CLINICAL GUIDELINE

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Screening for Colorectal Cancer in Asymptomatic Average-Risk Adults: A Guidance Statement From the American College of Physicians (Version 2)

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Description: The purpose of this updated guidance statement is to guide clinicians on screening for colorectal cancer (CRC) in asymptomatic average-risk adults. The intended audience is all clinicians. The population is asymptomatic adults at average risk for CRC.

Methods: This updated guidance statement was developed using recently published and critically appraised clinical guidelines from national guideline developers since the publication of the American College of Physicians' 2019 guidance statement, "Screening for Colorectal Cancer in Asymptomatic Average-Risk Adults." The authors searched for national guidelines from the United States and other countries published in English using PubMed and the Guidelines International Network library from 1 January 2018 to 24 April 2023. The authors also searched for updates of guidelines included in the first version of our guidance statement. The Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument was used to assess the quality of eligible guidelines. Two guidelines were selected for adoption and adaptation by raters on the basis of the highest average overall AGREE II quality scores. The evidence reviews and modeling studies for these 2 guidelines were also used to synthesize the evidence of diagnostic test accuracy, effectiveness, and harms of CRC screening interventions and to develop our guidance statements.

Guidance Statement 1: *Clinicians should start screening for colorectal cancer in asymptomatic average-risk adults at age 50 years.*

Guidance Statement 2: *Clinicians should consider not screening asymptomatic average-risk adults between the ages of 45 to 49 years. Clinicians should discuss the uncertainty around benefits and harms of screening in this population.*

Guidance Statement 3: *Clinicians should stop screening for colorectal cancer in asymptomatic average-risk adults older than 75 years or in asymptomatic average-risk adults with a life expectancy of 10 years or less.*

Guidance Statement 4a: *Clinicians should select a screening test for colorectal cancer in consultation with their patient based on a discussion of benefits, harms, costs, availability, frequency, and patient values and preferences.*

Guidance Statement 4b: *Clinicians should select among a fecal immunochemical or high-sensitivity guaiac fecal occult blood test every 2 years, colonoscopy every 10 years, or flexible sigmoidoscopy every 10 years plus a fecal immunochemical test every 2 years as a screening test for colorectal cancer.*

Guidance Statement 4c: *Clinicians should not use stool DNA, computed tomography colonography, capsule endoscopy, urine, or serum screening tests for colorectal cancer.*

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Colorectal cancer (CRC) is the fourth highest in incidence (153 020) and second in mortality (52 550) among cancer types in the United States (1). Between 2000 and 2019, CRC incidence slightly increased in persons younger than 50 years (6.0 to 8.7 per 100 000), decreased in those aged 50 to 64 years (85 to 74 per 100 000), and more sharply decreased in persons aged 65 years or older (305 to 158 per 100 000); decreases may be attributable to screening (2). Incidence of CRC varies by biological sex and race and ethnicity, with males and non-Hispanic American Indian or Alaska Native persons and non-Hispanic Black persons having the highest rates; however, absolute differences between biological sex and racial and ethnic groups are small (2).

See also:

Editorial comment. 1127
Summary for Patients I-20

Web-Only
Supplement

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The success of any screening program depends on screening strategy adherence (that is, type and frequency of a test, follow-up testing of abnormal results, and treatment). Benefits accrue from identification and removal of precancerous lesions or localized cancer that may progress and lead to morbidity and mortality; harms include false-positive results, physical and psychological harms, overdiagnosis, overtreatment, and financial and opportunity costs (3). Commonly used screening interventions include stool (fecal immunochemical tests [FIT], guaiac fecal occult blood tests [gFOBT], and stool DNA [sDNA] tests) and direct visualization tests (colonoscopy, flexible sigmoidoscopy [FS], and computed tomography colonography [CTC]).

Several clinical guidelines address CRC screening and vary on age to start and stop screening, screening tests and time intervals, and strength of recommendations. This guidance statement is an update of the American College of Physicians' (ACP) 2019 guidance statement, "Screening for Colorectal Cancer in Asymptomatic Average-Risk Adults" (4).

Scope, Population, and Intended Audience

The goal of this ACP guidance statement is to guide clinicians on age to start and stop screening and selection of type and frequency of screening tests in asymptomatic average-risk adults. This guidance is based on a critical review of existing guidelines and associated evidence reviews and modeling studies. Average risk for CRC is defined as no prior diagnosis of CRC, adenomatous polyps, or inflammatory bowel disease, and no personal diagnosis or family history of known genetic disorders that predispose a person to a high lifetime risk for CRC (for example, Lynch syndrome) (5, 6).

Methods

The methods article by ACP's Clinical Guidelines Committee describes the development process for ACP guidance statements, which differs from that for ACP clinical guidelines (7).

Search Results

A search of databases yielded 5 guidelines from the following organizations that met inclusion criteria (**Appendix Figure**, available at Annals.org): American Cancer Society (ACS), American College of Gastroenterology, American College of Radiology, U.S. Multi-Society Task Force on Colorectal Cancer, and U.S. Preventive Services Task Force (USPSTF).

Clinical Guidelines Quality Ratings

Guidelines by ACS and USPSTF were rated by most raters as "recommended with modifications" (4.6 of 7 and 5.2 of 7, respectively) and were used to develop our guidance statements. Three of the 5 raters recommended ACS recommendations with modifications, and 2 would not recommend them. All 5 raters recommended USPSTF's recommendations with modifications (**Supplement Table 1**, available at Annals.org).

The ACS used the 2016 USPSTF evidence review and decision modeling to develop its guideline (8). As a result, evidence used in this guidance statement is from USPSTF's 2021 evidence review (9, 10) and decision modeling (11). When synthesizing the evidence in this manuscript, we note how many new studies were identified by USPSTF's 2021 evidence review since its 2016 version. The decision modeling for USPSTF (11) was developed by the Cancer Intervention and Surveillance Modeling Network and consisted of 3 independently developed microsimulation models: Simulation Model of CRC (SimCRC), CRC Simulated Population Model for Incidence and Natural History (CRC-SPIN), and Microsimulation Screening Analysis (MISCAN). For benefits and harms outcomes, we abstracted and interpreted means of these 3 models (11). Unless stated otherwise, we refer to these 3 models as the modeling study. Additional methods for this update can be found in the **Supplement** (available at Annals.org).

Recommendations from eligible guidelines are displayed in **Supplement Tables 2** and **3** (available at Annals.org). **Supplement Tables 4** to **6** (available at Annals.org) display the evidence for diagnostic test accuracy, effectiveness, and harms of screening tests for CRC, respectively. The **Figure** summarizes our updated guidance statement.

Age to Start Screening for CRC

The evidence review did not identify studies that enrolled or reported results for initiating CRC screening in only adults younger than 50 years (9, 10). Evidence from 2 randomized controlled trials (RCTs; no new RCTs) assessed the effectiveness of gFOBT on CRC mortality by age (12, 13). Persons aged 60 years or older had larger reductions in CRC mortality compared with those younger than 60 years (12, 13). Evidence from 3 RCTs (no new RCTs, but additional follow-up data) of FS reported results by age (14–16). The NORCCAP (Norwegian Colorectal Cancer Prevention) (50 to 54 vs. 55 to 64 years) and UKFSST (UK Flexible Sigmoidoscopy Screening) trials (55 to 59 vs. 60 to 64 years) found no differences between age groups for CRC mortality (14, 15). However, the PLCO (Prostate, Lung, Colorectal, and Ovarian) Cancer Screening trial found a greater reduction in CRC mortality in those aged 65 to 74 years versus those aged 55 to 64 years (16). Two RCTs that evaluated FS by age found no differences in all-cause mortality (14, 15).

The modeling study evaluated FIT, sDNA, colonoscopy, CTC, and FS for starting screening at age 45 years versus 50 years (11). Starting screening at age 45 years compared with 50 years yielded more life-years gained (LYG; range: 22 to 27 per 1000 screened or 8 to 10 life-days gained per person) and prevented a small number of CRC cases (range, 2 to 3 per 1000 screened) and deaths (range, 0.9 to 1 per 1000 screened). However, there was also an increase in the number of colonoscopies (range, 161 to 784 per 1000 screened) and colonoscopy complications, such as cardiovascular and gastrointestinal events (for example, serious bleeding, perforation, myocardial infarction, and angina) (range, 0.1 to 2 more per 1000 screened) (11).

Age to Stop Screening for CRC

The evidence review did not identify studies that enrolled or reported results for CRC screening in only adults older than 75 years (9, 10).

Figure. Visual summary of the ACP guidance statement on CRC screening (version 2).

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ACP Guidance Statement (Version 2)
April 2023

Screening for Colorectal Cancer in Asymptomatic Average-Risk Adults

Population

- Adults who are asymptomatic and at average risk for CRC
  - Defined as no prior diagnosis of CRC, adenomatous polyps, or inflammatory bowel disease, and no personal or family history of known genetic disorders that predispose a person to a high lifetime risk for CRC (e.g., Lynch syndrome)

Intended Audience

- All clinicians

ACP Guidance on CRC Screening Strategies

- Select Among
  - FIT every 2 y;
  - gFOBT every 2 y;
  - Colonoscopy every 10 y; or
  - FS every 10 y plus a FIT every 2 y
- Do Not Use
  - Capsule endoscopy
  - CTC
  - Serum test
  - sDNA test
  - Urine test

ACP Guidance Statements

Guidance Statement 1: *Clinicians should start screening for colorectal cancer in asymptomatic average-risk adults at age 50 years.*

Guidance Statement 2: *Clinicians should consider not screening asymptomatic average-risk adults between the ages of 45 to 49 years. Clinicians should discuss the uncertainty around benefits and harms of screening in this population.*

Guidance Statement 3: *Clinicians should stop screening for colorectal cancer in asymptomatic average-risk adults older than 75 years or in asymptomatic average-risk adults with a life expectancy of 10 years or less.*

Guidance Statement 4:
4a. Clinicians should select a screening test for colorectal cancer in consultation with their patient based on a discussion of benefits, harms, costs, availability, frequency, and patient values and preferences. 4b. Clinicians should select among a fecal immunochemical or high-sensitivity guaiac fecal occult blood test every 2 years, colonoscopy every 10 years, or flexible sigmoidoscopy every 10 years plus a fecal immunochemical test every 2 years as a screening test for colorectal cancer.

4c. Clinicians should not use stool DNA, computed tomography colonography, capsule endoscopy, urine, or serum screening tests for colorectal cancer.

Clinical Considerations

Clinicians should assess their patients' baseline risk for CRC (e.g., personal and family history of CRC and polyps).

Starting CRC screening between the ages of 50 and 60 y or screening less frequently (e.g., colonoscopy every 15 y) is likely reasonable for some adults at average risk for CRC who prefer to be screened less frequently.

Clinicians should be attentive to race and ethnicity of patients who have experienced worse CRC health outcomes to ensure access to and receipt of recommended screening.

Success of any screening program is dependent on adherence to the screening frequency of a selected intervention, timely follow-up testing, and treatment. When selecting a CRC screening test, for example, a stool test may not be an ideal screening strategy for patients who may be unable or unwilling to follow up every other year.

Test quality, particularly for direct visualization tests, is dependent on the skill of the person doing the test and the quality of the samples collected. This includes ensuring optimal bowel preparation and access to a skilled professional performing a colonoscopy or FS. The importance of following instructions for optimal bowel preparation should be discussed, as it is critical to ensure quality and success of colonoscopy and FS.

Clinicians should consider the following additional factors related to colonoscopy and FS for CRC:
- Screening and diagnostic evaluation can occur during the same examination with a colonoscopy.
- A high-risk lesion or CRC found on FS may result in a follow-up colonoscopy.
- Screening with colonoscopy or FS is less frequent than stool tests.
- Colonoscopy and FS require bowel preparation that includes a clear liquid diet and NPO status before the procedure, travel to the screening location, and typically sedation (for colonoscopy).
- Patients undergoing colonoscopy need an attendant and transportation due to sedation or anesthesia.
- Bowel preparation, anesthesia, and sedation increase the risk for aspiration and dehydration.
- Colonoscopy and FS might be delayed due to clinician shortages and inadequate bowel preparation.
- Test availability of FS has declined in the United States.

Clinicians should consider the following additional factors related to FIT and gFOBT for CRC:
- All stool tests should be done on voided stool samples, not on samples obtained by a digital rectal examination.
- An abnormal result with a FIT or gFOBT requires a follow-up colonoscopy.
- FIT and gFOBT do not require bowel preparation, anesthesia, or sedation.
- FIT requires a single stool sample without dietary restrictions; gFOBT requires 3 stool samples and dietary restrictions.
- FIT and gFOBT require a higher frequency of screening compared with FS or colonoscopy.
- FIT and gFOBT can be done within the home.

ACP = American College of Physicians; CRC = colorectal cancer; CTC = computed tomography colonography; FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; gFOBT = guaiac fecal occult blood test; NPO = nothing by mouth; sDNA = stool DNA.

With perfect adherence to screening, the modeling study found that stopping screening at ages 80 and 85 years, compared with 75 years, had no to little additional LYG or CRC incidence and mortality prevented but conferred an increase in colonoscopies and a slight increase in colonoscopy complications (11).

Screening Tests for CRC

The updated evidence review by USPSTF found no new screening trials evaluating the effectiveness of stool or direct visualization tests. However, it identified new publications with longer follow-up periods evaluating gFOBT and FS (9, 10).

Stool Tests

gFOBT

Diagnostic Accuracy for CRC. Among commonly used high-sensitivity gFOBT, sensitivity ranged from 0.50 to 0.75 and specificity ranged from 0.96 to 0.98 (9, 10). The modeling study did not analyze gFOBT (11).

Effectiveness. The evidence review identified 5 RCTs (no new RCTs, but additional follow-up data) evaluating the effectiveness of gFOBT compared with no screening (9, 10). Five RCTs, with a range of 11- to 30-year follow-up, found that biennial gFOBT screening reduced CRC mortality at approximately 20 years (risk ratio [RR], 0.91 [95% CI, 0.84 to 0.98]) and 30 years (RR, 0.78 [CI, 0.65 to 0.93]) (12, 13, 17–19). One RCT evaluated annual gFOBT and found similar reductions in CRC mortality at 30 years (13). Four RCTs that evaluated gFOBT found no differences in all-cause mortality (12, 13, 17, 18).

Harms. There are no known direct serious harms because gFOBT is noninvasive. The evidence review found harms of colonoscopy after an abnormal gFOBT result (**Supplement Table 6**) (9, 10).

FIT

There are numerous FIT available, and diagnostic accuracy varies by type. The applicability of benefits and harms should be considered with that context.

Diagnostic Accuracy for CRC. Commonly used FIT had a sensitivity of 0.74 (CI, 0.64 to 0.83) and a specificity of 0.94 (CI, 0.93 to 0.96) (9, 10). The modeling study used a sensitivity of 0.74 and a slightly higher specificity of 0.97 (11).

Effectiveness. The evidence review identified 1 nonrandomized study (NRS; no new NRSs) that evaluated the effectiveness of FIT screening (9, 10). Screening with biennial FIT was associated with lower CRC mortality versus no screening (adjusted RR, 0.90 [CI, 0.84 to 0.95]) (20).

Harms. Fecal immunochemical tests are noninvasive and have no known serious harms. The evidence review found harms of colonoscopy after an abnormal FIT result (**Supplement Table 6**) (9, 10).

sDNA Tests

Diagnostic Accuracy for CRC. Among stool tests, sDNA tests had the highest sensitivity of 0.93 (CI, 0.87 to 1.0) but also the lowest specificity of 0.85 (CI, 0.84 to 0.86) (9, 10). Of note, the modeling study used a sensitivity of 0.94 and a higher specificity of 0.91 (11).

Effectiveness. The evidence review found no studies evaluating sDNA tests and CRC incidence and mortality or all-cause mortality (9, 10).

Harms. Stool DNA tests are noninvasive and have no known serious harms. The evidence review identified no studies evaluating harms of follow-up colonoscopy after an abnormal sDNA test result (9, 10). However, the false-positive rate of sDNA tests to detect CRC is higher than for gFOBT and FIT, which can lead to more colonoscopies, evaluations, and harms.

Direct Visualization Tests

Colonoscopy

Diagnostic Accuracy for CRC. Studies evaluating the sensitivity of colonoscopy for CRC were underpowered and found a wide range (0.18 to 1.0) (9, 10). Sensitivity was much higher with a narrower range for adenomas 6 mm or greater (range, 0.75 to 0.93) and 10 mm or greater (range, 0.89 to 0.95) (9, 10). Because of the limited data, the modeling study assumed a sensitivity for CRC of 0.95 (11) and used a specificity of 0.86 (21).

Effectiveness. The evidence review identified 2 NRSs (1 new NRS) evaluating the effectiveness of screening colonoscopy (9, 10). One NRS compared those who had at least 1 colonoscopy with those who had never received one and found that colonoscopy was associated with lower CRC mortality at 24 years of follow-up (adjusted hazard ratio, 0.32 [CI, 0.24 to 0.45]) (22). Both NRSs found colonoscopy reduced CRC incidence, but neither evaluated all-cause mortality (22, 23).

Harms. The evidence review identified 27 NRSs (6 new NRSs) for screening colonoscopy and reported 3.1 perforations per 10 000 procedures (CI, 2.3 to 4.0) (9, 10). The review also found 22 NRSs (7 new NRSs) and reported 14.6 serious bleeding events per 10 000 procedures (CI, 9.4 to 19.9) (9, 10). One NRS suggested a correlation between serious bleeding events and increasing age at screening (24). The evidence review found that perforation and risk for bleeding was slightly higher in mixed populations (that is, screening and diagnostic) (9, 10).

CTC

Diagnostic Accuracy for CRC. Sensitivity of CTC with bowel preparation ranged from 0.86 to 1; no studies reported diagnostic accuracy of CTC without bowel preparation (9, 10). The modeling study used a sensitivity of 0.84 and a specificity of 0.88 (25).

Effectiveness. The evidence review identified no eligible studies evaluating the effectiveness of CTC for CRC screening (9, 10).

Harms. The evidence review identified 17 NRSs (1 new NRS) finding no to little risk for serious harms of CTC (9, 10). Seven NRSs (1 new NRS) found 1.3 perforations per 10 000 procedures (CI, 0.0 to 2.9) (9, 10). The largest ($n = 40\,121$) of the 7 NRSs reported 7 perforations, all of which were asymptomatic and in patients undergoing manual insufflation (26). Four NRSs (24, 27–29) reported on CTC and serious bleeding events with only 1 NRS ($n = 1384$) observing 4 events (24). The review identified 27 NRSs (6 new NRSs) and showed that CTC detected a wide range of extracolonic findings that were deemed either potentially important and requiring follow-up (3.4% to 26.9%) or likely important or incompletely characterized and possibly requiring follow-up (1.3% to 11.4%) (9, 10). Whether extracolonic findings result in benefit or harm is uncertain. Data were inadequate to estimate serious harms from follow-up colonoscopy after an abnormal CTC test result (9, 10). Computed tomography colonography exposes patients to low-dose ionizing radiation, ranging from 0.8 to 5.3 mSv per examination (9, 10).

FS

Diagnostic Accuracy for CRC. The evidence review identified no studies evaluating the test accuracy of FS (9, 10). The modeling study assumed a sensitivity of 0.95 (11) and used a specificity of 0.87 (30).

Effectiveness. The evidence review identified 4 RCTs (no new RCTs, but additional follow-up data) evaluating the effectiveness of FS and colonoscopy referral if high-risk colonic lesions or CRC were detected (9, 10). The RCTs had 11 to 17 years of follow-up; only 1 RCT had 2 rounds of FS screening (54% attendance in the second screen) (16), whereas the other trials had just 1 round (14, 15, 31). Flexible sigmoidoscopy reduced CRC incidence and mortality (incidence rate ratio, 0.78 [CI, 0.74 to 0.83] and 0.74 [CI, 0.68 to 0.80], respectively); however, there was no difference in all-cause mortality (9, 10).

Harms. The evidence review identified 18 NRSs (4 new NRSs) evaluating serious FS harms. Among 10 NRSs (1 new NRS), the rate of serious bleeding events was 0.5 per 10 000 procedures (CI, 0 to 1.3). In 11 NRSs, perforations occurred at a rate of 0.2 per 10 000 procedures (CI, 0.1 to 0.4) (9, 10). Across 4 NRSs (2 new NRSs), a colonoscopy after an abnormal FS resulted in 20.7 serious bleeding events per 10 000 procedures (CI, 8.2 to 33.2) and 12 perforations per 10 000 procedures (CI, 7.5 to 16.5) (9, 10).

Other Screening Tests for CRC

The USPSTF also reviewed capsule endoscopy, serum, and urine tests (9, 10). A serum test is U.S. Food and Drug Administration–approved for CRC screening in persons who decline recommended screening tests (32). The evidence review found no studies on the effectiveness of capsule endoscopy, serum, or urine screening tests; 1 NRS of harms of screening capsule endoscopy; and 1 to 2 NRSs of each of these screening tests for diagnostic accuracy, mostly focused on adenomas (9, 10). One NRS ($n = 689$), designed as a diagnostic accuracy study, reported capsule endoscopy harms and found zero serious adverse events and 3 nonserious adverse events (9, 10).

Comparison of Different Screening Strategies

The evidence review identified 20 RCTs and 1 NRS (6 new RCTs) comparing screening tests for detecting CRC; none evaluated sDNA tests (9, 10). These comparative studies generally lacked statistical power to detect differences between groups and were limited to 1 round of CRC screening (9, 10).

The evidence review identified 5 RCTs comparing direct visualization screening tests and found no differences in detected CRC cases (9, 10). The review also identified 11 RCTs comparing stool and direct visualization tests. One-time testing of direct visualization identified more CRC cases than 1-time stool tests (9, 10), but 1 RCT comparing 4 rounds of FIT to 1-time colonoscopy or FIT showed no difference in detecting CRC (31).

The evidence review identified 8 RCTs comparing stool tests and, notably, found that FIT identified slightly more cases of CRC than gFOBT (9, 10).

Costs of Screening Tests

Supplement Table 7 (available at Annals.org) summarizes the costs of various screening tests and strategies in the United States. Neither ACS nor USPSTF considered cost or resource use in its recommendations (6, 8). Screening more frequently than recommended is unlikely to provide additional meaningful benefit (3). However, it will increase false-positive results, harms, and burden while using already limited health care resources. Additional issues with cancer screening in general include overdiagnosis (a condition or disease that would not cause symptoms or death during a person's lifetime) and associated overtreatment (unnecessary treatment) (3).

Multiple Chronic Conditions

Comorbidities reduce age-adjusted life expectancy and may influence CRC screening initiation, discontinuation, and frequency. Serious comorbidities include but are not limited to chronic obstructive pulmonary disease, diabetes, heart failure, moderate to severe liver disease, chronic hepatitis, advanced chronic kidney disease or end-stage kidney disease, and dementia (33). Due to the slow growth rate of most adenomas and subsequent CRC should it develop, the time needed to derive a benefit from screening is long (it takes 10 years to reduce 1 CRC death per 1000 persons screened) (34). The evidence review and modeling study suggest that any benefit from reducing mortality is outweighed by harms for patients with a life expectancy of less than 10 years, and possibly longer, due to age or comorbidities (9–11).

Differences by Race and Ethnicity

It is important to note that race and ethnicity are social constructs rather than biological risk factors. Differences in risk for diseases, including CRC, may be mediated by factors such as social determinants of health. Differences between racial and ethnic groups in

CRC incidence may be attributable to modifiable risk factors, including variation in screening rates among persons of different races and ethnicities (35).

Absolute differences in CRC incidence and mortality by racial and ethnic groups are small. Those who identify as non-Hispanic American Indian or Alaska Native and non-Hispanic Black have the highest CRC incidence (49 and 44.3 per 100 000, respectively), followed by non-Hispanic White (38.1 per 100 000), Hispanic (34.4 per 100 000), and non-Hispanic Asian or Pacific Islander (30.7 per 100 000) (2). Colorectal cancer mortality occurs in a similar pattern. Those who identify as non-Hispanic American Indian or Alaska Native and non-Hispanic Black have the highest rates (17.2 and 17.6 per 100 000, respectively), followed by non-Hispanic White (13.1 per 100 000), Hispanic (10.7 per 100 000), and non-Hispanic Asian or Pacific Islander (9.1 per 100 000) (2).

Among the limited number of studies that stratified results by race and ethnicity, sensitivity and specificity generally showed no differences between groups (9, 10). Four NRSs of screening colonoscopy and harms found mixed results by race and ethnicity (36–39).

Differences by Biological Sex

Males have a higher risk for developing and dying of CRC than females, although absolute differences are small (43.4 vs. 32.8 per 100 000 and 15.7 vs. 11.0 per 100 000, respectively) (2).

Three RCTs assessed the effectiveness of gFOBT on CRC mortality by sex (12, 13, 18). Two RCTs found no difference in CRC mortality by sex (12, 18); however, another trial found greater reductions in males than in females (13). Among males in the same RCT, the largest reductions in CRC mortality were in those aged 60 to 69 years, whereas females aged 70 years or older had the largest reductions (13).

Three RCTs of FS reported results by sex (14–16). In 2 RCTs, males had larger reductions in CRC mortality (15, 16), but no meaningful differences in effects were seen in the other trial (14). One RCT analyzed data by age and sex and found that males aged 50 to 54 years and 55 to 64 years had greater reductions in CRC mortality compared with females in the same age groups (15). Two RCTs found no sex differences in all-cause mortality (14, 15).

Evidence Gaps and Research Needs

Future research should focus on studying the benefits and harms of screening persons younger than 50 years and older than 75 years to further our understanding of the optimal CRC screening intervals and ages to start and stop. Ongoing comparative trials should better inform selection and frequency within (for example, colonoscopy every 10 or 15 years) and between (for example, FIT compared with sDNA) CRC screening tests.

Emerging Evidence

Following ACP guidance statement methods, we did not search for published studies beyond those identified in the reviewed guidelines. However, we believed the NordICC (Northern-European Initiative on Colorectal Cancer) trial, the first published randomized, pragmatic clinical trial on the effectiveness of screening colonoscopy, warranted brief commentary (40). Colorectal cancer and all-cause mortality were not different between the screening colonoscopy and usual care groups (0.28% vs. 0.31%; RR, 0.90 [CI, 0.64 to 1.16]; and 11.03% vs. 11.04%; RR, 0.99 [CI, 0.96 to 1.04], respectively) at 10-year follow-up in the intention-to-screen analysis (40). Only 42% of those invited to be screened received a colonoscopy. In a secondary analysis assuming all participants randomly assigned to be screened were screened, CRC mortality would have been lower than in the usual care group (0.15% screened vs. 0.30% receiving usual care; RR, 0.50 [CI, 0.27 to 0.77]) (40). Findings from NordICC and future published studies, especially comparative studies, should be used to inform CRC screening guidelines, evidence reviews, and microsimulation models.

ACP Guidance Statements

Age to Start Screening for CRC in Asymptomatic Average-Risk Adults

Guidance Statement 1: Clinicians should start screening for colorectal cancer in asymptomatic average-risk adults at age 50 years

There is a net benefit of CRC screening in average-risk adults starting at age 50 years. New evidence confirms our previous conclusion that CRC screening in adults aged 50 to 75 years reduces CRC incidence and mortality but not all-cause mortality (4, 9, 10). Results stratified by age and studies with a higher mean age showed that those aged 65 to 75 years had the greatest benefit. This may be anticipated as the median age at diagnosis of CRC is 67 years (41). Although a net screening benefit still existed in those aged 50 to 64 years, it was lower at younger age and deemed small in adults aged 50 to 54 years. A detailed rationale can be found in our previous guidance statement (4).

The USPSTF (grade A) and ACS (strong recommendation) guidelines also recommend screening in average-risk adults aged 50 to 75 years (6, 8).

Guidance Statement 2: Clinicians should consider not screening asymptomatic average-risk adults between the ages of 45 to 49 years. Clinicians should discuss the uncertainty around benefits and harms of screening in this population

First, no studies of effectiveness and harms only enrolled participants younger than 50 years or directly stratified results by this age group (9, 10). Sensitivity and specificity data of CRC screening tests in adults younger than 50 years are mainly on adenomas, not CRC (9, 10). In the absence of evidence, it is unknown if diagnostic accuracy of CRC screening tests would be similar to that in older populations. However, we know the predictive value of tests would be lower because the incidence of adenomas and CRC is lower in younger adults.

Second, there is a potential for exacerbating health care disparities, an important factor when considering expanding CRC screening to 45 to 49 years old, particularly given the uncertain net benefit. Opportunity costs and resources need to be weighed as decisions are made about unproven screening programs when there is a shortage of internal medicine physicians in the United States. These shortages lead to prolonged scheduling times for routine medical care services, including colonoscopies. The limited time and resources should be used on prioritizing CRC screening access for adults aged 50 to 75 years and other interventions with proven efficacy or cost savings.

Third, the decision modeling for USPSTF consisted of 3 independently created microsimulation models. Nevertheless, we have concerns about assumptions and parameters used in the modeling that likely provide estimates of screening effectiveness and harms that are optimistic compared with clinical settings. All models assumed perfect adherence which, regardless of age, would likely overestimate benefits of CRC screening and is not consistent with surveillance and empirical data (42–44). The sensitivity and specificity estimates used in the models were assumed or not always consistent with the evidence review (9–11). All 3 models did not simulate the pathway of serrated polyps to CRC (11). All adenomas had the potential to progress to CRC in SimCRC and CRC-SPIN. However, MISCAN allowed for some adenomas not to progress (11), which is important particularly for estimating benefit at younger ages. As a result, MISCAN was likely the most similar to a "real-world" setting for younger ages and produced 41% to 57% lower relative benefit in LYG and 0% to 75% lower benefits in CRC incidence and mortality compared with SimCRC and CRC-SPIN.

Fourth, the net benefit of screening is much less favorable in average-risk adults between ages 45 and 49 years than in those aged 50 to 75 years. At the population level, MISCAN found 13 to 17 LYG per 1000 screened starting at age 45 years compared with 50 years (11). This translates to 5 to 6 additional life-days gained per person. MISCAN also indicated a benefit of preventing CRC cases (1 to 2 per 1000 screened or a 0.1% to 0.2% reduction) and reducing CRC mortality (0.4 to 1 per 1000 screened or a 0.04% to 0.1% reduction) in those who started screening at age 45 years compared with 50 years (11). Although there has been a small increase in CRC incidence among persons aged 45 to 49 years (45), it is lower than in those aged 50 to 64 years and 65 to 74 years (35.1 vs. 71.9 vs. 128.9 per 100 000, respectively) (2). Harms that occur with CRC screening include cardiovascular and gastrointestinal events (for example, serious bleeding, perforation, myocardial infarction, and angina) (range, 0.1 to 2 more per 1000 screened), unnecessary follow-ups, and costs for findings deemed clinically unimportant.

Even if we assumed the modeling study had no limitations and accepted the results at face value, we would conclude that the small estimated benefits and harms roughly balance each other out, resulting in an inadequate net benefit to warrant CRC screening in average-risk adults aged 45 to 49 years. Clinicians should discuss the data on the diagnostic accuracy, incidence, uncertainty around benefits, and harms in average-risk adults aged 45 to 49 years.

The USPSTF (grade B) and ACS (qualified recommendation) recommend CRC screening in average-risk adults aged 45 to 49 years because of the increasing incidence of CRC in this age group, availability of accurate screening tests, and modeling results (6, 8).

Age to Stop Screening for CRC in Average-Risk Adults

Guidance Statement 3: Clinicians should stop screening for colorectal cancer in asymptomatic average-risk adults older than 75 years or in asymptomatic average-risk adults with a life expectancy of 10 years or less

There is no new evidence from RCTs about the benefits and harms of screening for adults older than 75 years or those with limited life expectancy (9, 10). In addition, despite favorable assumptions and parameters in the modeling study, stopping screening at ages 80 and 85 years, compared with 75 years, had no to little additional benefits with an increase in screening tests and a slight increase in serious harms (11). Although estimating life expectancy can be challenging and inaccurate, persons older than 75 years who are in good health and lack history of CRC screening may still derive a net benefit from 1-time screening. A detailed rationale is provided in our previous guidance statement (4). Additional consideration of these issues will need to be made between clinicians and patients when discussing stopping screening in older adults or in those who are in poorer health.

The USPSTF (grade C) guideline recommends selectively screening average-risk adults aged 76 to 85 years based on patients' overall health, prior screening history, and preferences (6). The ACS guideline (qualified recommendations) recommends individualized screening decisions for adults aged 76 through 85 years based on patient preferences, life expectancy, health status, and prior screening history and to discourage adults aged 85 years from continuing CRC screening (8).

Selecting a Screening Test and Frequency for CRC

Guidance Statement 4a. Clinicians should select a screening test for colorectal cancer in consultation with their patient based on a discussion of benefits, harms, costs, availability, frequency, and patient values and preferences

Guidance Statement 4b. Clinicians should select among a fecal immunochemical or high-sensitivity guaiac fecal occult blood test every 2 years, colonoscopy every 10 years, or flexible sigmoidoscopy every 10 years plus a fecal immunochemical test every 2 years as a screening test for colorectal cancer

Guidance Statement 4c. Clinicians should not use stool DNA, computed tomography colonography, capsule endoscopy, urine, or serum screening tests for colorectal cancer

Among effective screening strategies in Guidance Statement 4b, data are lacking to conclude superiority of one strategy over another (9, 10). Clinicians should also consider availability, cost, and patients' values and preferences.

There were no new RCTs evaluating the effectiveness of stool or direct visualization tests (9, 10). Clinicians should use a FIT or high-sensitivity gFOBT biennially instead of annually because we observed no differences in effectiveness between these screening intervals. Fewer tests would reduce patient burden and harms. For colonoscopy, modeling data suggest that screening for CRC every 10 years results in the largest net benefit; however, data also showed that screening every 15 years preserves most of the benefit in CRC mortality and LYG while reducing colonoscopy harms, burden, and costs (11). The frequency of colonoscopy and other screening tests should be reevaluated as more benefits and harms data beyond microsimulation models become available. A primary reason for selecting screening tests other than sDNA, serum, urine, CTC, and capsule endoscopy is that these screening tests have no studies of effectiveness. Stool DNA tests had a high sensitivity but lower specificity for CRC, which would lead to unnecessary colonoscopies and other evaluations. The number of unnecessary colonoscopies would also increase with more frequent use (USPSTF currently recommends screening every 1 to 3 years with sDNA). Our guidance statement considered cost, but USPSTF and ACS did not. Over a 10-year time frame, sDNA tests would have a cost equal to that of colonoscopy, whereas other accurate stool tests have lower cost (**Supplement Table 7**). Computed tomography colonography also leads to a high frequency of extracolonic findings of uncertain benefit or harm. A positive CTC requires follow-up colonoscopy, which reduces its utility as a direct visualization test. A detailed rationale can be found in our previous guidance statement (4).

The USPSTF recommends screening with FIT or a high-sensitivity gFOBT every year, an sDNA test every 1 to 3 years, CTC every 5 years, FS every 5 years, FS every 10 years with an annual FIT, or colonoscopy every 10 years (6). The ACS recommends the same screening strategies but recommends screening with an sDNA test every 3 years and does not specifically recommend using FS plus FIT (8).

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Note: Guidance statements are meant to guide clinicians using recent and critically appraised clinical guidelines. They are developed based on the highest-rated guidelines and associated evidence reviews and modeling studies and may not apply to all patients or individual clinical situations. They should not be used as a replacement for a clinician's judgment. Any reference to a product or process contained in a guidance statement is not intended as an endorsement of any specific commercial product. All ACP guidance statements are considered automatically withdrawn or invalid 5 years after publication or once an update has been issued.

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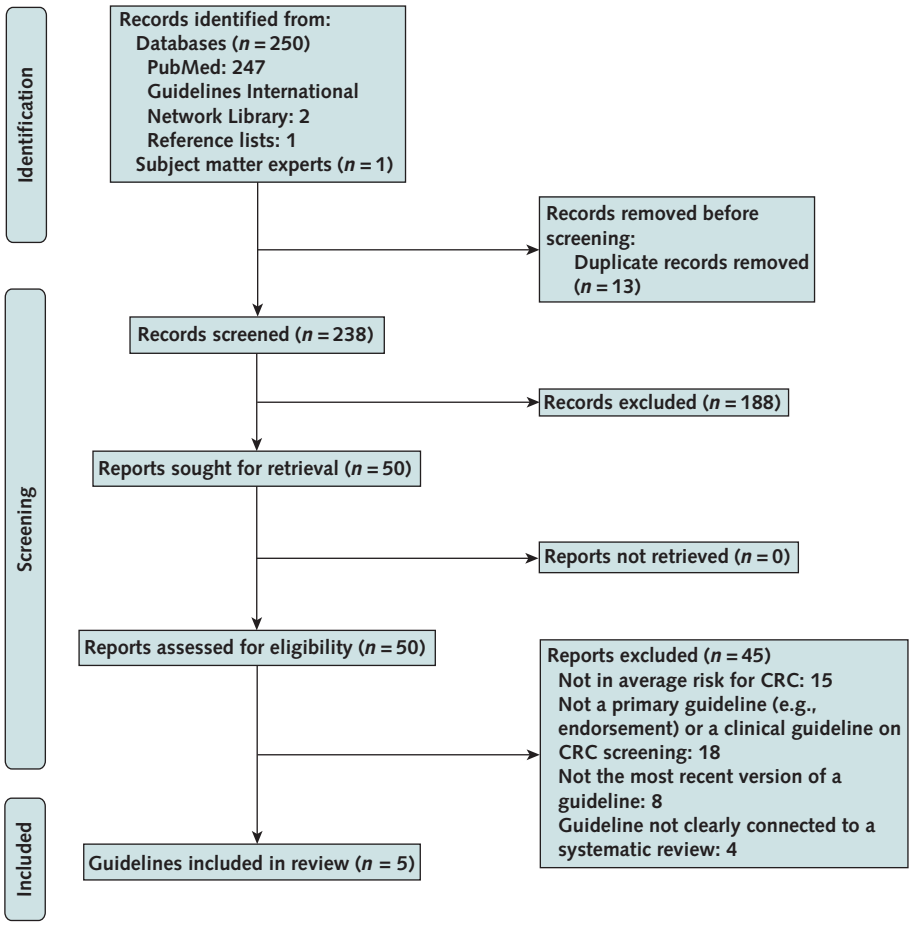
Appendix Figure. Study flow diagram.



CRC = colorectal cancer.