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A Practical Approach for Colorectal Cancer Screening



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Colorectal cancer remains a public health burden in the United States. Although randomized controlled trials have demonstrated that screening reduces colorectal cancer incidence and mortality, a large proportion of Americans remain unscreened. National efforts are underway to help increase our colorectal cancer screening rates to 80% by 2018. In this article, we will review several practical strategies for improving colorectal cancer screening in the average-risk population such as including patient preferences, promoting fecal immunochemical test as a screening option, and implementing an organized screening program. In addition, we will discuss practical approaches for colorectal cancer prevention in the increased or high-risk population.

RATIONALE FOR COLORECTAL CANCER SCREENING

Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths in the United States (US) and a common cause of morbidity and mortality worldwide.¹ In 2014, an estimated

136,830 people were diagnosed with CRC in the US and over 50,000 people died from this disease.² Most CRCs develop from a preclinical precursor, the adenomatous polyp (or adenoma), which can take many years to progress into an invasive cancer,^{3,4} making it an ideal target for early detection and prevention through screening. Randomized controlled trials have demonstrated that screening with either a fecal-based test or flexible sigmoidoscopy reduces CRC incidence and mortality.⁵⁻¹¹ Colonoscopy has also been shown to reduce CRC incidence and mortality from observational studies.¹²⁻¹⁷

Screening for CRC is now widely recommended. Several professional societies and the United States

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Preventive Services Task Force recommend that all average-risk individuals aged 50 to 75 years undergo CRC screening using at least one of the following methods: an annual high sensitivity fecal occult blood test (FOBT) or fecal immunochemical test (FIT), a flexible sigmoidoscopy every 5 years, or a colonoscopy every 10 years.¹⁸⁻²⁰

Despite these recommendations, CRC screening rates remain low. As of 2012, 35% of screening-eligible adults were not up-to-date with CRC screening recommendations, based on self-report.²¹ With the passage of the Affordable Care Act, millions of previously uninsured patients now have access to preventive services, including CRC screening. As a result, the American Cancer Society, National Colorectal Cancer Roundtable and over 400 health care organizations have pledged to achieve an 80% screening rate for CRC by 2018. In this review, we will highlight several practical approaches to improve CRC screening rates and prevention in the average- and high-risk populations.

PRACTICAL APPROACHES FOR THE AVERAGE-RISK POPULATION

Include Patient Preference for CRC Screening

One of the key impediments to increasing CRC screening rates while further decreasing CRC mortality is our focus on the clinicians' preferred screening test rather than on the patients' preferred screening test.²² In the US, colonoscopy is the most commonly used test for CRC screening²³ and is the preferred screening modality by several specialty societies.^{24,25} However, a one-size-fits-all approach with colonoscopy has several limitations. Despite colonoscopy's effectiveness in detecting prevalent cancers and removing adenomas,^{16,26} patients are concerned with its invasiveness and associated complication risks. Furthermore, patients may be reluctant to undergo a colonoscopy because of the bowel preparation, the potential cost of the screening or associated pathology fees, and the need to take time off from work.

Understanding and including patient preferences will be important to improving CRC screening rates and providing the greatest reduction in CRC mortality. Inadomi et al. demonstrated this by randomizing 997 average-risk patients from a racially diverse group to screening with 1) guaiac-based fecal occult blood

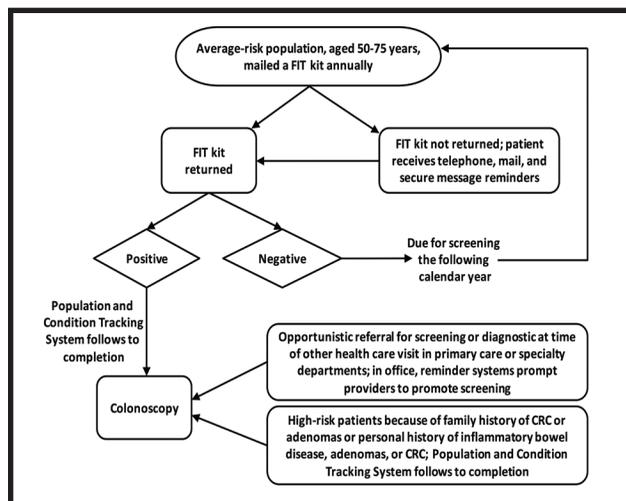


Figure 1. The overall colorectal cancer screening approach at Kaiser Permanente Northern California: a combination of organized and opportunistic screening. FIT: fecal immunochemical test

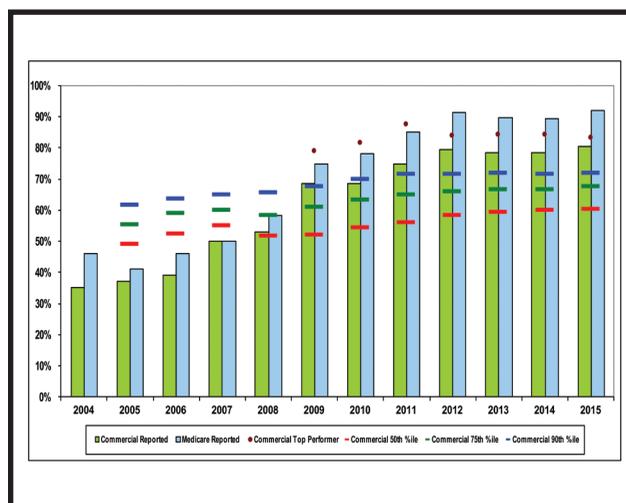


Figure 2. Publicly reported Healthcare Effectiveness Data and Information Set colorectal cancer screening rates for Kaiser Permanente, Northern California, for each year from 2004 to 2015. The Medicare population (light blue bars) are reported separately from the commercial population (green bars). The red, green, and blue hash marks represent the commercial 50th, 75th, and 90th percentiles, respectively. The red dots represent the commercial top performer each year. Note that each year's reported results refer to screening performance as of the end of the prior year.

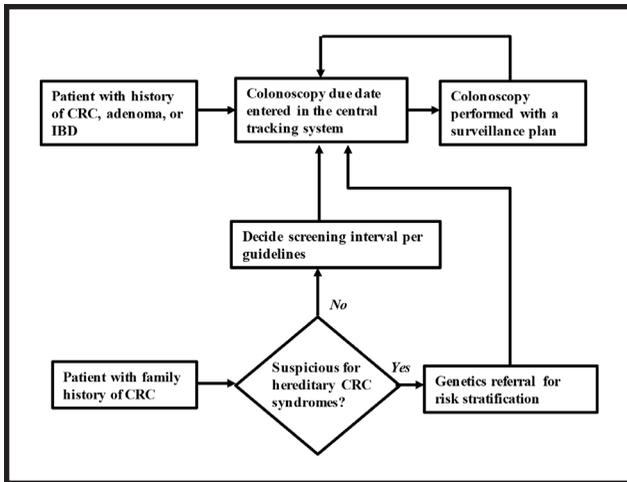


Figure 3. Organized screening strategy for individuals at increased or high risks for colorectal cancer at Kaiser Permanente Northern California

test (gFOBT), 2) colonoscopy, or 3) a choice between gFOBT or colonoscopy.²⁷ The primary outcome was completion of CRC screening within 12 months. Of the patients assigned to the colonoscopy only arm, about 38% completed screening. In contrast, 69% of those assigned to a choice between gFOBT and colonoscopy completed screening. Patients assigned to the gFOBT only arm had a similar screening completion rate (67%) as the choice group. The investigators also found that cultural influences may play a role in CRC screening adherence. Specifically, African-American, Asian, and Latino patients preferred non-invasive fecal testing (i.e., gFOBT), whereas Caucasian patients preferred colonoscopy. These results suggest that recommending colonoscopy only may have an adverse effect on CRC outcomes by reducing adherence to CRC screening in certain minority and underserved populations, which already have the lowest CRC screening rates in the US.²¹

Promote FIT as a Screening Option for CRC

While gFOBT is effective as a non-invasive option for CRC screening,⁵⁻⁸ its overall poor test performance characteristics²⁸ and the low longitudinal adherence to gFOBT in the Veteran Affairs and insured community populations potentially compromises its effectiveness in population CRC mortality reduction.^{29,30} Recently, fecal immunochemical tests (FIT), which directly measures stool hemoglobin using antibody technology, have been developed to improve the sensitivity and specificity

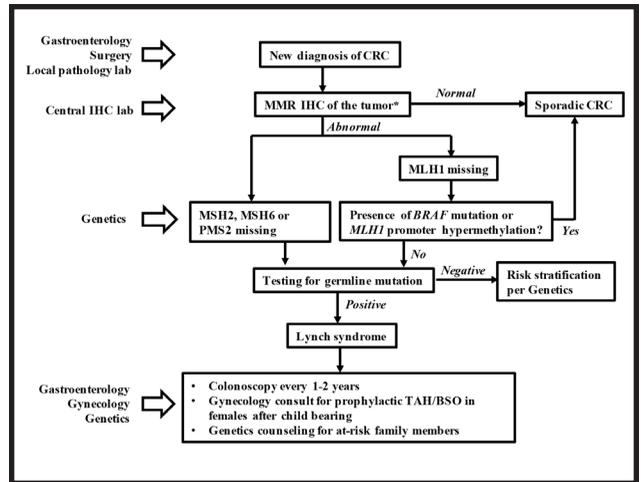


Figure 4. Universal screening algorithm for Lynch syndrome at Kaiser Permanente Northern California

for CRC. Several comparative effectiveness studies have shown that FIT has an improved sensitivity and specificity for CRC and advanced neoplasia compared to gFOBT.³¹ In a meta-analysis of 19 studies evaluating the performance of FIT for detecting CRC in average-risk adults, the pooled sensitivity of FIT for CRC was 79% with a corresponding specificity of 94%. The overall diagnostic accuracy of FIT for CRC was 95%.³² There is also growing evidence that FIT’s performance characteristics remain stable after multiple rounds of annual or biennial testing.³³⁻³⁶

Perhaps the greatest advantage of FIT is its convenience. Because nearly all FITs can be mailed, FIT can be conveniently completed in the comfort and privacy of the patient’s home.³¹ After test completion, FIT can be mailed to the lab directly where it can be processed using an automated reader, ensuring quality control. Thus, FIT allows patients to avoid the common concerns associated with colonoscopy such as bowel preparation, work absence, or the need for an escort home. FIT has the additional advantages over gFOBT in that FIT has no dietary or medication restrictions, and most FITs require only 1 stool sample.³¹

With regard to adherence, randomized trials have demonstrated higher adherence to CRC screening with FIT compared with colonoscopy. In the COLONPREV trial, Quintero et al. reported higher baseline adherence for FIT than for colonoscopy (34% versus 25%, respectively, P<0.001) with comparable CRC detection.³⁷ Recently, Gupta et al. also showed

Table 1. Summary of Screening Strategies for Individuals at Increased or High Risk for Colorectal Cancer

| Risk Category | Timing of Colonoscopy | Comments |
|--|---|--|
| Increased Risk | | |
| Personal history of CRC | | |
| Proximal colon not cleared before resection | 3-6 months after cancer resection | |
| CRC with curative resection; proximal colon cleared | 1 year after the resection or clearing colonoscopy, followed by colonoscopy at 3 years thereafter, then every 5 years | |
| Family history of CRC | | |
| CRC or adenomas in 1 FDR at age <60 years or 2 or more FDRs at any age | Every 5 years starting age 40 or 10 years before the youngest FDR case | |
| CRC or adenomas in 1 FDR at age ≥60 years, or CRC in 2 SDRs at any age | Every 10 years starting at age 40 | Other forms of testing such as FIT can be considered |
| Personal history of polyps | | |
| 1-2 small (<10mm) tubular adenomas | 5-10 years | |
| 3-10 tubular adenomas | 3 years | |
| >10 adenomas | <3 years | Consider polyposis syndrome and genetic evaluation |
| 1 or more large (≥10mm) tubular adenomas | 3 years | Repeat colonoscopy sooner if adenoma was removed piecemeal |
| Adenoma with villous histology or high-grade dysplasia | 3 years | |
| Sessile serrated adenoma (or sessile serrated polyp) | | |
| <10mm | 5 years | |
| ≥10mm, or with dysplasia | 3 years | |
| Traditional serrated adenoma | 3 years | |
| High Risk | | |
| Hereditary CRC syndromes | | |
| Lynch syndrome (HNPCC) | Every 1-2 years starting at age 20-25 years or 10 years before the youngest case in the immediate family | Consider screening for Lynch syndrome in all new CRCs |
| Familial adenomatous polyposis | Annual colonoscopy until colectomy | Consider colectomy |
| <i>MUTYH</i> -associated polyposis | Every 1-2 years depending on polyp burden | Consider colectomy based on polyp burden |
| Serrated polyposis syndrome | Every 1-3 years | |
| Inflammatory bowel disease | 8-10 years after the onset of pancolitis or 12-15 years after the onset of left-sided colitis | |

FDR: first-degree relative; SDR: second-degree relative

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higher FIT adherence (using mailed outreach) compared with colonoscopy (41% versus 25%, respectively) in an underserved average-risk population, which traditionally has been the most difficult populations to screen for CRC.³⁸ One important point to note is that although the protocol for the COLONPREV trial is for five total rounds of FIT screening,³⁷ both randomized studies only reported one round of FIT completion rates.^{37,38} However, population-based studies from the United States, Italy, and the Netherlands have shown that FIT adherence over multiple rounds of screening remains stable.^{33,34,36}

Implement an Organized Screening Program for CRC

Currently, the approach to CRC screening in the US is largely opportunistic, meaning that patients who come to the physician's office for a regular checkup or an unrelated acute medical issue are offered screening.²² Thus, people who visit a doctor regularly are more likely to be screened for CRC than those who do not. Not surprisingly, only 65% of the population is up-to-date with CRC screening in the US,²¹ with some populations more disproportionately affected than others. For example, Hispanics and African-Americans have lower CRC screening rates than non-Hispanic whites.²¹

In contrast, an organized screening program offers the promise of uniformly screening all eligible members of a population with a risk- and preference-based approach.¹⁵ The International Agency for Research on Cancer (IARC) defines an organized screening program as one that includes the following elements:³⁹

- An explicit policy with specified age categories, screening method, and screening interval
- A defined target population
- A management team responsible for implementation
- A healthcare team for decisions, care and follow-up of patients with positive screening tests
- A quality assurance structure for every step in the screening process
- A process for monitoring, evaluating, and identifying cancer occurrence in the population

There are several advantages of implementing an organized screening program. For example, an organized screening program can efficiently identify the target population (e.g., average-risk adults between 50-75 years of age) and contact them directly to arrange screening, rather than using a "convenience" approach whereby screening is mainly offered during health care visits conducted for other purposes. In addition, an organized screening program can efficiently monitor the quality of the screening process, such as timely referrals and appropriate follow-up of participants, and it provides greater protection against the harms of screening, including overuse and underuse of screening tests. However, adopting an organized screening program will require substantial information technology infrastructure for screening invitations, recalls, reminders, tracking of screening results, ensuring follow-up and tracking of clinical outcomes. Fortunately, most of the nation's healthcare systems have incorporated an electronic medical record (EMR) system, which can ease the implementation process.

Most countries in Europe and Asia have already implemented an organized CRC screening program in the average-risk population by means of a non-invasive stool test (e.g., gFOBT or FIT).⁴⁰ One US example of an organized screening program comes from Kaiser Permanente Northern California (KPNC), a healthcare delivery system with over 3.8 million members.⁴¹ Since 2007, KPNC has used its EMRs to identify average-risk members aged 50 to 75 years who are due for screening and target them with a mailed outreach FIT (**Figure 1**). Additionally, KPNC includes an opportunistic in-reach approach with FIT using EMR prompts to identify patients who are due for screening at the time of an office visit. Support staff at KPNC use these prompts to help remind patients of their need for screening, while they are waiting to be seen by their primary care provider. KPNC members (or their primary care physician) can request a screening colonoscopy using an electronic referral system. From 2004, when the Healthcare Effectiveness Data and Information Set (HEDIS) CRC screening rates were first publicly reported, to 2015, the proportion of the commercially insured population screened in accordance with HEDIS measures at KPNC has increased from 37% to 79% as a result of our organized screening program. In addition, the proportion of the Medicare population screened has increased from 41% to 90% (**Figure 2**). The average population screening rate across both populations is

over 82%. More importantly, unpublished data indicate this increase in screening is associated with a change in cancer stage and even the incidence of CRC in the KPNC population.

PRACTICAL APPROACHES FOR THE INCREASED OR HIGH RISK POPULATION

Implement an Organized Screening Approach for CRC

Similar to the average-risk population, organized screening offers substantial advantages over opportunistic screening for patients at increased or high risk for CRC. For instance, organized screening is able to programmatically select patients who need to be screened within certain timeframes based on their risks; this effectively prevents high-risk cases from being overlooked and, at the same time, avoids the harms and costs associated with over-surveillance. Individuals at increased risk or high risk for CRC can be categorized into several groups: 1) personal history of CRC; 2) personal history of colonic adenomas; 3) family history of CRC; and 4) other conditions associated with increased risks such as inflammatory bowel disease. The screening strategies for individuals at increased or high risk are different from the average-risk population. In general, colonoscopy is the preferred screening method in individuals at increased or high risk for CRC in most organized screening programs. We listed a concise summary of screening recommendations in accordance with current multi-society guidelines in **Table 1**.^{25,26,42}

At KPNC, a centralized tracking system is implemented to ensure a due colonoscopy exam is performed within the appropriate timeframe based on current society guidelines.^{26,42} When a patient is due for colonoscopy, an alarm-triggered referral is sent to the Gastroenterology Department to arrange the procedure with close follow-up until the procedure is performed and a new colonoscopy interval has been entered in the tracking system (**Figure 3**). This tracking tool is the centerpiece of the CRC prevention and surveillance system at KPNC, monitoring approximately 80,000 colonoscopies performed annually.

Adopt the “Universal Screening” Strategy for Lynch Syndrome Screening

Approximately 4-5% of patients with CRC harbor inheritable genetic mutations and have a high lifetime risk for CRC as well as extracolonic malignancies.⁴³

Among this group, less than 1% of all CRC cases have polyposis syndromes, characterized by significantly increased number of adenomas in the colon and upper gastrointestinal tract. The most common types of adenomatous polyposis syndromes include familial adenomatous polyposis (FAP) (due to mutations in the *APC* gene), and *MUTYH* (*MYH*)-associated polyposis (MAP) (due to mutations in the *MUTYH* gene). Genetics evaluation should be obtained and a surveillance colonoscopy performed every 1-2 years is indicated until total or subtotal colectomy is performed. Please see details of genetics evaluation in a separate review in this issue of *Practical Gastroenterology*.

Screening for Lynch syndrome (formerly known as hereditary nonpolyposis CRC, or HNPCC) deserves more discussion since this is the most common type of hereditary CRC syndromes in the world and has been historically under-recognized. Lynch Syndrome accounts for 2-4% of the CRC cases and is caused by mutation(s) in mismatch repair (MMR) genes in the human DNA repair machinery.⁴³ Patients with Lynch Syndrome have up to an 80% lifetime risk for CRC and up to 60% risk for endometrial cancer, as well as increased risks for cancers in other organs such as stomach, ovaries, small intestine, hepatobiliary tract, urinary tract, and brain. Individuals diagnosed with Lynch Syndrome should have a surveillance colonoscopy every 1-2 years. Female patients should be advised to consider prophylactic hysterectomy with bilateral salpingo-oophorectomy after their childbearing has been completed. The at-risk family members of Lynch Syndrome patients should receive genetic counseling to assess their risk of carrying a deleterious mutation.

Current multi-society guidelines support the “**universal screening**” strategy, which advocates screening all newly diagnosed CRCs for Lynch Syndrome.^{42,44,45} The most cost-effective approach is to start with immunohistochemistry (IHC) staining of the MMR proteins on the CRC specimen, followed by further genetic testing as indicated.⁴⁶ A recent study showed that reflex tumor testing for Lynch syndrome (equivalent to universal screening strategy) has been adopted in the majority of National Cancer Institute-designated comprehensive cancer centers in the United States, but only in a small percentage of community-based programs.⁴⁷ Successful implementation of universal screening program for Lynch Syndrome requires multidisciplinary collaboration among

gastroenterology, genetics, pathology, surgery and gynecology (for females). At KPNC, a universal screening program for Lynch syndrome has been established since 2014 (**Figure 4**). All surgically resected CRCs are screened for Lynch syndrome by performing IHC on the tumor specimens. Quality assurance is provided by pathologists at each facility to ensure all CRC cases undergo IHC staining, and by a regional genetics coordinator to ensure all abnormal IHC results are evaluated appropriately by the Genetics Department. For those individuals who are confirmed to carry a deleterious mutation, referrals are sent to the Gastroenterology Department for annual (or biannual) colonoscopy, and to the Gynecology Department (if the individual is a female) for discussion of prophylactic hysterectomy and bilateral salpingo-oophorectomy after child bearing has been completed. Using the screening algorithm shown in **Figure 4**, we have screened over 2,000 patients with CRC. This strategy has proven successful at acceptable costs, and can serve as an example for other institutions where universal screening for Lynch syndrome has not been implemented.

CONCLUSION

Over the past three decades, we have made great strides in reducing CRC incidence and mortality rates. However, many people remain unscreened and we are far from our goal of eliminating deaths from CRC. To achieve this goal, providers and healthcare systems need to consider screening strategies such as implementing an organized screening program, respecting patient preferences, and offering FIT as an alternative to colonoscopy. Fortunately, several forces in today's healthcare bode well for achieving higher CRC screening rates. EMRs increasingly make it possible for identifying a target population for risk-based screening. In addition, Accountable Care Organizations (ACO) are able to mobilize resources to remind patients about screening while in the office and perform mailed FIT outreach.

Having effective tools like an EMR system or an ACO is only one element of improving screening rates. Organizational commitment and alignment around screening targets is also essential. Having the right tools without agreement on goals or what is needed to achieve them will stall forward progress. Successful organizations will allow patients to choose between screening colonoscopy and more frequent, less sensitive non-invasive screening tests like FIT. Finally, while

primary care physicians are essential in encouraging patients to screen for CRC, they cannot be successful without the help of an organized system that provides reminders to patients who do not come in for regular office visits. ■

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