

Colorectal Cancer Screening Guideline

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Guidelines are systematically developed statements to assist patients and providers in choosing appropriate health care for specific clinical conditions. While guidelines are useful aids to assist providers in determining appropriate practices for many patients with specific clinical problems or prevention issues, guidelines are not meant to replace the clinical judgment of the individual provider or establish a standard of care. The recommendations contained in the guidelines may not be appropriate for use in all circumstances. The inclusion of a recommendation in a guideline does not imply coverage. A decision to adopt any particular recommendation must be made by the provider in light of the circumstances presented by the individual patient.

This evidence-based guideline was developed by **Kaiser Permanente Washington (KPWA)**. It was adapted from the 2016 Kaiser Permanente National Guideline, as well as the 2016 U.S. Preventive Services Task Force Screening for Colorectal Cancer Screening Guideline.

Major Changes as of July 2017

The guideline team reviewed the 2016 Colorectal Cancer Screening Guideline, determined there were no outstanding evidence gaps, and re-approved the guideline with only minor changes.

Background

Colorectal cancer (CRC) is the fourth most commonly diagnosed cancer and the second leading cause of cancer deaths in the United States. There is good evidence that CRC-related morbidity and mortality can be reduced through early detection and treatment of early-stage disease and through the identification and removal of adenomas, the precursor of colorectal cancers.

Definitions: Neoplastic Colorectal Polyps and Adenomas

Adenomatous polyps (also called **adenomas**) are growths with malignant potential, and are the most common type of colorectal polyp. Adenomatous polyps may be pathologically classified as follows (Shussman 2014):

- **Tubular adenomas** have the histological appearance of a branched tubular gland, most often pedunculated. They are the most common subtype of adenoma (68–80% of all the polyps removed).
- **Villous adenomas** have long finger-like projections on microscopy. They represent only 5–10% of adenomas. Compared with tubular adenomas, villous adenomas are more commonly sessile and more likely to have severe atypia or dysplasia.
- **Tubule-villous (or tubulovillous) adenomas** (TVAs) have elements of both the tubular and villous adenomas, with a 26–74% villous component. Approximately 10–25% of adenomas are tubule-villous.

All types of adenomas have some degree of dysplasia.

Serrated polyps have variable malignant potential, and may be classified as follows (Chetty 2015, Snover 2010):

- **Hyperplastic polyps** are the most common, usually small in size (< 5 mm), and predominantly located in the distal colon. They have low malignant potential.
- **Sessile serrated adenoma/polyps** (SSAs), with or without cytological dysplasia, may be large and flat, and are typically seen in the proximal colon. They have high malignant potential. SSAs with cytological dysplasia have very high malignant potential. (Rosty 2013)
- **Traditional serrated adenomas** (TSAs) have diffuse and often mild cytological dysplasia, and are predominantly located in the distal colon. They have high malignant potential.

Advanced adenomas are high-risk adenomas characterized by high-grade dysplasia, size \geq 10 mm, or any villous component.

Screening

Colorectal cancer risk groups

Average risk: Patients aged 50 years or older with no personal history of CRC or adenomas, no inflammatory bowel disease, and with a negative first- and second-degree family history for CRC.

Increased risk: Patients with a personal or family history of CRC or related conditions. (See Table 4.)

CRC screening recommendations by age group

Table 1. Colorectal cancer screening recommendations by age group	
Age	Recommendation
30 through 49 years	Review family history to identify patients at increased risk for CRC (Table 4) or at high risk for inherited cancer syndromes (see Referral to Genetics). For African-American patients whose family history is not known, consider beginning routine screening at age 45. ¹
50 through 75 years	Provide routine screening for patients at average risk (Table 2) and at increased risk (Table 4).
76 through 85 years	Consider routine screening only for patients who have not been up to date with screening prior to age 75 years and/or who are healthy enough to undergo treatment if CRC is detected and have a life expectancy of 10 years or more.
86 years and older	Screening is not recommended.
¹	There is evidence of a higher incidence of colorectal cancer in African-Americans, and a higher age-specific incidence rate for those under age 50, compared to other races. However, personal and family histories are the most important independent factors in determining age at initial screening and screening frequency. (Dimou 2009)

Recommended screening tests at KPWA medical facilities

The fecal immunochemical test (FIT)

Average-risk patients: Annual FIT is a simple method for screening average-risk patients as its net benefit is similar to the more invasive and resource-intensive recommended techniques. FIT is a simple and rapidly performed test that does not require preparation, sedation, or a doctor appointment. Its cost is minimal and conserves colonoscopy resources for patients who are at higher risk and for those who test positive on stool-screening tests. However, screening with FIT is effective only when performed annually and is not suitable for patients unable to adhere to the annual testing cycle. FIT is not the appropriate test for patients at increased risk for CRC because of family or personal history of cancer or other high-risk conditions (e.g., ulcerative colitis). A positive FIT **must** be followed by a colonoscopy.

Colonoscopy

Average-risk patients: Colonoscopy at 10-year intervals is an acceptable screening method for patients who prefer this approach or those who may have difficulty with adhering to an annual FIT testing regimen. Patients should be informed of the differences in potential risks associated with colonoscopy compared with annual FIT testing. For questions about colonoscopy coverage, patients can contact Member Services.

Increased-risk patients: Colonoscopy is the only screening method recommended for patients with a personal or family history of CRC or related conditions. See Table 4 for recommended screening frequency and age at initial screening.

Other screening tests

The following additional screening tests are less-preferred options. However, an adult who has had one of these tests is considered screened. Follow-up screening using a preferred option is recommended.

Flexible sigmoidoscopy

Average-risk patients: If a patient requests it, flexible sigmoidoscopy at 10-year intervals should only be done **in addition to** annual FIT screening. Flexible sigmoidoscopy is no longer performed in KPWA Primary Care settings. Patients who request flexible sigmoidoscopy should be referred to Gastroenterology. Modeling studies indicate that sigmoidoscopy plus annual stool testing is superior to sigmoidoscopy testing alone.

CT colonography

Virtual colonoscopy may be considered for patients with relative contraindications to colonoscopy. See [Clinical Review Criteria for Virtual Colonoscopy or CT Colonography](#) for specific criteria. The USPSTF recommendation (2016) concludes that the evidence is insufficient to assess the benefits and harms of computed tomography as a screening modality for colorectal cancer. CT colonography recommendations will be revisited when more evidence becomes available.

Stool DNA test (FIT-DNA, Cologuard)

The stool DNA test incorporates multiple molecular biomarkers with FIT. It was approved by the U.S. Food and Drug Administration (FDA) in 2014 for screening men and women aged 50 or older with an average risk of CRC. The test is covered by Medicare at 3-year intervals, as it is considered an acceptable testing modality by USPSTF. Coverage criteria may vary among health plans, so members should check with Member Services to be certain about coverage.

The USPSTF reviewed the evidence on the stool DNA test in its 2016 recommendation and noted that it had a higher single-test sensitivity than FIT alone in detecting colorectal cancer. However it has a lower specificity than that of FIT alone, which leads to increased false-positives and a higher risk of harms from follow-up colonoscopies. There is insufficient published data (to date) on the appropriate testing interval for stool DNA, as it has not been evaluated in randomized controlled trials or longitudinal prospective studies. This uncertainty surrounding the appropriate screening interval, coupled with concerns over the genetic component of the test, may potentially lead to over-screening. Both screening colonoscopy every 10 years and annual FIT are more effective and less costly than stool DNA.

Screening tests that are *not* recommended

The following test is **not** currently recommended as a primary screening tool for CRC:

- Double contrast barium enema.

Screening recommendations for patients at AVERAGE risk

Table 2. Colorectal cancer screening for patients at AVERAGE risk

“Average risk” is defined as aged 50 years or older with no personal history of CRC or adenomas, no inflammatory bowel disease, and with a negative family history for CRC.

Test	Age at initial screening	Frequency
Fecal immunochemical test (FIT)	50 years	Annually through age 75
Colonoscopy	50 years	Every 10 years through age 75

Shared decision making

Due to the lack of head-to-head trials comparing the net benefits of the different tests, efforts to reduce CRC deaths should focus on implementing strategies that maximize the number of patients who get screening of some type. The different CRC screening options are variably acceptable to patients; eliciting patient preferences is one step in improving adherence. Ideally, shared decision making between clinicians and patients incorporates information on local test availability and accuracy, as well as patient preference (USPSTF 2016).

Table 3. Shared decision making about CRC screening options—patients at AVERAGE risk

Advantages/benefits	Disadvantages/risks
FIT (fecal immunochemical test)	
<ul style="list-style-type: none"> • Can be done at home. • Quick. • Noninvasive. No risk of bowel tears or infections. • Does not require a doctor appointment or sedation. • Requires no advance preparation, dietary modification, or loss of time from work • Minimal handling of stool. • There is direct evidence that stool screening test (followed by colonoscopy when positive) decreases CRC mortality. • Single specimen required. 	<ul style="list-style-type: none"> • Requires handling of feces. • Colonoscopy is required if FIT is positive. • Must be done annually to be an effective screening method—adherence is important to the effectiveness of the program. • Cannot visually identify polyps.
Colonoscopy	
<ul style="list-style-type: none"> • Views entire colon. Direct visualization techniques offer greater sensitivity for detection of adenomas of all sizes. • Requires testing only every 10 years. • Only screening method with the potential to prevent CRC, as it allows not only for the detection but also the removal of polyps and precancerous lesions. 	<ul style="list-style-type: none"> • Requires full bowel prep. Effectiveness of colonoscopy diminished if bowel prep is incomplete. • Sedation needed. • Requires loss of time from work. • May be associated with a potential risk of bowel tears. • The evidence on the benefit of colonoscopy is indirect.
Flexible sigmoidoscopy	
<ul style="list-style-type: none"> • Office procedure. Does not usually require sedation. • Has strong evidence based on randomized trials. • Bowel preparation is tolerable. • There is direct evidence of its effectiveness as a CRC screening test when combined with a fecal blood test, such as FIT. 	<ul style="list-style-type: none"> • Can detect lesions only to level of insertion of the scope. No visualization of the proximal colon. • Colonoscopy necessary if abnormalities detected. • Should be done only in combination with annual FIT. • No evidence that it is more effective than annual FIT alone.

Screening recommendations for patients at INCREASED risk

Table 4. Colorectal cancer screening for patients at INCREASED risk			
"Increased risk" is defined as a personal or family history of CRC or related conditions.			
Recommendations are based on the following external guidelines: 2016 Kaiser Permanente, 2012 AGA, 2015 NCCN, and 2014 ICSI.			
Eligible population	Test	Age at initial screening	Frequency
Personal history			
CRC or adenomatous polyps	Colonoscopy	Consult with Gastroenterology.	Consult with Gastroenterology.
Inflammatory bowel disease (Crohn's disease, ulcerative colitis)	Colonoscopy	Consult with Gastroenterology.	Every 1–2 years
Family history			
1 first-degree relative ¹ with CRC diagnosed at age < 60 years or 2 first-degree relatives ¹ with CRC diagnosed at any age	Colonoscopy	Whichever comes first: Age 40 or 10 years prior to earliest age of diagnosis	Every 3–5 years
1 first-degree relative ¹ with CRC diagnosed at age ≥ 60 years	Colonoscopy	Age 50	Every 5 years May lengthen interval to every 10 years after ≥ 2 negative colonoscopies.
1 first-degree relative ¹ with advanced adenoma ² diagnosed at any age	Colonoscopy	Whichever comes first: Age 50 or Age of diagnosis	Repeat per colonoscopy findings.
1 second-degree relative ³ with CRC diagnosed at age < 50 years	Colonoscopy	Age 50	Repeat per colonoscopy findings.
¹ First-degree relative = parent, sibling, or child. ² Advanced adenomas meet any of these criteria: high-grade dysplasia, ≥ 10 mm, any villous component. ³ Second-degree relative = grandparent, aunt, uncle, niece, nephew.			

Referral to Genetics

Refer patients with any of the following to Genetics for further risk evaluation/assessment for high-risk cancer syndromes:

- Personal history of CRC before age 50
- Personal history of CRC and endometrial cancer at any age
- Personal history of CRC and ovarian cancer at any age
- Personal history of CRC and two first-degree relatives with history of colorectal, endometrial, or ovarian cancer at any age
- Family history of inherited syndromes such as Lynch, familial adenomatous polyposis (FAP), or familial diffuse gastric cancer
- Personal history of 10 or more adenomatous polyps
- Personal history of multiple primary colon cancers at any age

Follow-up

Table 5. Follow-up of screening test results Recommendations are consistent with 2012 AGA.		
Test	Result	Follow-up testing
FIT	Negative	Repeat screening in 1 year with one of the options for average-risk patients (Table 2).
	Positive	Refer for colonoscopy.
Colonoscopy	Normal or Hyperplastic polyp(s)	Screen again in 10 years with one of the options for average-risk patients (Table 2).
	Low-risk adenoma(s) ¹	Repeat colonoscopy in 5 years. Generally, if no lesions are found on the second colonoscopy, screen again in 10 years with one of the options for average-risk patients (Table 2).
	Advanced or multiple adenoma(s) ²	Consult with Gastroenterology to determine follow-up testing recommendations.
Flexible sigmoidoscopy	Normal or Hyperplastic polyp(s)	Continue annual screening with FIT, and <ul style="list-style-type: none"> • Repeat flexible sigmoidoscopy at 10 years, or • Do colonoscopy at 10 years. OR Continue annual screening with FIT alone.
	Adenoma(s)	Refer for colonoscopy.
¹ Low-risk adenomas = 1 or 2, < 10 mm, tubular, low-grade dysplasia. ² Advanced or multiple adenomas meet any of these criteria: ≥ 3 adenomas, high-grade dysplasia, ≥ 10 mm, any villous component.		

Evidence Summary

To develop and update the Colorectal Cancer Screening Guideline, the guideline team:

- Adapted recommendations from externally developed evidence-based guidelines and/or recommendations of organizations that establish community standards.
- Reviewed additional evidence using an evidence-based process, including systematic literature search, critical appraisal, and evidence synthesis.

External guidelines on CRC screening that met the quality standards are:

- U.S. Preventive Services Task Force. *Recommendation Statement: Colorectal Cancer: Screening*. June 2016.
- National Comprehensive Cancer Network. *NCCN Guidelines®: Colorectal Cancer Screening Version 1.2015*. 2015.
- Kaiser Permanente. *National Clinical Practice Guideline: Colorectal Cancer Screening*. December 2016
- Institute for Clinical Systems Improvement (ICSI) Workgroup. *Colorectal Cancer: Screening*. 2014.
- *Post polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline*. 2013.
- Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR; United States Multi-Society Task Force on Colorectal Cancer. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology*. 2012 Sep;143(3):844-857.

Screening average-risk individuals

Stool-based testing (fecal tests)

Evidence of benefit

The systematic review prepared for the USPSTF (Lin 2015) updated and confirmed that Hemoccult II is the only stool CRC screening test that was found to reduce CRC-specific mortality. One large RCT on annual screening versus no screening showed a 32% reduction in CRC-specific mortality after 11–30 years of follow-up, and 5 RCTs demonstrated that biennial screening reduced CRC mortality by 9–22%. Neither the annual nor the biennial stool screening was found to have an effect on all-cause mortality. Hemoccult II was replaced by Hemoccult SENSA, which is more sensitive in detecting CRC. Many screening programs and health systems are now using FIT instead, as it only requires one sample, and has eliminated dietary and medicine restrictions, leading to better compliance.

FIT versus guaiac FOBT (gFOBT)

A meta-analysis of 5 studies that compared adherence and detection rates of CRC screening by type of screening test (Hassan 2012) showed that FIT was superior to gFOBT for the adherence rate (51.66% and 40.91%, respectively) and detection rate for advanced neoplasia and cancer (1.14% with FIT and 0.46% with gFOBT, with a number needed to screen to detect an advanced adenoma [NNS] of 145). Another meta-analysis (Vart 2012) of 7 trials also showed that the participation rates for FIT were significantly higher than those for gFOBT.

In a randomized controlled trial conducted among Group Health Cooperative members, Chubak and colleagues (2013) compared the uptake of three different mailed high-sensitivity FOBTs. Recruitment materials were mailed to 9,922 members; 2,873 returned the baseline survey, 2,263 of whom were randomized to receive stool FIT (OC-Auto), FIT (InSure) or guaiac FOBT (Hemoccult SENSA). All participants received their stool test kits by mail, and were not blinded to the FOBT they received. The primary outcome of the trial was the return of any FOBT kit within 6 months of randomization date; 2234 participants were eligible for analysis.

Analysis of the results showed that 64% of the eligible participants returned any FOBT kit within 6 months. After accommodating loss to follow-up and competing endoscopy events, 69% of the OC-Auto group, 64% of the InSure group, and 61% of the Hemoccult SENSA group completed the assigned study FOBT within 6 months. Pairwise comparisons shows significant differences in uptake with OC-Auto compared with each of the other two groups, after correction for multiple comparisons. The difference in

uptake between InSure and SENSEA groups was statistically insignificant. The study had its strengths and limitations. It was conducted among Group Health members who chose to participate, which may limit generalization of the results.

Accuracy of fecal immunochemical tests for colorectal cancer

A meta-analysis that pooled the results of 19 studies (Lee 2014) showed that FIT has an overall high diagnostic accuracy for detecting CRC, and that the diagnostic performance of the test depends on the cutoff value for a positive test result. It also indicates that there are no significant differences in the sensitivity and specificity between a single sample versus 2 or 3 samples (table below).

FIT test diagnostic performance (Lee 2014)

	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Overall	0.79 (0.69–0.86)	0.94 (0.92–0.95)	13.10 (10.49–16.35)	0.23 (0.15–.033)
Cutoff for positive test				
< 20 µg/g ¹	0.86 (0.75–0.92)	0.91 (0.89–0.93)	9.8 (7.7–12.5)	18.7 (11.7–29.8)
20–50 µg/g	0.63 (0.43–0.79)	0.96 (0.94–0.97)	16.6 (12.9–21.4)	0.39 (0.24–0.63)
> 50 µg/g	0.67 (0.59–0.74)	0.96 (0.94–0.98)	18.7 (11.7–29.8)	0.34 (0.27–0.43)

¹ KPWA uses 20 µg/g as the cutoff.

Clarke and colleagues' meta-analysis (2015) of 19 RCTs and observational studies showed that men's uptake of FIT was significantly lower than the women's uptake (odds ratio 0.84; 95% CI, 0.75–0.95; $p < 0.01$).

In a large RCT with more than 50,000 participants, Quintero and colleagues (2012) compared one-time colonoscopy versus FIT every 2 years among asymptomatic adults aged 50–60 years. The primary outcome of the trial was the rate of death from CRC in 10 years. Interim analysis of the results shows that the rate of participation was significantly higher with FIT versus colonoscopy (34.2% vs. 24.6%, respectively). The number of detected CRCs was similar in the two study groups, with no significant difference in the stage of tumor detected, but more adenomas were detected in the colonoscopy group. (More details of the results are presented in the "Colonoscopy" section starting on p. 13.)

Evidence of harm

The updated systematic review for the USPSTF (Lin 2015) concluded that the main source of serious adverse events associated with the gFOBT or FIT is the colonoscopy performed after a positive fecal test. The review indicates that the estimates of harms are imprecise due to the limited number of studies. The pooled estimates from 5 trials and 2 observational studies were 8/10,000 perforations (95% CI, 2–32) and 1.9/1,000 (95% CI, 5–64) major bleeding following a diagnostic colonoscopy. Missed cancers (false negatives) are another source of harm associated with the stool testing.

Stool-based DNA (sDNA) and multitarget stool DNA tests

A 2014 multicenter cross-sectional study by Imperiale and colleagues evaluated a multitarget stool DNA test (Cologuard) as a tool for CRC screening. The test is produced by Exact Science (Madison, WI) the same manufacturer as its predecessor, the PreGen-Plus test. The multitarget sDNA test consists of molecular assays for KRAS mutations, aberrant NDRG4 and BMP3 methylation, and beta-actin, as well as an immunochemical assay for human hemoglobin.

The study compared the multitarget sDNA test versus FIT among 12,776 individuals (aged 50–84 years) at average risk for colorectal cancer who were scheduled to undergo screening colonoscopy. The gold standard was screening colonoscopy performed within 90 days after enrollment. The primary outcome of the study was the ability of the test to detect CRC, and the secondary outcome was the accuracy of the test in detecting advanced precancerous lesions, including advanced adenomas and sessile serrated polyps ≥ 1 cm in diameter.

Only 9,989 individuals (78.2% of those enrolled) could be evaluated; of these, 65 (0.7%) had CRC and 757 (7.6%) had advanced precancerous lesions on colonoscopy.

Sensitivity of multitarget sDNA and FIT for CRC, advanced and non-advanced adenomas (Imperiale 2014)

Findings	Colonoscopy	Multitarget DNA		FIT		p value
		n	Sensitivity (95% CI)	n	Sensitivity (95% CI)	
Colorectal cancer	65	60	92.3 (83.0–97.5)	48	73.8 (61.5–84.0)	0.002
Advanced precancerous lesions	757	321	42.4 (38.9–46.0)	180	23.8 (20.8–27.0)	< 0.001
Non-advanced adenomas	2,893	498	17.2 (15.9–18.6)	20	7.6 (6.7–8.6)	

The sensitivity of FIT was similar to the sDNA test for stages III and IV, but less sensitive for stages I and II.

Specificity of multitarget sDNA and FIT for CRC for findings on colonoscopy (Imperiale 2014)

Findings	Colonoscopy	Multitarget DNA		FIT		p value
		n	Specificity (95% CI)	n	Specificity (95% CI)	
All non-advanced adenomas, non-neoplastic findings and negative results on colonoscopy	9,167	1,231	86.6 (85.9–87.2)	472	94.9 (94.4–95.3)	< 0.001
Negative results	4,457	455	89.8 (88.9–90.7)	162	96.4 (95.8–96.9)	< 0.001

The area under the receiver operator characteristic curve (AUC) for the detection of colorectal cancer was 0.94 for sDNA and 0.89 for FIT ($p = 0.04$). The AUC for the detection of advanced colorectal neoplasia was 0.73 and 0.67 for sDNA and FIT respectively ($p < 0.001$).

The authors calculated the NNS to detect one cancer as 154 with colonoscopy, 166 with DNA testing, and 208 with FIT. This may be inaccurate as it reflects only one-time screening, whereas the intervals are different for each of the tests.

The study by Imperiale and colleagues had fair quality. However, it was funded by the manufacturer, included patients scheduled for colonoscopy, and, as the authors noted, enrollment was weighted toward individuals aged ≥ 65 years (almost two-thirds of evaluable patients were 65 years or older). In addition, more than 20% of the participants were not evaluable and the authors indicated that there were significant differences in age and race between them and those evaluated. The number of participants excluded due to problems with sample collection or assay application were significantly higher in the sDNA group versus the FIT group (6.3% versus 0.3%), thus there is a potential of missed cancers due to the complexity of the test.

Overall, the Imperiale results show that the multitarget sDNA test was more sensitive than the one-time-use FIT test but less specific, leading to $> 10\%$ false-positive results, which in turn would lead to more anxiety and unnecessary follow-up colonoscopies. The study compared sDNA to one-time FIT and used a relatively high FIT cutoff value for a positive test result. The manufacturer of the multitarget sDNA test suggests its use once every 3 years; however, this was not based on evidence, and the accuracy of that test performed every 3 years was not compared to FIT performed annually. The study had no long-term outcome to determine the appropriate screening interval with sDNA test and whether it would reduce the incidence of CRC or its related mortality.

The Imperiale study was reviewed by the Medical Technology Assessment Committee (MTAC) in October 2014, and did not meet the committee's evaluation criteria.

Stool-based DNA (sDNA) and multitarget stool DNA tests: evidence review for 2017 update

The literature search for the 2017 guideline update did not identify any more recent RCTs comparing stool DNA tests to other CRC screening tests. The longitudinal study evaluating the 3-year interval MT-sDNA test is ongoing.

The search revealed one prospective cross-sectional study that compared the accuracy of a MT-sDNA test to FIT for detection of screening-relevant colorectal neoplasia (SRN) in Alaska Native people (Redwood 2016), as well as a number of modeling studies that were performed to estimate the optimal ages for screening, recommendable CRC screening strategies, and/or optimal intervals for screening with the different tests.

The use of models allows virtual prospective studies to be performed on large cohorts. However, modeling has its limitations: It does not directly compare different screening strategies or tests, nor does it take into account variables such as the biology of CRC, differences between clinical practices, uptake of the test, adherence to the screening programs, or other factors related to test performance or each modeling study.

Five modeling studies were reviewed.

- A comparative modeling study performed for the USPSTF (Knudsen 2016) found that strategies including FIT-DNA with annual testing and with 3-year intervals were not among the model-recommended strategies. The recommended models were colonoscopy every 10 years, annual FIT, sigmoidoscopy every 10 years with annual FIT, and CT colonography every 5 years performed from ages 50 through 75, as they provided similar life years gained (LYG) and a comparable balance of benefit and screening burden.
- Overall results of a modeling study by Bazri and colleagues (2017) showed that: 1) Colonoscopy was the most effective screening strategy across a wide range of sensitivity analyses, 2) CT colonography and flexible sigmoidoscopy were the next two most effective strategies, respectively, 3) DNA stool testing was more expensive and less effective than colonoscopy, and 4) DNA stool testing was more effective than FOBT and FIT by a small margin. The difference in effectiveness among strategies was modest, with a maximum of 0.022 discounted LYG (1.2 weeks for colonoscopy versus no screening).

Sensitivity analysis showed that with increasing compliance, the effectiveness of all strategies increased and the total strategy cost decreased. Colonoscopy remained the most effective strategy and had the lowest cost.

- In another modeling study (Ladabaum 2016), analysis showed that in cohorts of persons adhering with every recommended screening cycle, colonoscopy yielded the greatest reduction in CRC incidence and related mortality. This was followed by annual FIT, which showed the greatest shift toward earlier stage of diagnosis. FIT yielded the highest quality-adjusted life years per person, followed by screening colonoscopy, MT-sDNA every 3 years, and FIT every 2 years.
- In two studies by Berger and colleagues (both 2016), model analysis suggested that a 3-year MT-sDNA test interval had a lower performance than colonoscopy every 10 years, but that it was still clinically acceptable and had a lower patient, clinician, and administrative burden than annual screening.
- Overall, the analyses suggest that screening colonoscopy every 10 years and annual FIT are both more effective and less costly than MT-sDNA.
- Microsimulation modeling studies comparing different intervals for stool DNA testing recommended the 3-year interval for the stool DNA test over 1-, 2-, or 5-year intervals.

The results of modeling studies have to be interpreted with caution due to several limitations, mainly the use of hypothetical populations and simulation in lieu of head-to-head comparisons, and the assumption of 100% compliance to the screening programs.

Other limitations shared by two or more of the modeling studies include but are not limited to:

- The models were based on simulation of the general U.S. population and are not intended for individual-level decision making. In addition, the results may not be applicable to other countries.

- Many of the data on sensitivity and specificity of the screening tests were based on a single round of screening rather than a screening program. There is no way to prove that the negative results of a test were true negatives and not false negatives (e.g., for the lesions that do not bleed).
- Adenoma size rather than histopathology was used as an indicator for advanced adenoma. The models also did not include the serrated polyp pathway.
- The sensitivity of colonoscopy was assumed to be the same for each adenoma within reach of the endoscope regardless of its location, which may not be true based on observational studies.
- The measure of benefits and burdens of screening used in the analysis were imperfect. The analyses measured life years gained and did not account for the quality of life. In addition, burden was measured by the number of colonoscopies, while the other tests may also carry their own burden and may be perceived differently by each individual.

Flexible sigmoidoscopy

Evidence of benefit

There is strong evidence that colorectal cancer screening with flexible sigmoidoscopy (FS) reduces the incidence of CRC and its related deaths, but has no significant effect on all-cause mortality.

Flexible sigmoidoscopy and Hemoccult II are the only two CRC screening tests that have been studied in well-conducted population-based screening randomized controlled trials (RCTs) and found to reduce CRC mortality. No studies to date have shown a significant effect on all-cause mortality (Lin 2015).

A more recent Norwegian RCT (Holme 2014) showed that one-time screening with FS or FS+FOBT reduced CRC incidence and mortality on a population level compared with no screening. Screening was effective both in the 50- to 54-year and the 55- to 64-year age groups. The study randomized 98,792 participants aged 50–64 years to either a sigmoidoscopic screening group (10,283 to receive one-time FS and 10,289 to receive one-time FS+FOBT) or a control group (N=78,220). The primary endpoint of the trial was CRC incidence and mortality. The median follow-up was 11.2 years in the screening group and 10.9 in the control group. Adherence with screening was 63% (65% in the FS-only group and 60.9% in the FS+FOBT group). During this follow-up period CRC was diagnosed in 253 participants in the screening group and 1,086 in the control group (112.6 versus 141.0 cases per 100,000 person-years) (absolute rate difference, 28.4 [95% CI, 12.1–44.7]; hazard ratio, 0.80 [95% CI, 0.70–0.92]). CRC incidence was reduced in both the 50- to 54-year age group and the 55- to 64-year age group. 71 participants died of colorectal cancer in the screening group versus 330 in the control group (31.4 versus 43.1 deaths per 100,000 person-years) (absolute rate difference, 11.7 [95% CI, 3.0–20.4]; hazard ratio, 0.73 [95% CI, 0.56–0.94]). There were no significant differences between the FS-only and FS+FOBT screening groups.

The Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) screening trial (Schoen 2012), sponsored by the National Cancer Institute, randomized 154,900 men and women aged 55–74 years to screening with FS with a repeat exam at 3–5 years or to usual care. The primary endpoint of the trial was death from CRC; secondary endpoints included incidence of CRC, stage of the disease, survival, all-cause mortality, and harms of screening. Most patients with abnormal FS results underwent colonoscopy for diagnostic follow-up. The results of the trial showed that after a median follow-up of 11.9 years, the incidence of CRC was significantly lower in the screened group than in the usual-care group (RR = 0.75; 95% CI, 0.72–0.85), with a number needed to invite for screening to prevent 1 case of CRC of 282 (95% CI, 210–427). The significant reduction in cancer incidence was observed for both distal and proximal colorectal cancers. CRC-related mortality was also significantly reduced in the screening versus standard care groups, with an RR of 0.74 (95% CI, 0.63–0.87) and a number needed to invite for screening to prevent 1 CRC-related death of 871 (95% CI, 567–1874). The benefit on CRC-related mortality was, however, site-specific; mortality was significantly reduced in individuals with distal CRC (RR = 0.50; 95% CI, 0.38–0.64) but unaffected in those with proximal CRC (RR = 0.97; 95% CI, 0.77–1.22). The trial had valid methodology; however, there was a high degree of contamination, as 47% of the participants in the usual-care group underwent FS or colonoscopy. This would mask the actual benefit of FS screening.

Similar results were observed in two other European trials. The UK trial (Atkin 2010) showed that one-time FS performed on patients between the ages of 55 and 64 significantly reduced the incidence of

colorectal cancer and its associated mortality. The number needed to screen to prevent 1 CRC diagnosis was 191 and the number needed to screen to prevent 1 CRC death was 489.

In a recent Cochrane review and meta-analysis (Tang 2015), the authors pooled the results of 4 RCTs (total N=459,814) that compared screening with flexible sigmoidoscopy versus no screening, to determine the time to benefit of using FS for CRC screening. Patients' ages ranged from 50 to 74 years and the length of follow-up was 1.2–11.9 years. The analysis showed that for every 1,000 subjects screened at 5 and 10 years, 0.3 and 1.2 CRC-related deaths were prevented respectively. It took 4.3 years (95% CI, 2.8–5.8) to prevent 1 CRC-related death for every 5,000 screenings and 9.4 years (95% CI, 7.6–11.3) to prevent 1 CRC death for every 1,000 FS screenings. The authors concluded that the results suggest that flexible sigmoidoscopy is most appropriate for older adults with a life expectancy greater than approximately 10 years.

Combined FOBT and flexible sigmoidoscopy

Hassan and colleagues' meta-analysis (2012) indicates that while the participation rate with the combined FS+ gFOBT/FIT testing was significantly lower than with gFOBT/FIT alone, the detection rates of advanced neoplasia or cancer were significantly higher with the combined testing.

The Norwegian trial (Holme 2014) discussed earlier also showed that adherence to screening was significantly lower in the combined FS+FOBT screening group versus the FS-only group. Adding one-time FOBT to flexible sigmoidoscopy did not lead to the detection of more advanced adenomas or additional screen-detected cancers.

Evidence of harm

The pooled estimates for harms associated with flexible sigmoidoscopy screening as reported in the USPSTF systematic evidence review (Lin 2015) are 1 perforation and 2 major bleeds per 10,000 procedures. Follow-up colonoscopy for positive screening FS is associated with an estimated 1.4 perforations and 3.4 bleeds per 1,000 diagnostic colonoscopies. Thus one FS screening with an assumed 25% referral to colonoscopy and 100% adherence would lead to 22–65 perforations and 12–158 major bleeds per 100,000 subjects screened. Other serious complications include hospitalization, myocardial infarction, and syncope; other GI conditions were not commonly defined or reported in the studies (Lin 2015).

Colonoscopy

Evidence of benefit

There is no direct evidence from randomized controlled trials to conclude that screening with colonoscopy reduces the risk of colorectal cancer mortality or colorectal cancer incidence. The evidence of benefit is indirect, derived from case-control and observational studies, and is mostly about detection rate of lesions that may be clinically important. A large case-control study conducted in Canada found a significant association between colonoscopy and a reduced risk of death from left-sided CRC (Baxter 2009).

A large prospective cohort study in Switzerland that involved 1,912 individuals screened by colonoscopy and 20,774 controls showed significantly lower CRC incidence and cancer-related mortality in the screened cohort (Manser 2012).

An ongoing trial, COLONPREV (Quintero 2012, Castells 2015), compares one-time colonoscopy versus FIT every 2 years in 53,302 asymptomatic adults aged 50–69 years. The primary outcome of the trial is the rate of death from CRC at 10 years. The study design allowed for crossover between the two study groups. Of those who tested positive with FIT, 86.4% underwent colonoscopy. An interim analysis of the trial showed that subjects in the FIT group were more likely to participate in screening than those in the colonoscopy group. An intention-to-treat analysis showed that the detection rate of CRC was 0.1% in each of the two study groups. Advanced adenomas were found in 1.9% of the colonoscopy group and 0.9% of the FIT group (OR = 2.30; 95% CI, 1.97–2.69; $p < 0.001$). Non-advanced adenomas were found in 4.2% and 0.4% in the two groups respectively (OR = 9.80; 95% CI, 8.10–11.85; $p < 0.001$). Detection of adenomas was most evident for lesions in the proximal colon. The number needed to screen (NNS) to find 1 CRC was 191 in the colonoscopy group and 281 in the FIT group. The NNS to find any advanced neoplasm was 10 and 36, respectively. The number of subjects who needed to undergo a colonoscopy to find 1 CRC was 191 in the colonoscopy group and 18 in the FIT group. The numbers to find any advanced neoplasm were 10 and 2, respectively.

Evidence of harm

The results of several published studies (Blotière 2013, Denis 2013, Quintero 2012, Ko 2010, and Arora 2009) show the following:

- Perforation and lower GI bleeding are the most serious complications associated with colonoscopy.
- The rates of perforation varied between studies from 0.01% to 0.1%.
- The rates of lower GI bleeding ranged from 0.1% to 0.6%.
- The risk for serious complications is higher among those who undergo snare polypectomy with cautery. This risk increases further if more than one polypectomy with cautery is performed.
- Other risk factors for perforation and bleeding include resection of polyps larger than 1 cm, resection of more than 4 polyps, advanced age, female sex, comorbid conditions, and emergency colonoscopies.

The risk of complications may be lower with screening versus diagnostic colonoscopy. In a study of Medicare beneficiaries, Warren and colleagues (2009) reported a risk of 2.4 serious complications per 1,000 screening colonoscopies; 4.2 out of 1,000 diagnostic colonoscopies, and 9.3 out of 1,000 colonoscopies with polypectomy. The USPSTF (2008) reported a rate of 2.8 serious complications per 1,000 screening colonoscopies in predominantly asymptomatic individuals.

Colonography (computed tomography colonoscopy, CTC, virtual colonoscopy)

The updated systematic review for the USPSTF (Lin 2015) found no published studies that evaluated the effectiveness of screening with colonography on cancer incidence or mortality.

An earlier meta-analysis (de Haan 2011) of 5 heterogeneous studies, dominated by one large study, estimated the sensitivity of colonography for patients with polyps or adenomas ≥ 6 mm as 75.9% and 82.9% respectively. The corresponding specificities were 94.6% and 91.4%. The pooled results indicate that colonography had an average sensitivity for detecting polyps or adenomas of < 10 mm in diameter, but performed better for polyps or adenomas that were ≥ 10 mm in diameter. Colonography did not miss any CRC (100% sensitivity). It had a high specificity for polyps of any size. Colonography was compared to colonoscopy, which is not 100% sensitive, and histologic verification was not performed in all studies.

Harms associated with colonography

The USPSTF systematic review found 15 studies that addressed serious adverse effects of screening CT colonography (CTC). The most commonly reported adverse event was perforation, which may be due to the insufflation. This occurred at a rate of $< 0.02\%$. Other reported non-serious events included abdominal pain, vasovagal syncope, and pre-syncope. Many of the studies did not report radiation exposure. The estimated radiation dose for one full-screening CTC examination was about 4.5–7 mSv according to 4 studies published between 2008 and 2013. The newer multidetector scanners and protocols may decrease the radiation exposure. The review did not identify any studies that directly measured the risk of cancer resulting from this radiation exposure. Incidental extra-colonic findings detected on CTC may be either a benefit or harm depending on the finding. (Lin 2015)

The USPSTF draft recommendation (2015) concluded that the evidence is insufficient to assess the benefits and harms of computed tomography as a screening modality for colorectal cancer.

Screening high-risk individuals

There is insufficient evidence on how to screen, how often to screen, or when to initiate screening for individuals at high risk of colorectal cancer. Recommendations in this guideline are based on expert opinion.

Managing diminutive colorectal polyps

The literature search did not reveal any trial that compared the two strategies of “resect and discard” versus “do not resect” for managing the diminutive polyps detected on colonoscopy.

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Guideline Development Process and Team

Development process

To develop the Colorectal Cancer Screening Guideline, the guideline team adapted recommendations from externally developed evidence-based guidelines and/or recommendations of organizations that establish community standards. The guideline team reviewed additional evidence in several areas. For details, see Evidence Summary and References.

This edition of the guideline was approved for publication by the Guideline Oversight Group in July 2017.

Team

The Colorectal Cancer Screening Guideline development team included representatives from the following specialties: family medicine, gastroenterology, and Kaiser Permanente Washington Health Research Institute.

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Disclosure of conflict of interest

Kaiser Permanente requires that team members participating on a guideline team disclose and resolve all potential conflicts of interest that arise from financial relationships between a guideline team member or guideline team member's spouse or partner and any commercial interests or proprietary entity that provides or produces health care–related products and/or services relevant to the content of the guideline.

Team members listed above have disclosed that their participation on the Colorectal Cancer Screening Guideline team includes no promotion of any commercial products or services, and that they have no relationships with commercial entities to report.