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Colorectal Cancer: Screening and Diagnosis

Jason Domagalski, MD, FAAFP; Medical Director, Physician Assistant Residency, Primary Care Clinic, Clement J. Zablocki VA Hospital, Milwaukee, WI

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Learning Objectives:

- Understand the epidemiology and risk factors of colorectal cancer (CRC)
- List the recommended screening methods for CRC and their advantages and limitations
- Describe the clinical guidelines for CRC screening in the United States
- Develop patient-centered communication skills to effectively encourage patients to participate in CRC screening programs
- Implement strategies to bridge the care gap between preventative care and CRC screening within the healthcare practice

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Colorectal Cancer: Epidemiology and risk factors

Colorectal cancer (CRC) is the third most diagnosed cancer in the United States, and the second most common cause of cancer-related deaths[1]. Globally, there were 1.9 million new CRC cases diagnosed in 2020, with 930,000 estimated deaths, whereas in the U.S, an estimated 150,000 new cases were diagnosed in 2023, with approximately 50,000 deaths[1]. Additionally, the number of CRC cases is increasing at the rate of 1-2% per year in individuals under 55 years old, with the Native American/Alaskan population and Black population experiencing the greatest rates of mortality[1]. CRC subtypes can be defined based on the location of the cancer in the large intestine (proximal colon, distal, or rectal) or based on the mechanism of occurrence (sporadic, hereditary, or colitis-associated). A number of environmental, lifestyle, and genetic factors may play a role in the carcinogenesis of CRC. For instance, physical inactivity is associated with elevated risk of CRC, whereas high levels of physical activity are associated with increased survival rate in CRC patients. Alcohol consutption, obesity, cigarette smoking, and consumption of red meat are associated with an increased risk of developing CRC. On the other hand, consumption of high fiber vegetables is associated with lower risk of developing CRC[2].

CRC screening for individuals at average risk of CRC are discussed here. Whereas recommendations for individuals with a family history of CRC, polyposis syndromes, or underlying inflammatory bowel disease are not discussed here. Most colorectal cancers develop from slow-growing benign colorectal polyps. This pathway from polyp to early cancer to late cancer provides an opportunity to intervene in disease development at the polyp or early cancer stage using screening tests.

CRC Screening: Challenges and Opportunities

Surveys of healthcare providers (HCP), clinicians, and primary care workers[3] have revealed that HCPs face two significant challenges with respect to CRC in the clinical setting. Firstly, a low screening rate is a significant barrier to improving mortality and survival in CRC[3]. It is important to note that the 5-year survival for CRC is ~90% when diagnosed at an early stage, and therefore, increasing screening rates is critical to improving mortality and survival rates[1]. Therefore, it is necessary to educate health care providers and primary care workers on the importance of screening, so that they may provide accurate and relevant information to patients. Secondly, a care gap exists between preventative care and CRC screening. This is often due to a lack of information amongst patients regarding the importance of screening, as well as the different types of tests available[4]. In this situation, this care gap can be addressed by providing communication strategies and medical education to care providers.

Unlike many other developed countries, the US does not have a national screening program where individuals are systematically invited/reminded to be screened at certain time points in their lives. Instead screening is opportunistic and *ad hoc*. Unlike other countries with national screening programs, individuals at average risk of CRC in the US are offered a choice of different screening tests, with different degrees of accuracy/efficacy (discussed below). Clinician biases/education, patient understanding, expenses, and insurance cover can all influence such choices.

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Table 1: Overview of screening methods, including descriptions, advantages, disadvantages, and their sensitivities and specificities.

Screening Method	Description	Advantages	Disadvantages	Sensitivity	Specificity
Fecal Occult Blood Test (FOBT)	Detects hidden blood in stool samples, which can indicate cancer or polyps.	• Non-invasive • Inexpensive • Easy to administer at home	• Requires multiple tests for accuracy • False positives/negatives • May miss small tumors or polyps	50-75%	96-99%
Fecal Immunochemical Test (FIT)	Detects blood in stool using antibodies specific to human hemoglobin.	• More accurate than gFOBT • Can be done at home • Fewer dietary restrictions compared to FOBT	• Only detects cancer with bleeding • Requires annual testing	74-81%	95-96%
Stool DNA Test (e.g., Cologuard)	Detects DNA mutations and blood in stool that may indicate cancer or precancerous growths.	• Non-invasive • Can detect early-stage cancers and advanced polyps • Can be done at home	• More expensive • False positives/negatives • May require follow-up colonoscopy	93%	89%
Colonoscopy	A procedure using a flexible tube to view the entire colon and rectum.	• Gold standard for detection • Can remove polyps and take biopsies during procedure	• Invasive • Expensive • Requires bowel preparation • Risk of complications (e.g., perforation) • Requires sedation and support for driving to appointment	95%	86-89%
Sigmoidoscopy	A flexible tube examines the lower part of the colon (sigmoid colon and rectum).	• Less invasive than colonoscopy • Lower cost • Shorter procedure time	• Only examines part of the colon • Polyps or cancers in other areas may be missed	95%	87%
CT Colonography (Virtual Colonoscopy)	A CT scan that creates detailed images of the colon.	• Non-invasive • Quick procedure • No sedation required	• Requires bowel prep • May miss small polyps • Limited ability to biopsy or remove polyps • May not be readily available at rural or remote locations	67-94%	86-98%
Flexible Sigmoidoscopy with FIT (Combination Screening)	Combines flexible sigmoidoscopy and FIT for a comprehensive approach.	• More accurate than either test alone • Can detect both blood and polyps	• Still misses cancers in the entire colon • Requires two different tests	95%	87%

Adapted from Refs 9 and 11.

Analysis of CRC incidence globally reveals that it appears to be higher in countries with a high human development index, and increases as a country adopts a more Western lifestyle. Thus, CRC remains an economic and social burden primarily in developed countries[1]. Nevertheless, unlike other types of cancers, CRC remains a highly preventable disease, if screening strategies can be implemented effectively. In the US, screening is primarily implemented on an *ad hoc* and opportunistic basis, whereas in European countries, a more systemic and organized approach has been implemented[4].

CRC Screening Guidelines for Average Risk Individuals

Globally, in countries where CRC screening is systematically conducted on a national basis, screening is recommended to be initiated at the age of 50[5]. However, in 2021, the United States Preventive Services Taskforce (USPSTF) recommended lowering the age of starting CRC screening to 45 for individuals at average risk of CRC[6]. Additionally, for African Americans, who are at higher risk of developing CRC, screening is now recommended to start at the age of 40 by the American College of Physicians[7]. These guidelines are broadly similar to the guidelines proposed by the American Cancer Society (ACS), which recommend starting screening at age 45 for individuals at average risk of developing CRC[8]. On the other hand the CRC screening guidelines proposed by the American College of Gastroenterologists (ACG) and published by the American Association of Family Physicians (AAFP) recommend regular CRC screening for average-risk individuals aged 50-75 years, and only urge physicians to *consider* screening for individuals aged 45[6].

Screening Tests Used in the Clinic

Several different types of screening tests are currently available for CRC (Table 1). These include stool-based tests, tests that involve direct visualization (colonoscopy), as well as emerging screening strategies that make use of molecular markers.

Stool-based tests

Stool-based tests rely on the detection of the presence of occult blood in the stool sample of the individual. The main principle behind stool-based tests is that CRC causes occult bleeding, which may be detected in the stool[9]. There are three main types of stool-based tests[9]: Guaiac-based fecal occult blood tests (gFOBT), fecal immunochemical tests (FIT), and fecal immunochemical test-DNA or multi-target stool DNA that includes FIT (FIT-DNA (mt-sDNA)).

gFOBT detects pseudo peroxidase activity in the stool, and is an indirect measure of hemoglobin in the stool[9]. Several controlled trials have demonstrated that screening with gFOBTs every 2 years results in a reduction of CRC mortality by 9-22%[9]. Specifically, several studies have also compared the efficacy of annual vs biennial gFOBT testing, and demonstrated a modest benefit for annual rather than biennial testing. gFOBT remains the most cost efficient of all CRC screening strategies as of 2025[11].

The FIT is an antibody-test that directly measures the level of hemoglobin in the stool. Unlike the gFOBT, the FIT has greater sensitivity, is not affected by diet, and requires only one stool sample, thus resulting in greater adherence among patients for screening[9]. Consequently, annual FIT has almost replaced the gFOBT as the stool test of choice when it comes to CRC screening[9]. Observational studies have demonstrated a 10% reduction in CRC incidence, and 62% reduction in CRC-associated mortality attributable to FIT[10].

Compared to gFOBT and FIT, which rely on the detection of hemoglobin in stool samples, the FIT-DNA or mt-sDNA test relies on the detection of abnormally methylated DNA regions within colorectal cancer cells that are shed in the stool[9]. The challenge in this test is in identifying the CRC DNA from the bacterial DNA, which are most abundant in blood. Similar to the FIT, there are no dietary modifications required, the mt-sDNA test has a sensitivity of 92% and specificity of 85%[9]. This test is recommended to be performed every 1-3 years rather than the annual or biennial screening recommended for FIT or gFOBT. The mt-sDNA has a number of advantages such as higher sensitivity, less frequent screening, but also suffers from the disadvantage of higher cost and higher false-positive rate compared to FIT[9, 17].

Overall stool-based tests have a number of advantages compared to invasive tests that require direct visualization, such as non-invasiveness, the ability to perform tests at home, and low cost[9].

Positive results on stool tests will need to be followed up with visualization investigations (below).

Direct visualization

There are four primary types of tests that involve direct visualization of the colon. These include: flexible sigmoidoscopy, colonoscopy, computer tomography colonography (CTC), and capsule colonoscopy.

Flexible sigmoidoscopy enables direct visualization of the distal portion of the colon, and the opportunity to biopsy as well as remove polyps. Prior preparation to successful testing involves the administration of enemas with or without oral magnesium citrate, and no sedation is required. Analysis of a number of long-term randomized controlled trials that compared the effects of flexible sigmoidoscopy compared to no screening demonstrated a significant decrease in CRC incidence as well as CRC-associated mortality[9]. Flexible sigmoidoscopy is recommended every 5 years by the USPTF[9].

Colonoscopy, is perhaps the most effective single application method for CRC screening, and is indicated after one or more non-invasive tests are positive[9]. Colonoscopy involves the use of a long flexible tube called a colonoscope that is fitted with a light and a camera, that enables the visualization of the entire colon as well as excision of any polyps that may be found. Colonoscopy requires individuals to undergo sedation, dietary modification, and purgative preparation, as well as the assistance of someone to transport them after the procedure[11]. Lastly, colonoscopy is associated with a small risk of colonic perforation or bleeding.

CTC or computed tomography colonography allows scan visualization of the entire colorectum. CTC is typically performed after administration of a bowel preparation, and an agent to radiographically tag stool for digital subtraction[11]. Compared to colonoscopy, CTC has a per-person sensitivity for adenomas that ranged from 66.7%-93.7% with specificity values ranging from 96%-97.9%[11]. CTC may be administered in a variety of settings ranging from urban hospital centers to tertiary community centers, and barriers to greater uptake of CTC may include lack of insurance reimbursement and the need for bowel cleansing, which is a major factor affecting patient adherence[18, 19].

Lastly, capsule colonoscopy involves the ingestion of a pill-sized camera that records images as it travels through the upper GI tract to reach the colon. This test is minimally invasive and requires no sedation but does require effective bowel preparation. Capsule colonoscopy is not currently recommended by the FDA or the USPSTF as a first-line screening test. Capsule colonoscopy is only recommended for patients whose colonoscopy results were indeterminate. Capsule colonoscopy results do need to be confirmed by a standard colonoscopy[11].

Emerging screening strategies

With the advent of genomic sequencing technology and the enhanced cost-effectiveness of sequencing in recent years, non-inva-

Key messages regarding CRC screening from the Colorectal Cancer Screening Messaging Guidebook:

- Low screening in CRC: 1 out of 3 adults aged 50-75 years is not getting screened as recommended
- 71% of unscreened individuals report being health conscious, yet they face several barriers to screening, such as procrastination, cost, unpleasantness, no family history
- Three factors may make screening easier: access to different CRC screening test alternatives, improved insurance coverage, education on screening
- Health care providers are overwhelmingly the preferred source of education regarding CRC screening, with 60% survey respondents

Adapted from: Colorectal Cancer Screening Messaging Guidebook (https://nccrt.org/wp-content/uploads/2023/11/2019-CRC-Communications-Guidebook-v13.pdf)

sive screening strategies such as circulating tumor-DNA based tests and blood based tests are currently being developed. Circulating tumor DNA (ctDNA)-based tests or liquid-biopsy based tests rely on the detection of DNA sequences from apoptotic tumor cells that are found in blood circulation[11]. Sequencing of these DNA fragments can reveal mutations present in tumor cell DNA, and reveal tumor-specific markers and also elucidate the tumor burden[11]. Similar to the detection of ctDNA in the circulation, CRC cells can also be detected in the circulation, which can be isolated from blood samples by using physicochemical or cell sorting techniques based on cell surface molecules[11]. ctDNA analysis can be used for prognosis or surveillance for recurrence in patients already diagnosed with CRC.

Several blood-based screening methodologies are currently being tested in clinical trials for CRC screening. In August 2024, the FDA granted approval to SHIELD, the first blood-based screening method approved for the primary screening of CRC[12]. One of the challenges of implementing a non-invasive blood-based screening methodology is that it must meet the stringent Centers for Medicare & Medicaid Services (CMS) guidelines to be covered by Medicare/Medicaid[13]. These include sensitivity greater than or equal to 74% and specificity of 90% or greater for colorectal cancer[13]. A recent report presented at the ESMO 2024 conference on a new blood based screening method provided promising preliminary results, with a sensitivity of 88% and specificity of 90.1% for CRC[14]. These results, therefore, highlight the great potential of this new screening methodology in both meeting the CMS guidelines and as a potential alternative to the current stool-based and colonoscopy based screening guidelines.

Lastly, apart from ctDNA markers, epigenetic markers involving an alteration in the methylation status of certain genes can be used for screening, to predict disease progression or to predict response to treatment. Methylome analyses have revealed that the CRC cell can accumulate several hundred abnormal methylation marks, which may alter the expression of tumorigenic genes[11]. Recently, an assay to detect methylation at the *septin9* gene was approved by the FDA for colorectal cancer screening. This assay can reliably identify CRC patients with 70% sensitivity, with a 10-20% false-positivity rate, and therefore this assay may have limited utility[11].

Overcoming Patient Barriers Regarding CRC Screening

Several studies have focused on the identification of barriers to CRC screening amongst different populations. These barriers exist at both the level of the HCPs as well as at the level of patients. For instance, a 2017 study identified a lack of provider recommendation, lack of time to discuss screening, and questions about the efficacy of screening as the primary provider barriers to screening. On the other hand, on the patient side, the study identified barriers such as screening cost, a lack of awareness, lack of health literacy, fear of discomfort and pain as important barriers. Systemic barriers to the uptake of CRC screening such as a lack of a reminder system, lack of support staff for follow-up, and a shortage of facilities to perform screening are also important[3].

Furthermore, on the patient side, belonging to a minority race and ethnicity, and socioeconomic challenges such as a lack of insurance and lower income are factors that are associated with lower rates of screening, and consequently later detection and worse outcomes[3,15]. These results have been borne out in a 2019 qualitative study which surveyed patients at primary care sites and a questionnaire asked the patients to self-report barriers to CRC screening. This study also identified similar barriers as had been identified in national surveys such as a lack of recommendation from their HCP, fear or worry about the procedure or outcome, financial implications, and logistical challenges, such as transportation and time. Other barriers included a lower health prioritization for CRC screening and concerns about possible discomfort associated with the screening procedure[16].

However, it is important to realize that none of these barriers are unsurmountable, and can be effectively addressed with patient education and continuing medical education for HCPs on the importance of CRC screening. These include patient literature, such as the 2019 Colorectal Cancer Screening Messaging Guidebook developed by the National Colorectal Cancer Roundtable[4]. Such literature provides effective communication strategies and facts about the importance of CRC screening to patients that can be easily understood by a layperson[4]. Moreover, patient education can also be effectively achieved through the development of educational videos, tutorials, and FAQs[9], Additionally, providers may make use of reminder prompts in the electronic health records system or use the Colorectal Cancer Risk Assessment Tool provided by the National Cancer Institute (https://ccrisktool.cancer.gov).

Conclusion

Colorectal cancer (CRC) is a highly preventable cancer and the incidence and mortality associated with it can be reduced by implementation of effective screening of patients. Several different screening methods are routinely used in clinical practice to detect CRC. Clinical practice guidelines on CRC screening have been issued by several professional associations in the United States. HCP education regarding these is critical to improving screening amongst target populations, with the ultimate goal of reducing CRC occurrence. Lastly, patient education regarding the importance of CRC screening may be the most effective tool to reducing the incidence of CRC and ensuring adherence to clinical practice guidelines regarding CRC screening.

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