup> Also, as a result of screening and advances in treatment, 5-year survival rates for patients with colorectal cancer have increased, from 48.6% in 1975 to 66.4% in 2009.<sup>2</sup>

When detected at a localized stage, the 5-year survival rate in colorectal cancer is greater than 90%. Unfortunately, it is diag-

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**Appalachia and the Mississippi Delta have not benefited from the decline in the national rate of colorectal cancer**

nosed early in only 39% of patients. And despite advances in treatment and a doubling of the 5-year survival rate in patients with advanced cancers since 1990,<sup>3</sup> the latter is only 14%. In most patients, cancer is diagnosed when it has spread to the lymph nodes (36%) or to distant organs (22%), and the survival rate declines to 71% after lymph-node spread, and 14% after metastasis to distant organs.

It is essential to screen people who have no symptoms, as symptoms such as gastrointestinal bleeding, unexplained abdominal pain or weight loss, a persistent change in bowel movements, and bowel obstruction typically do not arise until the disease is advanced and less amenable to cure.

## Increasing prevalence in younger adults

Curiously, the incidence of colorectal cancer is increasing in white US adults under age 50. Over the last 30 years, incidence rates have increased from 1.0% to 2.4% annually in adults ages 20 to 39.<sup>4</sup> Based on current trends, colon cancer rates are expected to increase by 90% for patients ages 20 to 34 and by 28% for patients 35 to 49 by 2030.<sup>5</sup>

Although recommendations vary for colorectal cancer screening in patients under age 50, clinicians should investigate symptoms such as rectal bleeding, unexplained iron deficiency anemia, progressive abdominal pain, and persistent changes in bowel movements.

## Other challenges

Despite the benefits of screening, it is underutilized. Although rates of compliance with screening recommendations have increased 10% over the last 10 years, only 65% of eligible adults currently comply.<sup>1,6</sup>

Additionally, certain areas of the country such as Appalachia and the Mississippi Delta have not benefited from the decline in the national rate of colorectal cancer.<sup>7</sup>

## ■ SCREENING GUIDELINES

Most guidelines say that colorectal cancer screening should begin at age 50 in people at average risk with no symptoms. However, the American College of Gastroenterology (ACG) recommends beginning screening at age 45 in African Americans, as this group has higher incidence and mortality rates of

colorectal cancer.<sup>8</sup> Also, the American Cancer Society recently recommended beginning screening at age 45 for all individuals.<sup>9</sup>

Screening can stop at age 75 for most patients, according to the ACG,<sup>8</sup> the US Multi-Society Task Force on Colorectal Cancer,<sup>10</sup> and the US Preventive Services Task Force (USPSTF).<sup>11</sup> However, the decision should be individualized for patients ages 76 to 85. Patients within that age group who are in good health and have not previously been screened are more likely to benefit than those who have previously been screened and had a negative screening test. Patients over age 85 should not begin or continue screening, because of diminished benefit of screening in this age group, shorter life expectancy, advanced comorbid conditions, and the risks of colonoscopy and cancer treatment.

Patients and clinicians are encouraged to collaborate in deciding which screening method is appropriate. Patients adhere better when they are given a choice in the matter.<sup>12–14</sup> And adherence is the key to effective colorectal cancer screening.

Familiarity with the key characteristics of currently available colorectal cancer screening tests will facilitate discussion with patients.

## Opportunistic vs programmatic screening

Screening can be classified according to the approach to the patient or population and the intent of the test. Most screening in the United States is opportunistic rather than programmatic—that is, the physician offers the patient screening at the point of service without systematic follow-up or patient re-engagement.

In a programmatic approach, the patient is offered screening through an organized program that streamlines services, reduces over-screening, and provides systematic follow-up of testing.

## ■ DISCUSSING THE OPTIONS

Currently approved screening options and intervals between examinations are summarized in **Table 1**.

Stool studies such as FOBT and FIT do not reliably detect cancer precursors such as adenomas and serrated neoplasms. If an FOBT is positive, follow-up diagnostic colonoscopy

TABLE 1

## Options in colorectal cancer prevention and detection

### Prevention

#### Preferred:

Colonoscopy every 10 years

#### Alternatives:

Flexible sigmoidoscopy every 5–10 years

Computed tomographic colonography every 5 years

### Detection

#### Preferred:

Fecal immunochemical testing every year

#### Alternatives:

Fecal occult blood testing every year

Fecal DNA testing every 3 years

Adapted from American College of Gastroenterology guidelines, reference 8.

is required. Unlike screening colonoscopy, diagnostic colonoscopy requires a copayment for Medicare patients, and this should be explained to the patient.

FIT and FOBT detect hemolyzed blood within a stool sample, FOBT by a chemical reaction, and FIT by detecting a globin-specific antibody. Colorectal cancer and some large adenomatous polyps may intermittently bleed and result in occult blood in the stool, iron deficiency anemia, or hematochezia.<sup>15</sup>

### Fecal occult blood testing

Historically, FOBT was the stool test of choice for screening. It uses an indirect enzymatic reaction to detect hemolyzed blood in the stool. When a specimen containing hemoglobin is added to guaiac paper and a drop of hydrogen peroxide is added to “develop” it, the peroxidase activity of hemoglobin turns the guaiac blue.

Screening with FOBT involves annual testing of 3 consecutively passed stools from different days; FOBT should not be performed at the time of digital rectal examination or if the patient is having overt rectal, urinary, or menstrual bleeding.

Dietary and medication restrictions before and during the testing period are critical, as red meat contains hemoglobin, and certain vegetables (eg, radishes, turnips, cauliflower, cucumbers) contain peroxidase, all of which can cause a false-positive result. Waiting 3 days after the stool sample is collected to develop it can mitigate the peroxidase activity of vegetables.<sup>16</sup> Vitamin C inhibits heme peroxidase activity and leads to false-negative results. Aspirin and high-dose nonsteroidal

anti-inflammatory drugs can promote bleeding throughout the intestinal tract.<sup>17</sup>

In randomized controlled trials,<sup>18–21</sup> screening with FOBT reduced colorectal cancer mortality rates by 15% to 33%. The 30-year follow-up of a large US trial<sup>22</sup> found a 32% relative reduction in mortality rates in patients randomized to annual screening, and a 22% relative reduction in those randomized to screening every 2 years. Despite the many possibilities for false-positive results, the specificity for detecting cancer has ranged from 86.7% to 97.3%, and the sensitivity from 37.1% to 79.4%, highlighting the benefit of colorectal cancer screening programs in unscreened populations.<sup>23–26</sup>

### FIT vs FOBT in current practice

FIT should replace FOBT as the preferred stool screening method. Instead of an enzymatic reaction that can be altered by food or medication, FIT utilizes an antibody specific to human globin to directly detect hemolyzed blood, thus eliminating the need to modify the diet or medications.<sup>27</sup> Additionally, only 1 stool specimen is needed, which may explain why the adherence rate was about 20% higher with FIT than with FOBT in most studies.<sup>28–30</sup>

FIT has a sensitivity of 69% to 86% for colorectal cancer and a specificity of 92% to 95%.<sup>31</sup> The sensitivity can be improved by lowering the threshold value for a positive test, but this is associated with a decrease in specificity. A single FIT has the same sensitivity and specificity as several samples.<sup>32</sup>

In a large retrospective US cohort study of programmatic screening with FIT, Jensen et al<sup>33</sup> reported that 48% of 670,841 people who

**FIT should replace FOBT as the preferred stool screening method**

were offered testing actually did the test. Of the 48% who participated in the first round and remained eligible, 75% to 86% participated in subsequent rounds over 4 years. Those who had a positive result on FIT were supposed to undergo colonoscopy, but 22% did not.

The US Multi-Society Task Force on Colorectal Cancer<sup>34</sup> suggests that FIT-based screening programs aim for a target FIT completion rate of more than 60% and a target colonoscopy completion rate of more than 80% of patients with positive FITs. These benchmarks were derived from adherence rates in international FIT screening studies in average-risk populations.<sup>35–39</sup> (Note that the large US cohort described above<sup>33</sup> did not meet these goals.) Ideally, every patient with a positive FIT should undergo diagnostic colonoscopy, but in reality only 50% to 83% actually do. Methods shown to improve adherence include structured screening programs with routine performance reports, provider feedback, and involvement of patient navigators.<sup>40–42</sup>

Accordingly, several aspects of stool-based testing need to be stressed with patients. Understanding that FOBT is recommended yearly is integral for optimal impact on colorectal cancer incidence and mortality rates.

Additionally, patients should be advised to undergo colonoscopy soon after a positive FIT, because delaying colonoscopy could give precancerous lesions time to progress in stage. The acceptable time between a positive FIT and colonoscopy has yet to be determined. However, a retrospective cohort study of 1.26 million screened patients with 107,000 positive FIT results demonstrated that the rates of cancer discovered on colonoscopy were similar when performed within 30 days or up to 10 months after a positive test. Detection rates increased from 3% to 4.8% at 10 months and to 7.9% at 12 months.<sup>43</sup>

In modeling studies, Meester et al<sup>44</sup> showed the estimated lifetime risk and mortality rates from colorectal cancer and life-years gained from screening are significantly better when colonoscopy is completed within 2 weeks rather than 1 year after a positive FIT. Each additional month after 2 weeks incrementally affected these outcomes, with a 1.4% in-

crease in cancer mortality. These data suggest that colonoscopy should be done soon after a positive FIT result and at a maximum of 10 months.<sup>43,44</sup>

Screening with FOBT is a multistep process for patients that includes receiving the test kit, collecting the sample, preparing it, returning it, undergoing colonoscopy after a positive test, and repeating in 1 year if negative. The screening program should identify patients at average risk in whom screening is appropriate, ensure delivery of the test, verify the quality of collected samples for laboratory testing against the manufacturer's recommendations, and report results. Report of a positive FOBT result should provide recommendations for follow-up.

Though evidence clearly supports screening annually or biennially (every 2 years) with FOBT, the ideal interval for FIT is undetermined. Modeling studies utilized by the USPSTF and Multi-Society Task Force demonstrate that colonoscopy and annual FIT result in similar life-years gained, while 2 population-based screening programs have demonstrated that a 2- or 3-year interval may be equally efficacious by lowering the threshold for a positive test.<sup>38,45</sup>

Randomized controlled trials of screening colonoscopy vs annual and biennial FIT are currently under way. Cost-effectiveness analysis has shown that offering single-sample FITs at more frequent (annual) intervals performs better than multisample testing at less frequent intervals.<sup>45–47</sup>

### Colonoscopy

Compared with stool-based screening, colonoscopy has advantages, including a 10-year screening interval if bowel preparation is adequate and the examination shows no neoplasia, the ability to inspect the entire colon, and the ability to diagnose and treat lesions in the same session.

Screening colonoscopy visualizes the entire colon in more than 98% of cases, although it requires adequate bowel preparation for maximal polyp detection. It can be done safely with or without sedation.<sup>48</sup>

While there are no available randomized controlled trial data on the impact of screening colonoscopy on cancer incidence

**Data suggest colonoscopy should be done soon after a positive FIT, and at a maximum of 10 months**



or mortality, extensive case-control and cohort studies consistently show that screening colonoscopy reduces cancer incidence and mortality rates.<sup>49–54</sup> A US Veterans Administration study of more than 32,000 patients reported a 50% reduction in overall colorectal cancer mortality.<sup>55</sup> In a microsimulation modeling study that assumed 100% adherence, colonoscopy every 10 years and annual FIT in individuals ages 50 to 75 provided similar life-years gained per 1,000 people screened (270 for colonoscopy, 244 for FIT).<sup>56</sup>

Well-established metrics for maximizing the effectiveness and quality of colonoscopy have been established (Table 2). The most important include the mucosa inspection time (withdrawal time) and adenoma detection rate.<sup>57</sup> Withdrawal time is directly correlated with adenoma detection, and a 6-minute minimum withdrawal time is recommended in screening colonoscopy examinations of patients at average risk when no polyps are found.<sup>58</sup> The adenoma detection rate is the strongest evidence-based metric, as each 1% increase in the adenoma detection rate over 19% is associated with a 3% decrease in the risk of colorectal cancer and a 5% decrease in death rate.<sup>59</sup> The average-risk screening adenoma detection rate differs based on sex: the rate is greater than 20% for women and greater than 30% for men.

Complications from screening, diagnostic, or therapeutic colonoscopy are infrequent but include perforation (4/10,000) and significant intestinal bleeding (8/10,000).<sup>56–62</sup>

Patients with a first-degree relative under age 60 with advanced adenomas or colorectal cancer are considered at high risk and should begin screening colonoscopy at age 40, with repeat colonoscopy at 5-year intervals, given a trend toward advanced neoplasia detection compared with FIT.<sup>63</sup>

Guidelines recently published by the Canadian Association of Gastroenterology and endorsed by the American Gastroenterological Association also support starting screening in high-risk individuals at age 40, with a surveillance interval of 5 to 10 years based on the number of first-degree relatives with colorectal cancer or adenomas.<sup>64</sup> Consensus statements were based on retrospective cohort, prospective case-controlled, and cross-sectional stud-

TABLE 2

### Quality indicators for colonoscopy

Complete examination with photographic documentation achieved in  $\geq 95\%$  of screening colonoscopies,  $\geq 90\%$  of diagnostic colonoscopies

Withdrawal time  $\geq 6$  minutes

Adenoma detection rate  $\geq 30\%$  in men,  $\geq 20\%$  in women

Adequate bowel preparation

Excellent technical approach

Complete polyp resection

Information from reference 57.

ies comparing the risk of colorectal cancer in individuals with a family history against those without a family history.

Randomized clinical trials comparing colonoscopy and FIT are under way. Interim analysis of a European trial in which asymptomatic adults ages 50 to 69 were randomized to 1-time colonoscopy (26,703 patients) vs FIT every 2 years (26,599 patients) found significantly higher participation rates in the FIT arm (34.2% vs 24.6%) but higher rates of nonadvanced adenomas (4.2% vs 0.4%) and advanced neoplasia (1.9% vs 0.9%) in the colonoscopy arm.<sup>65</sup> Cancer was detected in 0.1% in each arm. These findings correlate with those of another study showing higher participation with FIT but higher advanced neoplasia detection rates with colonoscopy.<sup>66</sup>

Detection of precursor lesions is vital, as removing neoplasms is the main strategy to reduce colorectal cancer incidence. Accordingly, the advantage of colonoscopy was illustrated by a study that determined that 53 patients would need to undergo screening colonoscopy to detect 1 advanced adenoma or cancerous lesion, compared with 264 for FIT.<sup>67</sup>

### STARTING SCREENING AT AGE 45

The American Cancer Society recently provided a qualified recommendation to start colorectal cancer screening in all individuals at age 45 rather than 50.<sup>9</sup> This recommendation was based on modeling studies demonstrating that starting screening at age 45 with

**The American Cancer Society issued a qualified recommendation to start colorectal cancer screening in all people at age 45**

colonoscopy every 10 years resulted in 25 life-years gained at the cost of 610 colonoscopies per 1,000 individuals. Alternative strategies included FIT, which resulted in an additional 26 life-years gained per 1,000 individuals screened, flexible sigmoidoscopy (23 life-years gained), and computed tomographic colonoscopy (22 life-years gained).

Rates of colorectal cancer are rising in adults under age 50, and 10,000 new cases are anticipated this year.<sup>2,3</sup> Currently, 22 million US adults are between the ages of 45 and 50. The system and support needed to perform screening in all adults over age 45 and a lack of direct evidence to support its benefits in the young population need to be considered before widespread acceptance of the American Cancer Society recommendations. However, if screening is considered, FIT with or without sigmoidoscopy may be appropriate, given that most cancers diagnosed in individuals under age 50 are left-sided.<sup>4,5</sup>

Screening has not been proven to reduce all-cause mortality. Randomized controlled trials of FOBT and observational studies of colonoscopy show that screening reduces cancer incidence and mortality. Until the currently ongoing randomized controlled trials comparing colonoscopy with FIT are completed, their comparative impact on colorectal cancer end points is unknown.

## PATIENT ADHERENCE IS KEY

FIT and colonoscopy are the most prevalent screening methods in the United States. Careful attention should be given to offer the screening option the patient is most likely to complete, as adherence is key to the benefit from colorectal cancer screening.

The National Colorectal Cancer Roundtable (nccrt.org), established in 1997 by the American Cancer Society and the US Centers for Disease Control and Prevention, is a national coalition of public and private organizations dedicated to reducing colorectal cancer incidence and mortality. The Roundtable waged a national campaign to achieve a colorectal cancer screening rate of 80% in eligible adults by 2018, a goal that was not met. Still, the potential for a substantial impact is a compelling reason to endorse adherence to colorectal cancer screening. The Roundtable provides many resources for physicians to enhance screening in their practice.

The United States has seen a steady decline in colorectal cancer incidence and mortality, mainly as a result of screening. Colorectal cancer is preventable with ensuring patients' adherence to screening. Screening rates have been shown to increase with patient-provider dialogue and with selection of a screening program the patient prefers and is most likely to complete.

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