IMPORTANCE  Colorectal cancer (CRC) remains a significant cause of morbidity and mortality in the United States.

OBJECTIVE  To systematically review the effectiveness, diagnostic accuracy, and harms of screening for CRC.

DATA SOURCES  Searches of MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials for relevant studies published from January 1, 2008, through December 31, 2014, with surveillance through February 23, 2016.

STUDY SELECTION  English-language studies conducted in asymptomatic populations at general risk of CRC.

DATA EXTRACTION AND SYNTHESIS  Two reviewers independently appraised the articles and extracted relevant study data from fair- or good-quality studies. Random-effects meta-analyses were conducted.

MAIN OUTCOMES AND MEASURES  Colorectal cancer incidence and mortality, test accuracy in detecting CRC or adenomas, and serious adverse events.

RESULTS  Four pragmatic randomized clinical trials (RCTs) evaluating 1-time or 2-time flexible sigmoidoscopy (n = 458,002) were associated with decreased CRC-specific mortality compared with no screening (incidence rate ratio, 0.73; 95% CI, 0.66-0.82). Five RCTs with multiple rounds of biennial screening with guaiac-based fecal occult blood testing (n = 419,966) showed reduced CRC-specific mortality (relative risk [RR], 0.91; 95% CI, 0.84-0.98, at 19.5 years to RR, 0.78; 95% CI, 0.65-0.93, at 30 years). Seven studies of computed tomographic colonography (CTC) with bowel preparation demonstrated per-person sensitivity and specificity to detect adenomas 6 mm and larger comparable with colonoscopy (sensitivity from 73% [95% CI, 58%-84%] to 98% [95% CI, 91%-100%]; specificity from 89% [95% CI, 84%-93%] to 91% [95% CI, 88%-93%]); variability and imprecision may be due to differences in study designs or CTC protocols. Sensitivity of colonoscopy to detect adenomas 6 mm or larger ranged from 75% (95% CI, 63%-84%) to 93% (95% CI, 88%-96%). On the basis of a single stool specimen, the most commonly evaluated families of fecal immunochemical tests (FITs) demonstrated good sensitivity (range, 73%-88%) and specificity (range, 90%-96%). One study (n = 9,989) found that FIT plus stool DNA test had better sensitivity in detecting CRC than FIT alone (92%) but lower specificity (84%). Serious adverse events from colonoscopy in asymptomatic persons included perforations (4/10,000 procedures, 95% CI, 2.5 in 10,000) and major bleeds (8/10,000 procedures, 95% CI, 5.14 in 10,000). Computed tomographic colonography may have harms resulting from low-dose ionizing radiation exposure or identification of extracolonic findings.

CONCLUSIONS AND RELEVANCE  Colonoscopy, flexible sigmoidoscopy, CTC, and stool tests have differing levels of evidence to support their use, ability to detect cancer and precursor lesions, and risk of serious adverse events in average-risk adults. Although CRC screening has a large body of supporting evidence, additional research is still needed.
A
though colorectal cancer (CRC) incidence has been declining over the past 20 years in the United States, it still causes significant morbidity and mortality. Despite increases in screening rates over the past 30 years, in 2012 an estimated 28% of eligible US adults had never been screened for CRC. A variety of tests are available for screening, including stool-based tests (eg, guaiac-based fecal occult blood testing [gFOBT], immunochemical-based fecal occult blood testing [FIT], stool DNA [sDNA] testing), endoscopy (eg, flexible sigmoidoscopy [SIG], colonoscopy), and imaging (eg, double-contrast barium enema, computed tomographic colonography [CTC]).

Currently, most US guideline organizations, including the US Preventive Services Task Force (USPSTF), recommend that options for CRC screening include colonoscopy every 10 years, an annual high-sensitivity gFOBT or FIT, and SIG every 5 years with high-sensitivity gFOBT or FIT. In 2008, the USPSTF recommended CRC screening using fecal occult blood testing, sigmoidoscopy, or colonoscopy beginning at age 50 years and continuing until age 75 years (A recommendation); selectively offering screening in adults aged 76 to 85 years (C recommendation); and against screening for colorectal cancer in adults older than 85 years (D recommendation). At that time, the USPSTF had insufficient evidence to assess the benefits and harms of CTC and sDNA testing as screening modalities. A systematic review was conducted to update relevant evidence since 2008 and to help inform a separate modeling exercise, which together were used by the USPSTF in its process of updating the 2008 CRC screening recommendations.

Methods
This review addressed 3 key questions (KQs) as shown in Figure 1. Additional methodological details regarding search strategies, detailed study inclusion criteria, quality assessment, excluded studies, and description of data analyses are publicly available in the full evidence report at http://www.uspreventiveservicestaskforce.org/Page/Document//colorectal-cancer-screening.
Data Sources and Searches
MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials were searched to locate primary studies informing the key questions (eMethods in the Supplement) that were published from the end of the previous review\(^6\) (January 1, 2008) through December 31, 2014. The database searches were supplemented with expert suggestions and by reviewing reference lists from all other relevant systematic reviews, including the 2008 USPSTF evidence report. The search also included selected gray literature sources, including ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform, for ongoing trials. Since December 2014, we continued to conduct ongoing surveillance through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and therefore the related USPSTF recommendation. The last surveillance was conducted on February 23, 2016. Although several potentially relevant new studies were identified,\(^6,9\) none of these studies would substantively change the review’s interpretation of findings or conclusions.

Study Selection
Two investigators independently reviewed 8492 titles and abstracts and 696 articles against the specified inclusion criteria (Figure 2). Discrepancies were resolved through consensus and consultation with a third investigator. Inclusion criteria were fair- and good-quality English-language studies of asymptomatic screening populations of individuals who were 40 years or older, either at average risk for CRC or not selected for inclusion based on CRC risk factors. Studies were included that evaluated the following screening tests: colonoscopy, SIG, CTC, gFOBT, FIT, FIT plus sDNA, or a blood test for methylated SEPT9 DNA (mSEPT9).

For KQ1, randomized clinical trials (RCTs) or otherwise controlled trials of CRC screening vs no screening, as well as trials comparing screening tests, that included outcomes of cancer incidence, CRC-specific mortality, or all-cause mortality were reviewed for inclusion. For tests without trial-level evidence (ie, colonoscopy, FIT), well-conducted prospective cohort or population-based nested case-control studies were examined.

For KQ2, diagnostic accuracy studies that used colonoscopy as a reference standard were included. Studies whose design was sub-
evidence of studies, the analyses were largely descriptive. Random-effects meta-analyses were conducted using the profile likelihood method\(^2\) to estimate the effect of SIG based on the pooled incidence rate ratio (events/person-year) for CRC incidence and mortality across the 4 major SIG trials. Random-effects models were also conducted using the restricted maximum likelihood estimation method to estimate rates of serious adverse events for colonoscopy and SIG. The presence and magnitude of statistical heterogeneity were assessed among pooled studies using the \(I^2\) statistic. All tests were 2-sided with a \(P\) value less than .05 indicating statistical significance. Meta-analyses were performed using R version 3.0.2 (R Project for Statistical Computing).\(^{23,24}\)

### Results

#### Effectiveness of Screening

**Key Question 1.** What is the effectiveness of screening programs based on the prespecified screening tests (alone or in combination) in reducing incidence of and mortality from colorectal cancer?

Twenty-five unique fair- or good-quality studies\(^{25-49}\) (published in 47 articles\(^{29-71}\)) were found that assessed the effectiveness or comparative effectiveness of screening tests on CRC incidence and mortality. These studies included 1 cohort study of screening colonoscopy,\(^{36}\) 4 RCTs of SIG (in 7 articles),\(^{25,39,41,50,60,66,71}\) and 6 trials (in 11 articles) of Hemoccult II gFOBT (References 29, 33-35, 40, 44, 59, 62-64, 67). In addition, 15 comparative effectiveness studies (in 22 articles) were found that were primarily designed to assess the relative uptake and CRC yield between different screening modalities (References 26-28, 30-32, 37, 38, 42, 43, 45-49, 54-58, 65, 69). Due to limitations in study designs, the observational colonoscopy study and comparative effectiveness studies are not discussed further in this article. Summarized below are the results for CRC-specific mortality, as results for CRC incidence were consistent with CRC mortality findings.

#### Flexible Sigmodoscopy

Four large, fair-quality, pragmatic RCTs (\(n = 458,002\)) evaluated the effectiveness of 1 or 2 rounds of SIG in average-risk adults aged 50 to 74 years (Table 1).\(^{25,39,41,50,60,66,71}\) Adherence to SIG in these trials ranged from 58% to 84%, and rates of diagnostic colonoscopy ranged from 5% to 33% due to differences in referral criteria. Based on pooled intention-to-treat analyses, SIG was associated with lower CRC-specific mortality compared with no screening at 11 to 12 years of follow-up (incidence rate ratio, 0.73; 95% CI, 0.66-0.82; \(I^2 = 0\%\)) (Figure 3); however, the association with mortality benefit was limited to distal CRC (incidence rate ratio, 0.63; 95% CI, 0.49-0.84; \(I^2 = 44\%\) (eFigure 1 in the Supplement). In 1 trial, conducted in Norway, half of the participants randomized to SIG also received a single FIT test; the SIG-plus-FIT group had lower CRC mortality than the SIG-only group did (hazard ratio, 0.62; 95% CI, 0.42-0.90).\(^{60}\)

gFOBT

Five larger, older, pragmatic RCTs (\(n = 419,966\)) with 11 to 30 years of follow-up evaluated the effectiveness of annual or biennial screening programs with Hemoccult II (Table 1) (References 29, 33, 34, 40, 44, 59, 63, 64, 67). Based on intention-to-treat analyses, compared with no screening, biennial screening with Hemoccult II resulted in a reduction in CRC-specific mortality after 2 to 9 rounds of...
screening (relative risk [RR], 0.91; 95% CI, 0.84-0.98, at 19.5 years to RR, 0.78; 95% CI, 0.65-0.93, at 30 years). Based on 1 trial, conducted in the United States, annual screening with Hemoccult II after 11 rounds of screening resulted in greater reductions (RR, 0.68; 95% CI, 0.56-0.82) than biennial screening at 30 years did (RR, 0.78; 95% CI, 0.65-0.93).

### Diagnostic Accuracy of Screening

**Key Question 2.** What are the test performance characteristics of the prespecified screening tests (alone or in combination) for detecting colorectal cancer, advanced adenomas, or adenomatous polyps based on size?

Thirty-three unique diagnostic accuracy studies (published in 44 articles) were found that evaluated the 1-time performance of a screening test compared with an adequate reference standard, including 9 studies of screening CTC (in 10 articles), 1 study of follow-up CRC mortality for the screened group vs the control (hazard ratio, 0.73; 95% CI, 0.56-0.94; P = .02). To present consistent results across studies, we show unadjusted results here.

<ref>

**Table 1. Effectiveness of Screening to Reduce Colorectal Cancer Mortality: Flexible Sigmoidoscopy and Hemoccult II RCTs (Key Question 1)**

<table>
<thead>
<tr>
<th>Screening Tool and Reference</th>
<th>Quality*</th>
<th>Country</th>
<th>Patient Age Range, y</th>
<th>No. of Participants</th>
<th>No. of Screening Rounds</th>
<th>Screening Interval, y</th>
<th>Follow-up Period, y</th>
<th>Positive Screening Results, %†</th>
<th>CRC, %‡</th>
<th>No. of CRC Deaths/100 000 Person-Years</th>
<th>RR (95% CI)</th>
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<tbody>
<tr>
<td>Hemoccult II§</td>
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<tr>
<td>Minnesota Colon Cancer Control Study (biennial), 2013</td>
<td>Good</td>
<td>United States</td>
<td>50-80</td>
<td>Intervention (annual): 15 570 Control: 15 394</td>
<td>11</td>
<td>1</td>
<td>30</td>
<td>NR§</td>
<td>2.9§</td>
<td>Intervention: 50 Control: 63</td>
<td>0.78 (0.65-0.93)</td>
</tr>
<tr>
<td>Göteborg, 2008</td>
<td>Fair</td>
<td>Sweden</td>
<td>60-64</td>
<td>Intervention: 34 144 Control: 34 164</td>
<td>2-3</td>
<td>1-9</td>
<td>19</td>
<td>3.8†</td>
<td>2.2</td>
<td>Intervention: 53 Control: 64</td>
<td>0.84 (0.71-0.99)</td>
</tr>
<tr>
<td>Burgundy, 2004</td>
<td>Fair</td>
<td>France</td>
<td>45-74</td>
<td>Intervention: 45 642 Control: 45 557</td>
<td>6</td>
<td>2</td>
<td>11</td>
<td>2.1</td>
<td>1.5</td>
<td>Intervention: 53 Control: 64</td>
<td>0.84 (0.71-0.99)</td>
</tr>
<tr>
<td>Funen, 2004</td>
<td>Good</td>
<td>Denmark</td>
<td>45-75</td>
<td>Intervention: 30 967 Control: 30 966</td>
<td>9</td>
<td>2</td>
<td>17</td>
<td>1.0</td>
<td>2.8</td>
<td>Intervention: 84 Control: 100</td>
<td>0.84 (0.73-0.96)</td>
</tr>
</tbody>
</table>

Abbreviations: CRC, colorectal cancer; NA, not applicable; NR, not reported; RCT, randomized clinical trial; RR, relative risk.

* The comparator for each of these RCTs was a control group that was not offered any CRC screening.

§ Assessed using criteria from the US Preventive Services Task Force. 26

† Median follow-up time for flexible sigmoidoscopy, longest follow-up time for Hemoccult II.

§ For flexible sigmoidoscopy, this refers to the percentage of patients who were referred to colonoscopy out of those who received their flexible sigmoidoscopy. For Hemoccult II, it refers to the percentage of patients who tested positive out of those who took the test in round 1 only.

The percentage of CRC cases that occurred during the follow-up period among those included in the study at baseline.

* Calculated RR (not study reported).

§ NORCCAP reported a statistically significant decrease in CRC mortality for the screened group vs the control (hazard ratio, 0.73; 95% CI, 0.56-0.94; P = .02). To present consistent results across studies, we show unadjusted results here.

One trial in Finland has not reported CRC mortality. 26, 62

§ Study included rehydrated tests: in Göteborg, 91.7% of all tests were rehydrated; in the Minnesota Colon Cancer Control Study, 82.5% of all tests were rehydrated.

Refers to all 3 groups of the trial (annual, biennial, and control).
circulating mSEPT9. The study of mSEPT9 (not approved by the US Food and Drug Administration [FDA] for screening) and studies evaluating Hemoccult Sensa and FITs that only applied the colonoscopy reference standard to positive stool tests are not discussed further in this article.

Direct Visualization Tests
Nine fair- or good-quality studies (n = 6497) evaluated the diagnostic accuracy of multidetector CTC in average-risk screening populations (Table 2) (References 81, 82, 85-87, 89, 93, 99, 101, 114). The 2 largest and best-quality studies were multicenter trials...
conducted in the United States evaluating CTC with bowel preparation and fecal tagging. Overall, the studies were not powered to estimate test performance to detect CRC. Based on 7 studies of CTC with bowel preparation (n = 5328), the per-person sensitivity to detect adenomas 10 mm and larger ranged from 67% (95% CI, 45%-84%) to 94% (95% CI, 84%-98%), and specificity ranged from 98% (95% CI, 96%-99%) to 96% (95% CI, 95%-97%). The per-person sensitivity to detect adenomas 6 mm and larger ranged from 73% (95% CI, 58%-84%) to 98% (95% CI, 91%-100%), and specificity ranged from 89% (95% CI, 84%-93%) to 91% (95% CI, 88%-93%). Two studies (N = 1169) evaluated CTC without bowel preparation. Although the data were limited, the sensitivity of CTC without bowel preparation to detect adenomas 6 mm and larger appeared to be lower than the sensitivity of CTC protocols including bowel preparation.

Four (n = 4821) of the 9 CTC studies allowed for the estimation of sensitivity of colonoscopy generalizable to community practice. Compared with CTC or colonoscopy plus CTC (eg, segmental unblinding), the sensitivity for colonoscopy to detect adenomas 10 mm and larger ranged from 89% (95% CI, 78%-96%) to 98% (95% CI, 74%-100%) and for adenomas 6 mm and larger ranged from 75% (95% CI, 63%-84%) to 93% (95% CI, 88%-96%) (see full report). Therefore, CTC with bowel preparation had sensitivity to detect adenomas 6 mm and larger comparable with colonoscopy, albeit with wider variability in estimated performance. It is unclear whether the observed variation in CTC performance was due to differences in study design, populations, bowel preparation, CTC technologies, or differences in reader experience or reading protocols.

### Harms of Screening

#### Key Question 3a. What are the adverse effects of the different screening tests (either as single application or in a screening program)?

#### Key Question 3b. Do adverse effects vary by important subpopulations (eg, age)?

Ninety-eight fair- or good-quality studies (References 27, 29, 37-39, 45, 48, 64, 66, 77, 78, 81, 82, 85-87, 89, 92, 93, 97, 99, 101, 116-191) in 113 articles (References 27, 29, 34, 37-39, 44, 45, 48, 50, 53, 64, 66, 70, 77, 78, 81, 82, 85-87, 89, 92, 93, 97, 99, 101, 114, 116-200) were included that evaluated the harms of CRC screening. These studies included 14 studies of screening programs using stool testing or SIG, 55 studies of colonoscopy in asymptomatic adults, (References 37, 45, 77, 78, 85, 97, 101, 116, 117, 119-124, 126, 128-131, 133, 136, 140, 142, 144, 147, 148, 150, 151, 153-156, 158, 159, 161-163, 170-178, 180-183, 187-190) 18 studies of screening SIG, (References 27, 38, 39, 43, 48, 50, 66, 143, 146, 151, 157, 162, 176, 183, 185, 186, 191-194, 200) and 15 studies of screening CTC in asymptomatic adults (References 45, 81, 82, 85, 87, 89, 101, 118, 135, 145, 150, 162, 169, 179). Twelve CTC studies provided estimates of radiation exposure per examination. (References 81, 82, 85-87, 89, 93, 99, 101, 118, 135, 162) and another 21 CTC studies reported information on extracolononic findings (References 45, 85, 99, 101, 114, 125, 127, 134, 137-139, 141, 150, 152, 160, 164, 166-168, 184, 195, 198).

### Endoscopy Harms

Approximately half of colonoscopy harms studies (29/55 studies) were in explicitly screening or asymptomatic populations (eTable 2 in the Supplement). By pooling 26 studies (n = 3 414 108) in screening populations or generally asymptomatic persons, (References 37, 45, 77, 78, 85, 97, 101, 120, 121, 124, 126, 130, 131, 136, 150, 156, 163, 170, 174, 176, 180-182, 188-190) it was estimated that the risk of perforations from colonoscopy was 4 in 10 000 procedures (95% CI, 2.5 in 10 000; P = 86%) (Figure 4). On the basis of 22 of those studies (n = 3 347 101), (References 37, 45, 77, 85, 97, 101, 120, 121, 124, 126, 130, 131, 156, 163, 170, 174, 180-182, 188-190) it was estimated that the risk of major bleeding from colonoscopy was 8 in 10 000 procedures (95% CI, 5.14 in 10 000; P = 97%) (Figure 5). Only eight studies (n = 204 614) explicitly reported if perforation or major bleeding was related to polypectomy or...
<table>
<thead>
<tr>
<th>Study</th>
<th>Quality</th>
<th>Mean Patient Age, y</th>
<th>Cohort Size</th>
<th>Test Family Name</th>
<th>Cutoff, μg Hb/g Feces</th>
<th>No. of Stool Samples per Person</th>
<th>CRC %</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>Advanced Adenomas Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
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<td><strong>Qualitative FIT Tests</strong></td>
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<tr>
<td>Levy et al,91 2014b</td>
<td>Fair</td>
<td>56.9</td>
<td>308</td>
<td>Clearview (cassette)</td>
<td>6</td>
<td>NR</td>
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<td>Clearview (test strip)</td>
<td>44</td>
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<td>QuickVue</td>
<td>50</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Chiu et al,78 2013</td>
<td>Good</td>
<td>18 296</td>
<td>4539</td>
<td>OC-Light</td>
<td>10</td>
<td>1</td>
<td>0.15</td>
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<td>93 (92-93)</td>
<td>28 (25-32)</td>
<td>94 (93-94)</td>
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<td>Hemosure</td>
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<td>54 (32-74)</td>
<td>89 (88-90)</td>
<td>37 (30-44)</td>
<td>91 (90-91)</td>
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<td>Brenner et al,107 2010</td>
<td>Good</td>
<td>1319</td>
<td>Bionexia Hb</td>
<td>NR</td>
<td>NR</td>
<td>0.8</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>52 (44-61)</td>
<td>80 (77-82)</td>
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<td>72 (63-79)</td>
<td>56 (54-59)</td>
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<td>30</td>
<td>NR</td>
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<td>NR</td>
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<td>25 (18-33)</td>
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<td>49 (41-58)</td>
<td>81 (79-84)</td>
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<td>50</td>
<td>NR</td>
<td>NR</td>
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<td>NR</td>
<td>56 (48-64)</td>
<td>68 (65-70)</td>
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<td>Cheng et al,77 2002</td>
<td>Fair</td>
<td>46.8</td>
<td>7411</td>
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<td>88 (66-97)</td>
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<td>-1000</td>
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<td>56 (33-76)</td>
<td>97 (96-97)</td>
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<td>Fair</td>
<td>NR</td>
<td>4611</td>
<td>Monohaem</td>
<td>-1000</td>
<td>2</td>
<td>0.39</td>
<td>83 (62-95)</td>
<td>95 (95-96)</td>
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<td>-1000</td>
<td>3</td>
<td>89 (69-98)</td>
<td>93 (92-94)</td>
<td>NR</td>
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<td><strong>Quantitative FIT Tests</strong></td>
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<tr>
<td>Hernandez et al,103 2014</td>
<td>Good</td>
<td>57.6</td>
<td>779</td>
<td>OC FIT-CHEK</td>
<td>10</td>
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<td>0.6</td>
<td>100 (62-100)</td>
<td>92 (90-94)</td>
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<td></td>
<td>20</td>
<td>1</td>
<td>100 (62-100)</td>
<td>94 (92-95)</td>
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<td></td>
<td>20</td>
<td>2</td>
<td>100 (62-100)</td>
<td>90 (88-92)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Imperiale et al,85 2014</td>
<td>Fair</td>
<td>64.2</td>
<td>9989</td>
<td>OC FIT-CHEK</td>
<td>20</td>
<td>1</td>
<td>0.65</td>
<td>74 (62-83)</td>
<td>93 (93-94)</td>
<td>24 (21-27)</td>
<td>95 (94-95)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cologuard (FIT plus stool DNA test)</td>
<td>NA</td>
<td>92 (84-97)</td>
<td>84 (84-85)</td>
<td>42 (39-46)</td>
<td>87 (86-87)</td>
</tr>
<tr>
<td>Lee et al,104 2014</td>
<td>Good</td>
<td>58</td>
<td>NR</td>
<td>Hemo Techt NS-Pius C system</td>
<td>6.3</td>
<td>NR</td>
<td>NR</td>
<td>86 (57-98)</td>
<td>94 (93-95)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Brenner and Tao,84 2013</td>
<td>Good</td>
<td>62.7</td>
<td>2220</td>
<td>OC FIT-CHEK</td>
<td>20</td>
<td>1</td>
<td>0.67</td>
<td>73 (48-90)</td>
<td>96 (95-96)</td>
<td>22 (17-28)</td>
<td>97 (97-98)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2220</td>
<td>2</td>
<td>60 (35-81)</td>
<td>95 (94-96)</td>
<td>21 (16-27)</td>
<td>97 (96-98)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RIDASCREEN Hb</td>
<td>2</td>
<td>1</td>
<td>53 (29-76)</td>
<td>95 (94-96)</td>
<td>18 (13-24)</td>
<td>97 (96-98)</td>
<td></td>
</tr>
<tr>
<td>de Wijkerslooth et al,80 2012</td>
<td>Good</td>
<td>60</td>
<td>1256</td>
<td>OC FIT-CHEK</td>
<td>10</td>
<td>1</td>
<td>0.64</td>
<td>88 (55-99)</td>
<td>91 (89-92)</td>
<td>34 (26-43)</td>
<td>93 (92-95)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td>1</td>
<td>75 (41-94)</td>
<td>95 (93-96)</td>
<td>28 (20-37)</td>
<td>97 (96-98)</td>
</tr>
<tr>
<td>Park et al,88 2010</td>
<td>Fair</td>
<td>59.3</td>
<td>770</td>
<td>OC FIT-CHEK</td>
<td>10</td>
<td>3</td>
<td>1.7</td>
<td>92 (69-99)</td>
<td>87 (85-89)</td>
<td>44 (32-57)</td>
<td>89.8 (87.4-91.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>757</td>
<td>20</td>
<td>3</td>
<td>92.3 (69.3-99.2)</td>
<td>90.1 (87.8-92.1)</td>
<td>33.9 (22.8-46.5)</td>
</tr>
<tr>
<td>Graser et al,82 2009</td>
<td>Good</td>
<td>60.5</td>
<td>285</td>
<td>FOB Gold</td>
<td>NR</td>
<td>2</td>
<td>0.33</td>
<td>100 (14.7-100)</td>
<td>NR</td>
<td>29.2 (14.1-48.9)</td>
<td>85.8 (81.1-89.6)</td>
</tr>
<tr>
<td>Morikawa et al,84 2005</td>
<td>Fair</td>
<td>48</td>
<td>21 805</td>
<td>Magstream/ HemeSelect</td>
<td>100-200</td>
<td>1</td>
<td>0.4</td>
<td>65.8 (54.9-75.6)</td>
<td>94.6 (94.1-94.9)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Sohn et al,100 2005</td>
<td>Fair</td>
<td>48.9</td>
<td>3794</td>
<td>OC Hemodia</td>
<td>20</td>
<td>1</td>
<td>0.3</td>
<td>25.0</td>
<td>NR</td>
<td>6.0</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: CRC, colorectal cancer; FIT, fecal immunochemical test; Hb, hemoglobin; NA, not applicable; NR, not reported. *Quality assessed using criteria from Quality Assessment of Diagnostic Accuracy Studies (QUADAS)20 and QUADAS 2 Instrument. †Results reported for advanced neoplasia (composite of CRC and advanced adenoma) only. ‡Median.
biopsy (References 45, 85, 120, 136, 158, 173, 178). Based on this limited subset of studies reporting adequate information, 36% (15/42) of perforations and 96% (49/51) of major bleeding events were from polypectomy.

All 18 SIG harms studies were conducted in general-risk screening populations (eTable 3 in the Supplement). Based on the results of 16 studies (n = 329698), (References 38, 39, 43, 48, 50, 66, 143, 146, 151, 157, 183, 185, 186, 191, 192) perforations from SIG in average-risk screening populations were relatively uncommon: the pooled point estimate was 1 in 10000 procedures (95% CI, 0.4-1.4 in 10000; 2 = 18.4%). In 10 studies (n = 137987), (References 27, 38, 48, 50, 66, 143, 146, 157, 185, 186) major bleeding episodes from SIG were also relatively uncommon, with a pooled point estimate of 2 in 10000 procedures (95% CI, 0.7-4 in 10000; 2 = 52.5%) (Figure 6 and Figure 7). Flexible sigmoidoscopy, however, may require follow-up diagnostic or therapeutic colonoscopy. From 5 SIG screening trials, the pooled estimate was 14 perforations per 10000 procedures (95% CI, 9-26 in 10000) and 34 major bleeds per 10000 procedures (95% CI, 5-63 in 10000) for follow-up colonoscopy for positive screening SIG from 4 trials.

Other serious harms from endoscopy were not routinely reported or consistently defined. Only 2 studies compared harms other than perforation and bleeding in persons who had a colonoscopy vs those who had not. Both of these studies found no statistically significant higher risks of serious harms (including myocardial infarction, cerebrovascular accident, other cardiovascular events, and mortality) attributable to colonoscopy. Because of reporting bias around serious harms other than perforation and bleeding, as well as the lack of evidence for other serious harms attributable to colonoscopy in the few studies with control groups, these data were not quantitatively pooled.

Nineteen studies examined differential harms of colonoscopy by age group (References 116, 119, 122, 123, 128, 129, 131, 136, 140, 154, 156, 159, 161, 170, 172, 174, 187, 189, 190). These studies generally found increasing rates of serious adverse events with increasing age, including perforation and bleeding.

CTC Harms

Fifteen fair- or good-quality studies addressed serious adverse effects of screening CTC (eTable 4 in the Supplement) (References 45, 81, 82, 85, 87, 89, 101, 118, 135, 145, 150, 162, 169, 179). Evidence suggested little to no risk of serious adverse events, including perforation, from CTC based on 11 prospective studies (n = 10 272) performed in screening populations (References 45, 81, 82, 85, 87, 89, 101, 118, 135, 145, 150, 162, 169, 179).

Many of the CTC studies in this review did not report actual radiation exposure or provide sufficient information to calculate it. Based on 4 included diagnostic accuracy studies of CTC, 91,82,85,101

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Perforations</th>
<th>No. of Procedures</th>
<th>Event Rate per 10000 Procedures (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Castro et al,126 2013</td>
<td>3</td>
<td>3355</td>
<td>8.94 (2.87-27.69)</td>
</tr>
<tr>
<td>Chiu et al,78 2013</td>
<td>0</td>
<td>18296</td>
<td>0.27 (0.02-4.37)</td>
</tr>
<tr>
<td>Ng et al,97 2013</td>
<td>0</td>
<td>4539</td>
<td>1.10 (0.07-17.58)</td>
</tr>
<tr>
<td>Po et al,170 2012</td>
<td>439</td>
<td>282139</td>
<td>1.56 (1.42-1.71)</td>
</tr>
<tr>
<td>Sussia et al,182 2012</td>
<td>0</td>
<td>839</td>
<td>5.95 (0.37-94.40)</td>
</tr>
<tr>
<td>Quintero et al,37 2012</td>
<td>1</td>
<td>4953</td>
<td>2.02 (0.28-14.32)</td>
</tr>
<tr>
<td>Stoop et al,45 2012</td>
<td>0</td>
<td>1276</td>
<td>3.92 (0.24-62.27)</td>
</tr>
<tr>
<td>Zalis et al,101 2012</td>
<td>0</td>
<td>618</td>
<td>8.08 (0.51-127.74)</td>
</tr>
<tr>
<td>Ferlltisch et al,156 2011</td>
<td>3</td>
<td>44350</td>
<td>0.68 (2.22-2.10)</td>
</tr>
<tr>
<td>Sennore et al,156 2011</td>
<td>0</td>
<td>1198</td>
<td>4.17 (0.26-66.29)</td>
</tr>
<tr>
<td>Ko et al,150 2010</td>
<td>4</td>
<td>21375</td>
<td>1.87 (0.70-4.98)</td>
</tr>
<tr>
<td>Bair et al,136 2009</td>
<td>1</td>
<td>3741</td>
<td>2.67 (0.38-18.95)</td>
</tr>
<tr>
<td>Bokemeyer et al,134 2009</td>
<td>55</td>
<td>269144</td>
<td>2.04 (1.57-2.66)</td>
</tr>
<tr>
<td>Johnson et al,45 2008</td>
<td>0</td>
<td>2551</td>
<td>1.97 (0.12-31.49)</td>
</tr>
<tr>
<td>Kim et al,150 2007</td>
<td>7</td>
<td>3163</td>
<td>22.13 (10.55-46.35)</td>
</tr>
<tr>
<td>Cotterhill et al,136 2005</td>
<td>0</td>
<td>324</td>
<td>15.38 (0.96-240.92)</td>
</tr>
<tr>
<td>Nelson et al,183 2002</td>
<td>0</td>
<td>3196</td>
<td>5.56 (10.24-24.95)</td>
</tr>
<tr>
<td>Cheng et al,71 2002</td>
<td>2</td>
<td>7411</td>
<td>2.70 (0.67-10.78)</td>
</tr>
<tr>
<td><strong>Retrospective studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zafar et al,185 2014</td>
<td>46</td>
<td>54039</td>
<td>8.51 (6.38-11.16)</td>
</tr>
<tr>
<td>Stock et al,180 2013</td>
<td>7</td>
<td>8658</td>
<td>8.09 (3.85-16.95)</td>
</tr>
<tr>
<td>Rutter et al,134 2012</td>
<td>21</td>
<td>43456</td>
<td>4.83 (3.15-7.41)</td>
</tr>
<tr>
<td>Xirasagar et al,188 2010</td>
<td>2</td>
<td>10958</td>
<td>1.83 (0.46-7.29)</td>
</tr>
<tr>
<td>Berhane and Denning,121 2009</td>
<td>2</td>
<td>11808</td>
<td>1.69 (0.42-6.77)</td>
</tr>
<tr>
<td>Crispin et al,131 2009</td>
<td>22</td>
<td>55993</td>
<td>3.93 (2.59-5.97)</td>
</tr>
<tr>
<td>Strul et al,181 2006</td>
<td>0</td>
<td>1177</td>
<td>4.24 (0.27-67.47)</td>
</tr>
<tr>
<td>Levin et al,156 2006</td>
<td>15</td>
<td>16318</td>
<td>9.19 (5.54-15.24)</td>
</tr>
</tbody>
</table>

Restricted maximum likelihood model

I² = 88.25%

Note: 1 trial was excluded from the meta-analysis because of a very small number of participants (n = 63).199 There were no episodes of serious bleeding or perforation in the study.
the estimated radiation dose for 1 full-screening CTC examination (dual positioning supine and prone) was about 4.5 to 7 mSv. In 3 additional recent CTC screening studies,118,135,162 (2004-2008), the estimated radiation dose decreased to a range of 1 to less than 5 mSv.

CTC Extracolonic Findings

Incidental extracolonic findings detected on CTC can be beneficial or harmful depending on the finding. Twenty-one studies (n = 38293) (References 45,85,99,101,125,127,134,137-139,141,150,152,160,164,166-168,184,195,198) in 22 articles (References 45,85,99,101,114,125,127,134,137-139,141,150,152,160,164,166-168,184,195,198) (7 studies with overlapping populations reported different types extracolonic findings) reported on extracolonic findings in asymptomatic persons (Table 5 in the Supplement). In general, these studies varied greatly in their ability to accurately assess follow-up and the duration of follow-up.

Overall, extracolonic findings were common, occurring in 27% to 69% of examinations. Similarly, the studies suggested a very wide range of findings needing additional workup: 5% to 37% had E3 or E4 findings, and 1.7% to 12% had E4 findings. Among the studies that also reported medical follow-up of extracolonic findings, 1.4% to 11% went on to diagnostic evaluation, which is similar to the prevalence of E4 category findings. Among studies that adequately reported subsequent treatment, only up to 3% required definitive medical or surgical treatment. Extracolonic cancers were not common, occurring in 0.5% of persons undergoing CTC examinations. In the largest series of examinations (n = 10,286), which had about 4 years of follow-up, 0.35% of examinations revealed an extracolonic malignancy, 32 of which received definitive treatment.167 Abdominal aortic aneurysms were identified in 1.4% of persons or fewer. In our active surveillance of the literature, we identified 1 additional study evaluating extracolonic findings in screening CTC (n = 7952).7 This study’s population overlapped with several already included studies and reported that 2.5% of examinations had E4 category findings, consistent with findings from included studies.150,164,166-168,195,198

Discussion

Colorectal cancer screening continues to be a necessary and active field of research. Since the 2008 USPSTF recommendation was published, 95 new studies were identified, including more evidence on (1) the effectiveness of SIG for reducing CRC mortality, (2) the test performance of screening CTC and decreasing radiation exposure from CTC, and (3) the test performance of a number of FDA-approved FITs (including 1 FIT plus sDNA test). Colonoscopy, SIG, CTC, and stool testing (gFOBT, FIT, and FIT plus sDNA test) each have differing levels of evidence to support their use, ability to detect cancer and precursor lesions, and risk of serious adverse events in screening average-risk adults for CRC (Table 4).

To date, no CRC screening modality has been shown to reduce all-cause mortality. Robust data from well-conducted population-based screening RCTs have demonstrated that both Hemoccult II and SIG can reduce CRC mortality, although neither of these tests is widely used for screening in the United States. Therefore, the
empirical data on the performance of CRC screening programs using modalities used in clinical practice today are limited. Expensive, large population-based RCTs of newer stool tests may not always be necessary, as evidence-based reasoning supports that screening with stool tests with sensitivity and specificity that are both as good as, or better than, Hemoccult II would result in CRC mortality reductions similar to or better than reductions shown in existing trials.\textsuperscript{201} Based on this review, stool tests that meet those requirements are available, including specific single-stool sample FITs. However, FITs are not homogenous: they use different assays and have different diagnostic performance levels. The FDA-approved OC-Light and OC FIT-CHEK tests have the most evidence to support their use. Stool tests that maximize sensitivity (eg, FIT plus sDNA test, multiple sample FITs, or quantitative FIT using lower cutoffs) have lower specificity and therefore need new trials or modeling exercises to understand the tradeoff of higher false-positive findings. In addition, stool tests vary in cost; for example, the Centers for Medicare & Medicaid Services reimbursement is $23 per FIT vs $493 per FIT plus sDNA test.\textsuperscript{202}

Even though its superiority in a program of screening has not been empirically established, colonoscopy remains the criterion standard for assessing the test performance of other CRC screening tests. Moreover, colonoscopy is significantly more invasive than other available tests and thus carries a greater possibility of procedural complications, as well as harms of overdagnosis and overtreatment of smaller lesions (ie, <10 mm). Three large RCTs of screening colonoscopy in average-risk adults are underway and will provide information about the long-term CRC incidence and mortality outcomes. The
Table 4. Summary of Evidence by Key Question and Screening Test

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Study Design</th>
<th>No. of Studies</th>
<th>No. of Participants</th>
<th>Summary of Findings (Includes Consistency, Precision)</th>
<th>Applicability(^a)</th>
<th>Limitations (Includes Reporting Bias)</th>
<th>Overall Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key Question 1: Effectiveness of Screening(^b)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIG</td>
<td>RCT</td>
<td>4</td>
<td>458 002</td>
<td>SIG consistently decreased CRC-specific mortality compared with no screening at 11-12 y of follow-up (IRR, 0.73; 95% CI, 0.66-0.82). Mortality benefit was limited to distal CRC.</td>
<td>Fair to poor. No longer widely used in the United States.</td>
<td>Only 1 trial evaluated more than a single round of screening. Variation in referral criteria led to differing rates of follow-up colonoscopy.</td>
<td>Fair to good</td>
</tr>
<tr>
<td>gFOBT, Hemoccult II</td>
<td>RCT</td>
<td>5</td>
<td>442 088</td>
<td>Biennial screening with Hemoccult II compared with no screening consistently resulted in reduction of CRC-specific mortality (ranging 9%-22% after 2-9 rounds of screening with 11-30 y of follow-up).</td>
<td>Poor. No longer widely used.</td>
<td>Variation in number of screening rounds, use of rehydrated samples, definition of “test positive,” and recommended diagnostic follow-up.</td>
<td>Fair to good</td>
</tr>
<tr>
<td><strong>Key Question 2: Diagnostic Accuracy of Screening(^c)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>Prospective</td>
<td>4</td>
<td>4821</td>
<td>Comparing colonoscopy with CTC or CTC plus colonoscopy; per-person (or per-lesion) sensitivity for adenomas ≥10 mm was 89%-98%, and per-person sensitivity for adenomas ≥6 mm was 75%-93%.</td>
<td>Fair. Colonoscopies were conducted or supervised by “experienced” specialists.</td>
<td>Studies were not designed to assess diagnostic accuracy to detect cancers. Limited studies with large number of endoscopists that were applicable to community practice.</td>
<td>Fair to good</td>
</tr>
<tr>
<td>CTC</td>
<td>Prospective</td>
<td>9</td>
<td>6497</td>
<td>The per-person sensitivity and specificity of CTC using bowel preparation to detect adenomas ≥10 mm ranged 67%-94% and 86%-98%, respectively. The per-person sensitivity and specificity to detect adenomas ≥6 mm ranged 73%-98% and 80%-93%, respectively. In 2 studies, sensitivity without bowel preparation to detect adenomas was lower than that of CTC protocols using bowel preparation.</td>
<td>Fair. Mostly single-center studies, with ≥3 highly trained radiologists. Current practice may use different technologies and protocols.</td>
<td>Studies were not designed to assess diagnostic accuracy to detect cancers. Unclear if the variation of test performance was due to differences in study design, populations, bowel preparation, CTC technology, reader experience, or reading protocols.</td>
<td>Fair to good</td>
</tr>
<tr>
<td>FIT</td>
<td>Prospective</td>
<td>6 Qualitative</td>
<td>36 808</td>
<td>In studies with colonoscopy follow-up for all, FIT sensitivity varied considerably across assays for each outcome. OC-Light had the highest sensitivity and specificity for CRC, from 88% and 91%, respectively, to 79% and 93%, respectively. OC FIT-CHEK had the best sensitivity and specificity for CRC, from 73% and 96%, respectively, to 92% and 87%.</td>
<td>Fair to good. There is a wide range in costs for specific tests (OC-Light, OC FIT-CHEK, ColoGuard). Quantitative FITs included some that are older and now discontinued.</td>
<td>Variation in test performance resulted from the use of 18 different FITs (FIT families), different numbers of stool samples, and to some extent different assay cutoff values. Sparse data on most individual tests limited comparisons.</td>
<td>Fair to good</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 Quantitative</td>
<td>40 134</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 FIT plus sDNA</td>
<td></td>
<td>9989</td>
<td></td>
<td>A FIT plus sDNA assay (ColoGuard) had better sensitivity but lower specificity, 92% (95% CI, 84-97) and 64% (95% CI, 84-85), respectively, compared with OC FIT-CHEK.</td>
<td>Fair to good.</td>
<td>FIT plus sDNA was limited to a single study with 6% inadequate stool samples.</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
Evidence continues to accrue that CTC adequately detects CRC and large potential precursor lesions. Although the risk of immediate harms from screening CTC (eg, bowel perforation from insufflation) is very low, it is unclear what (if any) true harm is posed by cumulative exposure to low-dose radiation or detection of extracolonic findings. Although the radiation dose appears to be decreasing over time due to technological and protocol advancements, it still ranges as high as 7 mSv per examination (dual positioning). Given that the average amount of radiation one is exposed to from background sources in the United States is about 3 mSv per year, ionizing radiation from a single CTC examination is low. However, current expert recommendations are to repeat CTC every 5 years, and even low doses of ionizing radiation could cumulatively convey a small
excess risk of cancer.\textsuperscript{208,209} From empirical evidence to date, it remains unclear whether detection of extracolonic findings represents a net benefit or harm.

This evidence report and systematic review did not address several important issues: screening in high-risk adults (ie, those with known family history of CRC), risk assessment to tailor screening, test acceptability, availability of or access to screening tests, methods to increase screening adherence, potential harms of overdiagnosis or unnecessary polypectomy, overuse or misuse of screening, and surveillance after adenoma detection. This review was commissioned along with a separate set of microsimulation decision models from the Cancer Intervention and Surveillance Modeling Network (CISNET) that addressed other important gaps in evidence, including ages to start and stop screening, screening intervals, and targeted or tailored screening.\textsuperscript{210} The review was limited to evidence conducted in countries with the highest applicability to US practice; in addition, only articles published in English were considered for inclusion.

Unlike other routinely recommended or conducted cancer screening, there are multiple viable options for CRC screening. These options have various levels of evidence to support their use, aims (eg, to detect cancers, potential precursor lesions, or both), test acceptability and adherence, intervals of time to repeat screening, need for follow-up testing (including surveillance incurred), associated serious harms, availability in practice, cost, and advocacy for their use. This complexity is compounded by testing whose quality is more operator-dependent (eg, colonoscopy, CTC), as well as rapid technologic advancements in improving existing tests or developing new tests.

Empirical studies, trials, or well-designed cohort studies with average-risk populations are still needed to evaluate programs of screening using colonoscopy, the best-performing stool tests, and effect of CTC on cancer mortality and cancer incidence. Also needed are studies of diagnostic accuracy to confirm the screening test performance of promising stool tests based on high sensitivity to detect CRC or advanced adenomas with thus far limited reproducibility (ie, only 1 study). Diagnostic accuracy studies, particularly those evaluating new or more complex technologies, should report percentages of inadequate or indeterminate results. It is also important to understand the contribution of technological advancements to existing technology (eg, enhancements to optical colonoscopy or CTC) on test performance in average-risk adults as well as on reducing harms (eg, decreasing radiation exposure, less aggressive bowel preparation). More complete and consistent reporting regarding downstream benefits and harms from initial detection (ie, subsequent workup and definitive treatment) of C-RADS E3 and E4 findings need to be published in observational studies or trials with longer-term follow-up. Data are still needed on the differential uptake of and adherence to screening modalities and on continued adherence to repeated rounds of screening and diagnostic follow-up to screening over longer periods.

Conclusions

Colonoscopy, flexible sigmoidoscopy, CTC, and various stool tests have differing levels of evidence to support their use in CRC screening, ability to detect CRC and precursor lesions, and risk of serious adverse events in average-risk adults. Although CRC screening has a large body of supporting evidence, additional research is still needed to weigh the relative benefits and harms of each test within a program of screening.

ARTICLE INFORMATION

Author Contributions: Dr Lin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Lin, Piper, Perdue, Whitlock. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Lin, Piper, Rutter, Webber. Critical revision of the manuscript for important intellectual content: Lin, Piper, Perdue, Rutter, O’Connor, Smith, Whitlock. Statistical analysis: Lin, Piper, Rutter, O’Connor, Smith. Obtained funding: Lin, Whitlock. Administrative, technical, or material support: Piper, Perdue, Webber. Study supervision: Lin, Whitlock.

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Additional Information: A draft version of this evidence report underwent external peer review from 6 content experts (James Allison, MD, University of California, San Francisco; Samir Gupta, MD, MScS, University of California, San Diego; Theodore R. Levin, MD, Kaiser Permanente; David Lieberman, MD, Oregon Health & Science University; Perry Pickhardt, MD, MPH, University of Wisconsin; David Ransohoff, MD, University of North Carolina at Chapel Hill) and 4 federal partners: Centers for Disease Control and Prevention, National Institutes of Health, US Department of Veterans Affairs, and Indian Health Service. Comments were presented to the USPSTF during its deliberation of the evidence and were considered in preparing the final evidence review.

Editorial Disclaimer: This evidence report is presented as a document in support of the accompanying USPSTF Recommendation Statement. It did not undergo additional peer review after submission to JAMA.

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