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Colorectal Cancer Screening in Average Risk Patients

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Introduction

Colorectal cancer (CRC) is the third leading cause of cancer mortality among both men and women in the United States.¹ In 2016, 134,490 new cases of and 49,190 deaths from CRC are expected, with about 90% occurring in adults over age 50.² CRC typically has a long, detectable latent period, making it a good candidate for screening. Screening for CRC has been shown to be both effective at reducing mortality and cost-effective from a societal perspective.³ However, CRC screening is underutilized, particularly among vulnerable populations, including racial/ethnic minorities and groups with low socioeconomic status.⁴ Multiple guidelines recommend that adults age 50–75 complete regular screening.^{1,5,6} Principal tests currently in use in the United States include colonoscopy and fecal occult blood testing (guaiac-based [gFOBT] and immunochemical[FIT]).⁷

In this chapter, we review risk factors for CRC, current screening recommendations from North American guideline organizations, and some of the tradeoffs associated with different screening strategies. Finally, we describe key elements of a high-quality clinical screening program and review interventions shown to be successful at improving CRC screening.

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Biological rationale for screening

CRC can develop through several molecular pathways, described in detail in other focused reviews.^{8–10} A stepwise accumulation of mutations in tumor suppressor and oncogenes leads to chromosomal instability in colorectal epithelial cells and the formation of precursor adenomatous polyps, which progress through higher grades of dysplasia to eventual carcinoma. This sequence typically takes place over 10 years or longer, forming the basis for screening recommendations for colonoscopic examination with removal of all visible adenomas every 10 years.¹¹ Stool-based tests rely on the propensity of adenomas to bleed with more advanced size and neoplasia, allowing detection of the majority of polyps and/or cancers while they are still easily treatable.^{12,13} While this paradigm has proven useful for reducing CRC mortality¹², alternate carcinogenesis pathways, such as microsatellite instability and the serrated polyp pathway, can deviate from this sequence, often manifesting as right-sided, difficult-to-visualize lesions that may bleed less in earlier stages and progress through the polyp-to-carcinoma sequence in under 10 years.^{8,10,14}

Risk Factors

Modifiable risk factors for CRC include heavy smoking, heavy alcohol intake, red and processed meat consumption, physical inactivity, and obesity.¹⁵ Dietary fiber, calcium, folate, and fish oil are associated with lower CRC risk, though interventions targeting these associations have been disappointing.¹⁶ Non-modifiable risk factors include familial risk, male sex, older age, and race/ethnicity. Socioeconomic status and other barriers to healthcare access likely mediate the majority of increased incidence in minorities¹⁷, though African-Americans may also possess independent elevated risk.¹⁸ Ashkenazi Jewish populations are also at higher risk, due to high prevalence of adenomatous polyposis coli gene mutations.¹⁹ The effect-size of non-familial, non-syndromic risk is generally too small to alter guideline recommendations for screening, though the ACG recommends screening African-Americans from age 45.²⁰

Familial and Genetic Risk—The genetic basis for most familial risk is not well characterized, and while only elevating risk 2–4 fold, contributes to 20–25% of incident CRC in the general population.²¹ Having a first- or second-degree relative with CRC or even a history of adenomatous polyps increases one's risk, and often affects screening recommendations. Risk increases with number of family members, closer relation, and younger age at diagnosis, as well as presence of cancer versus adenoma alone.²¹ The extreme of familial risk is the set of well-defined, monogenetic hereditary cancer syndromes, increasing lifetime risk from 10% (Cowden syndrome) to nearly 100% (classic familial adenomatous polyposis).²²

A hereditary cancer syndrome should be suspected based on personal or family history of multiple malignancies and/or suggestive endoscopic findings. Evidence is lacking on the optimal timing of obtaining a complete family cancer history for the average medical patient, but experts recommend a minimum initial query at 20 years of age, so that patients with cancer syndromes may have timely referral for genetic counseling, confirmatory testing, and the corresponding colonoscopic screening programs.^{22,23} The history should include the types and ages of onset of *any* cancers in first- or second-degree relatives,²² and

should be confirmed or updated periodically (some have suggested an interval of every 5–10 years).²⁴ Regarding non-syndromic familial risk, a history of CRC in multiple first-degree relatives (FDR's), or any FDR younger than 60 warrants commencement of earlier screening. Experts recommend that these patients receive colonoscopy (rather than other screening methods) at an interval of every 5 years, starting at age 40 or 10 years before the age of the relative's diagnosis, whichever comes first.^{20,25}

Other medical conditions—Several non-Mendelian medical conditions also appear to influence CRC risk, including type 2 diabetes²⁶, prior cholecystectomy²⁷, prior cytotoxic chemotherapy or abdominal radiation^{8,28}, and prolonged immunosuppression²⁹, though it is unclear if and how these should affect screening recommendations. Acromegaly and prior ureterosigmoidostomy⁸ present progressively greater risks, but the medical condition that contributes the most increased risk at the population level is inflammatory bowel disease (IBD: Crohn's disease, ulcerative colitis).³⁰ Patients with IBD should be screened with colonoscopy beginning 8 years after diagnosis, except for cases of ulcerative proctitis or proctosigmoiditis, which can be screened according to average-risk population guidelines.³⁰

Tests used for screening

In 2016, the USPSTF reviewed evidence regarding the benefits and harms of screening approaches including colonoscopy, FSIG, computed tomography colonography (CTC), gFOBT, FIT, and the multitargeted stool DNA test. The task force concluded with “high certainty” that CRC screening in average-risk, adults aged 50 to 75 years was substantially beneficial. They found that multiple, effective screening strategies available and that each was supported by different levels of evidence, with unique advantages and disadvantages.¹¹

Benefits and harms of different screening approaches—To help formulate recommendations, the USPSTF commissioned modeling studies to compare the benefits and harms of different screening strategies. Benefits of screening were measured using life years gained (LYG) and reduction in incidence and mortality from CRC. To assess harms, modelers used the lifetime number of colonoscopies required (colonoscopy burden) as a proxy for the morbidity and cost associated with each screening strategy.³ The models suggested that the following screening strategies were the most “efficient” in terms of optimizing LYG per additional colonoscopy: annual FIT, annual FIT plus FSIG every 10-years, primary colonoscopy every 10 years, and CTC every 5 years.³ However, although CTC was found to be efficient by these measures, the task force noted a lack of evidence regarding other potentially important harms of CTC, particularly with respect to incidental extracolonic findings and radiation exposure.^{3,11} Below, we briefly summarize modeled projections of the key benefits (LYG and deaths averted) and harms (colonoscopy burden) accruing in 1000 individuals screened using four of the most common screening approaches, FIT, gFOBT, FIT+ FSIG, and colonoscopy (Table 1).

Annual gFOBT and FIT are projected to provide similar benefits, but FIT, being as sensitive and more specific than gFOBT, would result in somewhat fewer lifetime colonoscopies. FIT also offers some advantages over gFOBT in terms of the process for test completion; some FIT assays require only one sample (instead of three with gFOBT), a feature that can

improve adherence.³¹ FSIG every ten years paired with annual FIT achieves a slightly higher mortality benefit than gFOBT/FIT alone, but results in more lifetime colonoscopies, and thus more potential for colonoscopy-related complications. Colonoscopy every ten years as a primary screening strategy achieves the largest morbidity and mortality benefit of the recommended screening strategies. However, it also requires substantial preparation and recovery time³² leads to the highest number of lifetime colonoscopies (more than two-fold that of FIT) and, thus, the highest rate of complications following screening.

Cost of Testing—All USPSTF-recommended screening tests are covered at full cost under the Affordable Care Act.³³ However, cost to patients associated with different strategies will vary highly depending on insurance type and test results, as abnormal results lead to additional or more frequent testing.

Screening Guidelines

For average risk adults, North American guideline organizations are largely concordant with the USPSTF on recommendations of multiple screening strategies (Table 2). Guidelines differ primarily on inclusion and relative strength of recommendation for colonoscopy, CTC, gFOBT and stool DNA tests, as well as whether pairing FSIG with a program of stool-based testing provides a worthwhile advantage over FSIG alone.^{11,20,25,34,35} All guidelines recommend colonoscopy for follow-up of any abnormal non-colonoscopy screening test. Patients with adenomatous polyps on endoscopy should be followed under a published surveillance protocol.³⁶ Patients with only one or two small (< 10 mm) tubular adenomas on initial colonoscopy are at low risk for CRC and require a surveillance interval of 5–10 years.³⁶

The ACG endorses a colonoscopy-based strategy as part of an overall preference for cancer “prevention” tests over cancer “detection” tests, and an alternative to the “menu of options” approach of the USMSTF.²⁰ The Canadian guidelines round out the other end of the spectrum, emphasizing RCT-level evidence and availability in Canada in their endorsement of only fecal tests or FSIG, and recommending against CT colonography or primary colonoscopy.³⁵ Starting age for average risk individuals is 50 years according to all guidelines.

Screening in Older Adults and Those with Limited Life Expectancy—Guidelines generally recommend against CRC screening adults over age 85.^{11,20,34,35,37} For adults between the ages of 75 and 85 who have previously completed regular screening, life expectancy should be considered in screening cessation decisions. Patients with life-expectancy of less than 5–10 years are unlikely to benefit from additional CRC screening, as the mortality benefit does not begin to accrue for at least five years after initiation.³⁸ Furthermore, the risk of severe complications, such as a severe gastrointestinal bleeding after polypectomy, is increased in older populations. When the balance of benefits and harms is unclear, decisions about stopping screening should be made through a shared decision-making process, incorporating life expectancy, comorbidity, and patient preference.

Implementation considerations

Features of a high-quality screening program—CRC screening should be viewed as a program of coordinated steps, rather than a single screening test. These steps must occur reliably in order for screening to reduce CRC mortality. A high-quality CRC screening program should deliver appropriate screening to a substantial proportion of patients by using both visit-based and non-visit based protocols that systematically ensure the following steps occur:

1. Identification of patients due either for initial or repeat screening, including identifying those in the higher CRC risk tiers
2. Patient education about screening, including decision support if more than one screening option is available to patients
3. Test ordering
4. Tracking of ordered screening tests and providing sufficient patient support to ensure test completion
5. Follow-up of abnormal screening findings and adherence to repeat screening

Which test(s) to offer: As recognized by recent USPSTF guidelines, there is no direct evidence that one screening approach is clearly superior to others, particularly when colonoscopy burden, cost, availability, patient preferences, and adherence are considered.¹¹ In fact, although colonoscopy has been the dominant primary screening strategy in the US in recent years and is widely viewed as the most effective *single* CRC screening test, emerging evidence suggests that patients' screening preferences and adherence are critical factors determining the impact a screening *program* will have on CRC mortality. For example, recent interim analysis of a European trial directly comparing colonoscopy and FIT-based strategies found that individuals initially invited for FIT-based strategy were more likely to participate in screening than were those initially invited for colonoscopy screening, resulting in an equal number of early stage CRCs detected in each study arm.³⁹ Further, accumulating evidence from studies in North America suggests that offering stool testing with gFOBT or FIT is key to increasing screening rates. For example, Inadomi et al, found that offering colonoscopy alone yielded a lower screening completion rate (38%), compared to offering gFOBT/FIT alone (67%) or a choice of either test (69%), in vulnerable patients.⁴⁰

Decision aids: One way to systematically and explicitly offer a choice of screening tests is by using a patient decision aid. Trials of decision aids show they increase screening-related knowledge, intent, and test ordering.⁴¹ Decision aids have also been shown to increase screening completion, although the effect is typically modest (about 8 percentage points vs usual care).⁴²

Patient navigation: In this context, the term “patient navigation” can refer broadly to interventions delivered by non-physicians to help patients overcome barriers to CRC screening. Patient navigators can be linked to clinical practices, health systems, community organizations, or payers. Accumulating evidence suggests that patient navigation is a

promising intervention that is particularly helpful in increasing CRC screening in vulnerable populations.^{43–47}

Other strategies: Other visit-based and non-visit based strategies have been shown to be effective in improving screening rates within practices and integrated systems.⁴⁸ Visit-based strategies can include reminder systems to help care teams identify patients due for screening.^{49,50} Practices should consider creating standing orders that permit non-physician team members to offer and track the return of gFOBT/FIT kits without requiring physician orders for individual patients. Other strategies that have been shown to improve screening rates include offering screening during nurse-driven influenza vaccination clinics.⁵¹ Non-visit-based outreach to patients due for screening including mailed reminders with or without FIT kits, or mailing gFOBT cards timed to a scheduled clinic appointment can increase screening.^{52–55}

Combined interventions: Considering the steps involved in the CRC screening process and the heterogeneity of populations and health system delivery contexts in North America, it is doubtful that any single intervention type will lead to high rates of CRC screening adherence in a given practice, community, or region. Instead, complementary interventions designed to address barriers at different steps along the screening process are likely to yield larger impacts than single interventions.

Adherence to repeat gFOBT/FIT testing and follow up of abnormal results: To reduce CRC mortality, gFOBT or FIT testing should be done annually, or at least biennially. Without systems to support repeat testing, adherence to these stool based programs is likely to be suboptimal. For example, a follow-up study of a successful CRC screening intervention trial found a substantial reduction in adherence to stool-based screening in the years after the active intervention was removed.⁵⁶ Conversely, other studies have shown that adherence to stool testing can be maintained at high levels interventions through use of interventions such as mailed reminders and telephone/text outreach.⁵⁷ Ensuring high rates of follow-up of abnormal stool screening tests for CRC is also critical for stool-based screening regimens to be effective. Patient navigation and programs of physician-directed reminder feedback plus academic detailing can increase diagnostic resolution of abnormal screening stool tests.^{58,59}

The importance of team-based care: Regardless of which screening implementation strategies are chosen, competing demands currently experienced by primary care providers requires that non-physicians be enlisted as part of a team-based, systematic approach to CRC screening.⁶⁰ Although CRC screening is widely understood to represent high-value care from a societal perspective, fee-for-service payment models have not traditionally reimbursed primary practices for staff time needed for systematic screening activities such as visit planning, registry development and maintenance, outreach, and navigation. It is hoped that changes in payment models will provide primary care “medical homes” with the resources required to implement high-quality CRC screening programs.

Overuse of screening: Unfortunately, in addition to substantial underuse of CRC screening overall, there is also evidence of overuse of screening in patient populations unlikely to derive net benefit from screening due to advanced age or comorbidities.^{61–65}

CRC screening programs should incorporate systems that take into account not only a patient's risk of CRC but also life expectancy, health status, and individual preferences.

Primary Prevention

Although no primary prevention strategy is so effective as to obviate the need for screening, our understanding of primary prevention strategies is evolving.

Aspirin: Aspirin appears to reduce the risk of colorectal cancer and adenomas after 5 to 10 years of use, though its use for this indication has been controversial because of the associated bleeding risks. Nevertheless, because aspirin also prevents cardiovascular disease (CVD) events, the USPSTF recommended in 2016 that low-dose aspirin be used for the primary prevention of CVD and CRC in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years (Grade B recommendation).⁶⁶

Lifestyle and diet: Despite lack of robust trial evidence for the effect on CRC incidence of modifying lifestyle risk factors, the general health and cardiovascular benefits of avoiding smoking, heavy alcohol use, weight gain and physical inactivity allow for strong recommendations for these behaviors. Likewise, experts recommend CRC risk reduction by replacing red meat, processed foods and refined starches in the diet with poultry, fish, and plant sources as the primary source of protein; unsaturated fats as the primary source of fat; and unrefined grains, legumes and fruits as the primary source of carbohydrates.⁶⁷

Summary

Colorectal cancer (CRC) contributes a major burden of cancer mortality in North America. Although there are multiple effective screening approaches that can reduce CRC mortality, screening remains underused. Implementation of systematic, population-based screening interventions that address multiple steps involved in the screening process is key to improving CRC screening rates. In planning for implementation, decision makers should consider the overall impact of screening *programs* (rather than individual screening tests), as well as factors such as adherence, patient preferences, and available resources. Offering patients stool-based testing with gFOBT/FIT is likely to improve uptake compared with offering colonoscopy alone. However, programs that offer stool testing must include the population health infrastructure needed to promote adherence to repeat testing and follow-up of abnormal tests.

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KEY POINTS

- Colorectal cancer (CRC) is the third most common cause of cancer death in the US, occurring primarily in individuals over age 50.
- Current evidence suggests that any of several recommended screening strategies can effectively reduce CRC mortality; commonly used approaches are primary endoscopic visualization procedures (colonoscopy and flexible sigmoidoscopy), and fecal tests for occult blood.
- Screening strategies vary with respect to their associated benefits, harms, costs, and patient experience. Offering patients stool-based screening is important for increasing screening uptake.
- Rather than a single test, CRC screening should be viewed as a cascade of events that must occur with fidelity in order for screening to be effective.
- A high-quality screening program requires substantial infrastructure to systematically identify the population at risk, provide education and decision support, and promote test ordering and completion; for fecal tests, systematic support facilitates adherence to regular testing as well as follow-up of abnormal tests.

SYNOPSIS

Colorectal cancer (CRC) contributes a major burden of cancer mortality in the United States. There are multiple effective screening approaches that can reduce CRC mortality. These approaches are supported by different levels of evidence, and each has its own advantages and disadvantages.

Implementing a systematic approach to screening that addresses the multiple steps involved in the screening process is essential to improving population-level CRC screening. Implementation decision makers should consider the overall characteristics of screening programs (rather than individual screening tests), including patient preferences, adherence, and resources. Offering patients stool-based screening is important for increasing screening uptake. However, programs that offer stool testing must support the population health infrastructure needed to promote adherence to repeat testing and follow-up of abnormal tests.

Table 1.

Test performance and other characteristics of commonly performed CRC screening tests, per 1000 people screened

	Sensitivity/ Specificity ^{1,2}	Life years gained ²	CRC Cases Averted (%) ²	CRC deaths averted (%) ²	Lifetime COLOs ²	Complications ²	Nature of test
gFOBT (1 yr)	62–79% 87–96%	232–261	33–54 (49–75%)	20–23 (73–82%)	2230–2287	11	No preparation, no recovery time, 3 stool samples, completed at home yearly
FIT (1 yr)	10µg cutoff: 79–88% 91–93% 20µg cutoff: 73–75% 91–95%	231–260	31–52 (47–72%)	20–23 (72–81%)	1739–1899	10–11	No preparation, no recovery time, 1 stool sample, completed at home yearly
FIT-DNA (3 yr)	92% 84%	215–250	29–49 (43–68%)	19–22 (68–78%)	1701–1827	9–10	No preparation, no recovery time, 1 stool sample, completed at home every 3 years
FSIG (10 yr) FIT (1 yr)	FSIG 60%–70% as sensitive COLO ³	246–270	38–57 (76–85%)	22–24 (77–85%)	2248–2490	11–12	FSIG: ½ day prep time, 1 hour recovery time, completed every 10 years in a medical facility
COLO (10 yr)	Reference	248–275	42–63 (62–88%)	22–24 (79–90%)	4007–4101	14–15	24 hours prep time, 1 day recovery time, completed every 10 years in a medical facility
CTC (5 yr)	67–94% 85–98% ⁴	226–265	34–56 (51–78%)	20–24 (72–85%)	1654–1927	10–11	24 hours prep time, 1 hour recovery time, completed every 5 years in a medical facility

¹ Per 1 time use of test

² Knudsen, 2016; Zauber 2015; USPSTF 2016

³ Operator dependent, no evidence comparing FSIG directly to COLO

⁴ Sensitivity and specificity for detecting adenomas 10mm

⁵ Complications include gastrointestinal events (bleeding, perforation, eg) and cardiopulmonary events (myocardial infarction, angina, cardiac/respiratory arrest, etc)

Table 2.

Comparison of colorectal cancer screening recommendations of North American guidelines committees.

	USPSTF	ACG	MSTF/ACS/ACR	ACP	CPSTF
Recommendations	<ul style="list-style-type: none"> Colonoscopy every 10 years CT colonography every 5 years¹ FSIG every 10 years plus FIT every year gFOBT² or FIT 	<p><i>Preferred:</i></p> <ul style="list-style-type: none"> Colonoscopy every 10 years CT colonography every 5 years FS every 5–10 years FIT every year <p><i>Acceptable when all other options declined or unavailable:</i></p> <ul style="list-style-type: none"> gFOBT² annually or stool DNA every 3 years 	<ul style="list-style-type: none"> Colonoscopy every 10 years CT colonography every 5 years FSIG every 5 years DCBE every 5 years gFOBT², FIT every year Stool DNA at uncertain intervals, but more frequent than every 5 years³ 	<ul style="list-style-type: none"> Colonoscopy every 10 years FSIG every 5 years FSIG every 5 years plus FIT or gFOBT² every 3 years gFOBT² or FIT every year 	<ul style="list-style-type: none"> FSIG every 10 years gFOBT² or FIT every 2 years
Starting age, average risk	50	50, except 45 in African-Americans	50	50	50–60 ⁴
Stopping age⁵	75–85, depending on individual risk, life-expectancy and values	Not discussed	Not discussed	75–85, depending on individual risk, life-expectancy and values	75

USPSTF: United States Preventive Services Task Force; **ACG:** American College of Gastroenterology; **MSTF:** Multi-Society Task Force; **ACS:** American Cancer Society; **ACR:** American College of Radiology; **CT:** computed tomography; **FS:** flexible sigmoidoscopy; **gFOBT:** guaiac-based fecal occult blood test; **FIT:** Fecal immunochemical test; **DCBE:** double contrast barium enema

¹ Only equivalent to other strategies if the burden of screening metric is lifetime colonoscopies, not lifetime cathartic bowel preparations. Does not account for possible risks of frequent, low-dose radiation, or incidental extra-colonic findings.

² Should always be “high-sensitivity” (e.g. Hemoccult Sensa) guaiac-based test if used

³ Combined FIT-DNA test not available at time of publication

⁴ Canadian guidelines weight recommendation strength by age, with ages 50–59 receiving a “weak” recommendation for screening, and ages 60–74 a “strong” recommendation

⁵ Assuming personal history of appropriate screening without diagnosis of a high-risk condition