Colorectal Cancer Screening

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ABSTRACT

Colorectal cancer (CRC) continues to be one of the most commonly diagnosed cancers and contributes significantly to many cancer-related deaths despite sustained progress in diagnostic and treatment options. Many forms of CRC can be prevented through early and routine screening, when precancerous lesions may be detected and removed before they undergo malignant transformation or metastasis. Despite widespread efforts to improve CRC screening rates, at least 40% of age-eligible adults do not adhere to screening guidelines. A new generation of noninvasive, molecular-based diagnostic tests with high sensitivities and specificities has the potential to improve screening rates through optimal risk stratification of patients who may benefit from more invasive screening techniques. This review presents various guidelines and methods that are currently available for CRC screening, summarizes the rationale behind utilization of novel molecular-based diagnostic tests for CRC screening and prevention, and discusses appropriate screening techniques and intervals in populations of varying risk.

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second most common type of cancer-related death in the United States. In 2013, 136,119 people were diagnosed and 51,813 people died from CRC in the United States.[1] The cumulative lifetime risk for colon cancer is 1 in 20 in men and 1 in 22 in women.[2] Death rates from colon cancer have been on the decline in the United States, which is primarily attributable to the adoption of widespread screening that allows for early detection and removal of colorectal polyps. Moreover, substantial improvements in colon cancer treatment have been achieved over the past few decades.[3] However, CRC rates are increasing in historically low-risk countries such as Japan, Korea, and China and in eastern Europe.[4] Higher colon cancer rates reported in these geographic areas likely result from westernization of global diets, obesity, smoking, alcohol consumption, lack of exercise, instability in the microbiome, and carcinogenic substances in food.[5-10]

The purpose of this review is to present current guidelines and methods available for CRC screening, discuss novel molecular-based CRC diagnostic tests, and discuss appropriate screening techniques and intervals in various populations. In order to gather information for this review, we searched recent CRC screening guidelines, related articles, and appropriate references using the PubMed database.

COLORECTAL SCREENING GUIDELINES

Colonoscopy and other screening modalities have contributed to decreased rates of colon cancer death through early identification and removal of precancerous polyps.[11] With the advent of novel molecular technologies and increased understanding of the molecular changes leading to cancer, new methods hold promise for risk stratification of patients to determine those who may benefit from more invasive screening tests.[12] Importantly, recent guidelines released by the US Preventive Services Task Force (USPSTF) in June 2016 confirmed that CRC screening in average-risk, asymptomatic adults between the ages of 50 and

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Table 1. Comparison of Various Screening Recommendations Issued by Different Organizations for Average-Risk, Asymptomatic Individuals

Organization	Year	Age to Begin Screening (Years)	Age to Discontinue Screening (Years)	Tests Recommended for Cancer Prevention and Interval/Procedural-Based Tests	Tests Recommended for Cancer Detection and Interval/ Stool-Based Tests	Preferred Screening Method	Ref
US Preventive Services Task Force	2016	50	75	Colonoscopy (10 yrs) Flexible sigmoidoscopy (5 yrs) Flexible sigmoidoscopy with FIT (sigmoidoscopy every 10 yrs, FIT every 1 yr) CT colonography (5 yrs)	FOBT (1 yr) FIT (1 yr) FIT with stool DNA (1 or 3 yrs)	None	13
American Cancer Society, US Multi-Society Task Force on Colorectal Cancer, and American College of Radiology	2008	50	Not specified	Colonoscopy (10 yrs) Flexible sigmoidoscopy (5 yrs) CT colonography (5 yrs) Double-contrast barium enema (5 yrs)	FOBT (1 year) FIT (1 year) Stool DNA (interval uncertain)	Cancer prevention	14
American College of Physicians	2012	50	75 or individuals with <10-year life expectancy	Colonoscopy (10 yrs) Flexible sigmoidoscopy (5 yrs) Stool DNA (interval uncertain)	FOBT (1 yr) FIT (1 yr)	None	15
American College of Gastroenterology	2009	50 (45 for African Americans)	Not specified	Colonoscopy (10 yrs) Flexible sigmoidoscopy (5 yrs) CT colonography (5 yrs)	FIT (1 yr) FOBT (1 yr) Stool DNA (3 yrs)	Cancer prevention (colonoscopy) over detection (FIT)	16

Abbreviations: Ref, reference; FOBT, fecal occult blood test; FIT, fecal immunochemical test; CT, computed tomography.

75 years is substantially underused despite its demonstrated benefits.[13] Moreover, these guidelines suggest that although the multiple screening strategies described later in this article have differing levels of evidence to support their utility, there are no data that shows that a select test provides a greater net benefit. In addition to these USPSTF guidelines, other organizations including a joint venture between the American Cancer Society (ACS), the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology,[14] the American College of Physicians (ACP),[15] and the American College of Gastroenterology (ACG)[16] also have issued CRC screening guidelines for cancer prevention and detection strategies. While all organizations recommend routine CRC screening beginning at age 50 in asymptomatic average-risk adults, preferred screening methods, frequency intervals, and age to discontinue screening vary across guidelines. Similarities and differences between these guidelines are summarized in Table 1. As discussed later in this article, guidelines from the various organizations also differ with regard to the definition of high-risk individuals and optimal screening strategies in these patients.

COLORECTAL SCREENING OPTIONS

As described below and in Table 2, numerous procedural- and laboratory-based screening modalities with variable sensitivity, specificity, positive/negative predictive values, and cost have emerged to expand the list of available CRC screening methods. Due to high sensitivity and specificity and facilitation of immediate polyp removal, colonoscopy remains the gold standard for CRC screening. Thus, it follows that a major limitation of imaging-, stool-, and blood-based testing modalities is the potential for a two-step approach where individuals with a positive screening test are advised to undergo follow-up colonoscopy. This may result in early diagnostic gaps and the potential for diagnostic delays or patients lost to follow-up. Moreover, given the low sensitivity of stool- and blood-based tests for precancerous polyps as compared to colonoscopy, a larger number of precancerous polyps have the potential to go undetected and untreated. As the impact of two-step CRC methods on patient compliance with follow-up testing is unknown, shared decision making with physicians should occur prior to screening. In particular, patients should be informed of the risks and benefits of screening and how a positive test result will be managed prior to screening. On a similar note, patient recollection of dates and results from prior colonoscopies is unreliable and consultation of medical records is therefore important for verification of screening history and interval.[17]

Procedural-Based Screening

Colonoscopy has been widely available since the 1970s, at which time it was used for polypectomies. Screening guidelines became widely adopted in the 1990s based on randomized controlled trials demonstrating that CRC screening with fecal occult blood testing (FOBT) followed by a colonoscopy for a positive result

Table 2. Comparison of Sensitivity and Specificity of Various Screening Modalities for Detection of Colorectal Cancer[30,47]

Test	Sample	Sensitivity	Specificity	Positive Predictive Value[a]	Negative Predictive Value[a]	Availability	Approximate Cost Before Insurance
Colonoscopy	Anatomic	95%	90%	0.4%	>99.99%	Specialist	$800 - $1,000*
FOBT	Stool	70% (64%-80%)	92.5% (87%-96%)[18]	0.4%	>99.98%	In-vitro diagnostic	$5[b]
FIT	Stool	70% (61%-91%)	95% (91%-98%)	0.6%	>99.98%	In-vitro diagnostic	$22[b]
CT colonography	Imaging	89% (84%-93%)	75% (59%-87%)	0.1%	>99.99%	Radiology	$400 - $800[b]
ColonSentry	Blood	72%	70%	0.1%	>99.98%	Laboratory developed test	Up to $350[c]
SEPT9-based tests	Blood	67%-96%	81%-99%	0.1%-3.9%	>99.98%->99.99%	Laboratory developed test	Up to $350[c]
Cologuard	Stool	92% (83-98%)	87% (86-87%)	0.3%	>99.99%	Laboratory developed test	$649[d]

Abbreviations: FOBT, fecal occult blood test; FIT, fecal immunochemical test; CT, computed tomography.

[a]Calculated based on prevalence rate of 41.9 CRC cases/100,000 (age adjusted to the 2000 US standard population) obtained from the American Cancer Society/North American Association of Central Cancer Registries 2015 (https://cancerstatisticscenter.cancer.org).

[b]Obtained from Colon Cancer Alliance: http://www.ccalliance.org.

[c]Based on general estimates for blood-based DNA amplification tests.

[d]Obtained from Cologuard website: http://www.cologuardtest.com.

was associated with a significant reduction in colon-cancer related mortality.[19,20] Observational studies demonstrated a 30% to 60% reduction in the risk of incident CRC and mortality from isolated screening colonoscopy versus colonoscopy based on positive FOBT results.[21,22] Colonoscopy remains the current standard of care in the United States for CRC screening, and the USPSTF recommends colorectal screening for individuals between the ages of 50 and 75.[13,23] Currently, the most common screening algorithm used in the United States for average-risk individuals involves a colonoscopy every 10 years based on the slow growth cycle (10-15 years) for most small polyps to grow and transform into CRCs.[11] Decreased interval screening is indicated when there is a family history of CRC or when high-risk polyps have been identified.[24,25] Despite high-quality published societal guidelines, screening in the United States is limited to approximately 58% of at-risk men and women.[26]

Flexible sigmoidoscopy also is included for colorectal screening in the United States guidelines as reductions in CRC incidence and mortality have been demonstrated with this procedure.[27] When used for screening, flexible sigmoidoscopy is recommended every 5 years in average-risk individuals. As the benefits of sigmoidoscopy are limited to the distal colon, this approach has been utilized largely for screening in cases where a full colonoscopy may not be initially feasible. Such technical limitations may be due to obstructive cancer, extensive looping of the colon, traverse angulation, or excessive mucosa friability. Given the gradual shift from left-sided CRC to right-sided CRC that has been consistently observed since the 1960s, colonoscopy continues to dominate endoscopic screening modalities.[28,29]

In recent years, use of computed tomography (CT) colonography has replaced the double-contrast barium enema as the radiographic screening alternative to colonoscopy.[16] However, CT colonography remains controversial and this procedure is generally not covered by insurance unless there are contraindications to other more traditional forms of CRC screening.[30] When used for screening, the suggested interval is 5 years in average-risk individuals, but this recommended interval is somewhat uncertain until additional data become available.[31] Like colonoscopy, CT colonography requires bowel cleansing and colon distention for an optimal study. The procedure itself is relatively fast, well-tolerated, and does not require anesthesia or a post-procedural recovery period. The radiation dose is approximately 4-5 mSv (for reference, a 2-view chest x-ray is about 0.1 mSv), which may be further reduced using optimized protocols to decrease radiation exposure.[32] Unfortunately, CT colonography does not allow for simultaneous polyp removal or determination of the histologic nature of a lesion and false positive/negative CT colonography findings may result from residual material and/or insufficient distension. It is also important to note that extracolonic findings, the majority of which are benign and not clinically significant, have the potential to add unnecessary health care costs and anxiety, although clinically significant lesions may be detected at earlier, more treatable stages as well.[32] Studies have shown mixed

Table 3. Varying Definitions of Increased-/High-Risk Individuals According to Screening Guidelines

Organization	Description of Increased/High-Risk Individuals	Additional Notes	Reference
US Preventive Services Task Force	Family history of CRC (a first-degree relative with early-onset CRC or multiple first-degree relatives with CRC)	Older age, male sex, and African-American race at higher risk for development of CRC	13
American Cancer Society, US Multi-Society Task Force on Colorectal Cancer, and American College of Radiology	Family history of CRC, polyps, or hereditary CRC syndrome; personal history of CRC, chronic inflammatory bowel disease (ulcerative colitis or Crohn's disease)		14
American College of Physicians	Risk factors include age, African-American race, family history of CRC, polyps, or hereditary CRC syndrome (especially before age 50 years)	Individualized risk assessment should be performed by clinicians to determine when to begin screening	15
American College of Gastroenterology	Patients with a single first-degree relative diagnosed with CRC or advanced adenoma before age 60 years or those with 2 first-degree relatives with CRC or advanced adenomas	Patients with a single first-degree relative diagnosed with CRC or advanced adenoma at age 60 years or older are considered average-risk	16

Abbreviation: CRC, colorectal cancer.

sensitivity and specificity for small lesions <5 mm as compared to larger lesions >9 mm.[30] In general, the accuracy of polyp detection by CT colonography improves with increasing lesion size and is comparable with traditional colonoscopy for polyps 10 mm or larger.[31] However, the detection of flat polyps and those smaller than 10 mm by CT colonography is inferior and should be considered when weighing screening options.[31]

Laboratory-Based Screening

Annual or biennial fecal occult blood testing (FOBT) and fecal immunochemical testing (FIT) are widely available and frequently used for CRC screening. These tests identify at-risk individuals based on the presence of microscopic blood in the stool and are considered very cost-effective relative to colonoscopy (Table 2). Colorectal polyps tend to be more friable and thus bleed more readily compared to normal colonic mucosa, making detection by this test a viable screening method. FOBT and FIT are based on different analytical principals as FOBT indirectly detects blood through nonspecific, peroxide-mediated oxidation of guaiac that may be affected by diet and/or chemicals.[33] In contrast, FIT utilizes an antiglobin antibody that is specific for detection of human hemoglobin.[33] Therefore, it follows that screening with FIT has superior sensitivity and specificity compared to FOBT due to the use of human-specific globin antibodies that are not affected by diet or medications.[34] Moreover, although consecutive testing of multiple FOBT samples increases the sensitivity of the test, only 1 sample is required for FIT screening.

Effectiveness of fecal screening has been demonstrated in randomized controlled trials (RCT),[22] and in populations where colonoscopy is underutilized, alternative testing results in fewer CRC deaths.[35] Regardless, fecal-based screening tests have been criticized for their low sensitivity despite relatively high specificity (Table 2) and this has resulted in practitioner concerns over legal liability for missed lesions.[36] As a result, adoption of FOBT or FIT for primary population screening has been limited in the United States. Several nations around the world—including Australia, Canada, France, and Spain—with insufficient colonoscopy capacity or low acceptance of the colonoscopic approach, utilize these assays and several rely on these tests exclusively for screening.[22,25] It is important to note that lack of availability or acceptance (as opposed to cost savings) tends to drive fecal screening programs. Recent evidence suggests that colonoscopy as compared to an initial FIT approach is a more cost-effective method for screening adenoma, advanced neoplasia, and a composite endpoint of advanced neoplasia or stage I CRC.[37]

Genetic-Based Screening

Both genetic and epigenetic alterations contribute to CRC. As described below, targets of the new molecular CRC screening methods include abnormal proteins or mRNA expression, gene mutations, or aberrantly methylated genes present in stool or body fluids. These tests are based on fundamental findings such as the identification of microsatellite instability and hypermethylated CpG (cytosine-phosphate-guanine) islands in gene-promoter regions that facilitate tumorigenesis of various cancers including CRC.[38,39] Hypermethylation of CpG islands in gene promoters can silence tumor suppressors. Similarly, hypomethylation of repetitive genetic elements can turn on oncogenes or create other genomic instability. Additional epigenetic alterations that have been identified in CRC involve the *APC, CTNNB1, KRAS*,[40] *BRAF, SMAD4, TGFBR2, TP53, PIK3CA, ARID1A, SOX9, FAM123B*, and *ERBB2* genes.[12]

New molecular-based modalities based on genetic and epigenetic alterations have emerged and are changing the approach to CRC screening. In October 2014, the Centers for Medicare and Medicaid Services announced that it would provide reimburse-

Table 4. Genetic Syndromes That Increase Risk for Colorectal Cancer[49]

Syndrome	Responsible Genetic Mutation	Description	Recommended Age of Screening Onset (Years)	Recommended Screening Method and Interval	Additional Notes
Familial adenomatous polyposis (FAP) gene	Tumor suppressor *APC*	Development of numerous polyps by teenage years; eventually exhibit hundreds to thousands of colorectal polyps; average age of onset of CRC is 39 years; risk of CRC approaches 100% by age 45	10-12	Colonoscopy or flexible sigmoidoscopy (1 year)	Patients with a milder variant [attenuated FAP (AFAP)] characterized by development of <100 polyps require slightly less aggressive screening that can begin at a later age and be repeated every 1-2 years
Lynch syndrome or hereditary nonpolyposis colorectal cancer	Mismatch repair genes *LH1, MSH2*, *MMSH6*, or *PMS2*) or a related gene, *EPCAM*	Most common form of inherited CRC; tumors exhibit microsatellite instability involving changes in the length if nucleotide sequence repeats in tumor DNA; lifetime risk of CRC is 80%	20-25 or 10 years younger than the earliest case in the family	Colonoscopy (1-2 years)	Families with *MSH6* or *PMS2* mutations require less aggressive screening at the risk of CRC is less diagnosis later
MUTYH-associated polyposis (MAP)	Base excision repair gene *MUTYH*	Most commonly found in patients presenting with 20 to 99 adenomas; lifetime risk of CRC in biallelic carriers is 70%-75%	25-30 years	Colonoscopy (1-2 years)	
Juvenile polyposis syndrome	Tumor suppressor genes *SMAD4* or *DMPR1A*	Development of dozens to many hundred juvenile polyps in stomach, intestine, colon, and rectum; generally diagnosed in the first 2 decades of life; risk of CRC approaches 68% by age 68	12	Colonoscopy (1-3 years)	
Peutz-Jeghers syndrome	Cell polarity gene *STK11*	Defined by distinct hamartomatous polyps and characteristic mucosal and cutaneous pigmentation; lifetime risk of CRC is 39%	8	Colonoscopy (variable based on initial findings)	Additional increased risk for gastrointestinal and extra-intestinal cancers
Hereditary mixed polyposis syndrome	Unknown	Originally described in large Ashkenazi Jewish family; affected individuals exhibit several different types of polyps and adenocarcinomas; mean age of polyp occurrence is 28 years	20	Colonoscopy (1-2 years)	
Serrated polyposis	Unknown	Predisposition to serrated polyps and development of CRC; estimated lifetime risk of CRC is >50%	20	Colonoscopy (1-2 years)	

ment for the first FDA-approved, noninvasive stool-based DNA test from Exact Sciences (Cologuard) for average-risk patients. This test evaluates the presence of blood (immunochemical assay for human hemoglobin) and DNA (aberrantly methylated *BMP3* and *NFRG4* promoter regions, *KRA*S mutations, and β-actin expression) in a patient's stool sample that may be indicative of precancerous or cancerous polyps. Cologuard is currently recommended every 3 years in average-risk individuals that fit the screening parameters.[41] Advantages of the test include the avoidance of bowel preparation, performance of the test at home without any time lost from work, and absence of any procedural-related complications. The cost of Cologuard, while higher than that of FIT or FOBT, remains less than colonoscopy (Table 2). Moreover, this multitarget testing has been shown to have higher sensitivity than FIT[42,43] that is on par with standard colonoscopy for CRC detection. As the number of private insurance companies accepting this alternative continues to expand, this novel modality is likely to be integrated into a new algorithm for cost-effective screening.

Several blood-based molecular tests are also available in the United States, including Quest Diagnostics' ColoVantage, Abbott's mS9, Epi's proColon, and GeneNews' ColonSentry. ColoVantage, mS9, and proColon all are based on the *SEPT9* gene. The product of the *SEPT9* gene gives rise to a septin protein involved in cytokinesis and exhibits aberrant methylation of its promoter region in CRC tissue as compared to normal colonic mucosal tissue.[44] Although the original *SEPT9*-based tests have lower sensitivity as compared to Cologuard, next-generation *SEPT9* tests such as proColon 2.0 have optimized polymerase chain reaction (PCR) protocols with improved sensitivity. Of note, in April 2016 Epi's proColon was the first blood-based test to be approved for CRC screening by the FDA.[13] In contrast, ColonSentry is based on a

7-gene messenger RNA panel (including the A*NXA3, CLEC4D, LMNB1, PRRG4, TNFAIP6, VNN1*, and *IL2RB* genes) that is thought to reflect subtle alterations in peripheral gene expression in response to disease as opposed to serving as direct, tumor-derived biomarkers.[45,46] Sensitivity of the ColonSentry test is similar to that observed for the first-generation *SEPT9* tests. As shown in Table 2, sensitivities of these blood-based tests are lower than that of Cologuard or colonoscopy.[47]

Screening Methods for Increased-Risk and High-Risk Patients

Among the many accepted cancer screening methods and intervals, the majority are considered appropriate for patients at average-risk. Approximately 70% of CRC is considered sporadic or average-risk and has an average age of onset of 69 years old. While the lifetime risk of colon cancer is reported at approximately 5%, individuals with 1 first-degree affected relative have a 2- to 3-fold increased risk and individuals with 2 first-degree affected relatives have a 3- to 4-fold increased risk.[48] Definitions of increased-/high-risk based on personal history, family history, and/or genetics differ slightly across guidelines and are summarized in Table 3. ACG guidelines recommend that increased-risk and high-risk patients utilize colonoscopy as their screening method as negative results from alternative approaches are not sufficient to negate the need for colonoscopy due to the high pretest probability of disease. In general, ACG guidelines also suggest that screening should occur every 5 years starting at age 40 or 10 years younger than the earliest diagnosis in the family.[16] Additional detailed protocols that involve screening more often and at an earlier age for individuals at increased-/high-risk for CRC have been reported in CRC screening guidelines as well.[14,16]

The remainder of CRC occurs in high-risk individuals with genetic CRC syndromes or inflammatory bowel disease.[11] Specific conditions that convey an increased genetic risk include FAP (along with Gardner syndrome and Turcot syndrome), Lynch syndrome or hereditary nonpolyposis colorectal cancer, juvenile polyposis syndrome, Peutz-Jeghers syndrome, and mutY Homolog (MUTYH)-associated polyposis.[14,48-50] As summarized in Table 4, patients affected with these syndromes require further adjustments to screening schedules, including earlier and more frequent examinations. With increased genetic testing, additional familial mutations will likely be identified in the near future.

SUMMARY

Colonoscopy and other screening modalities have contributed to decreased rates of colon cancer death through early identification and removal of precancerous polyps. Together with updated USPSTF screening guidelines, the emergence of a variety of more sophisticated and noninvasive tests with greater sensitivities and specificities is beginning to shift the paradigm of CRC screening. In countries where there are limited financial and personnel resources or in situations where patients opt for an initially less invasive test, a two-step approach is a reasonable consideration and remains aligned with current screening practices. However, prior to choosing a two-step screening method, patients must be informed of the benefits and limitations of current screening options and understand that a positive test result would lead to further invasive diagnostic testing through colonoscopy. Following the appropriate lag time for implementation, new screening strategies have the potential to lead to further reductions in health care costs by providing a targeted and individualized approach to colonoscopic examination.

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