

Screening for Colorectal Cancer: A Targeted, Updated Systematic Review for the U.S. Preventive Services Task Force

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Background: In 2002, the U.S. Preventive Services Task Force (USPSTF) recommended colorectal cancer screening for adults 50 years of age or older but concluded that evidence was insufficient to prioritize among screening tests or evaluate newer tests, such as computed tomographic (CT) colonography.

Purpose: To review evidence related to knowledge gaps identified by the 2002 recommendation and to consider community performance of screening endoscopy, including harms.

Data Sources: MEDLINE, Cochrane Library, expert suggestions, and bibliographic reviews.

Study Selection: Eligible studies reported performance of colorectal cancer screening tests or health outcomes in average-risk populations and were at least of fair quality according to design-specific USPSTF criteria, as determined by 2 reviewers.

Data Extraction: Two reviewers verified extracted data.

Data Synthesis: Four fecal immunochemical tests have superior sensitivity (range, 61% to 91%), and some have similar specificity (97% to 98%), to the Hemoccult II fecal occult blood test (Beckman Coulter, Fullerton, California). Tradeoffs between superior sensitivity and reduced specificity occur with high-sensitivity guaiac tests and fecal DNA, with other important

uncertainties for fecal DNA. In settings with sufficient quality control, CT colonography is as sensitive as colonoscopy for large adenomas and colorectal cancer. Uncertainties remain for smaller polyps and frequency of colonoscopy referral. We did not find good estimates of community endoscopy accuracy; serious harms occur in 2.8 per 1000 screening colonoscopies and are 10-fold less common with flexible sigmoidoscopy.

Limitation: The accuracy and harms of screening tests were reviewed after only a single application.

Conclusion: Fecal tests with better sensitivity and similar specificity are reasonable substitutes for traditional fecal occult blood testing, although modeling may be needed to determine all tradeoffs. Computed tomographic colonography seems as likely as colonoscopy to detect lesions 10 mm or greater but may be less sensitive for smaller adenomas. Potential radiation-related harms, the effect of extracolonic findings, and the accuracy of test performance of CT colonography in community settings remain uncertain. Emphasis on quality standards is important for implementing any operator-dependent colorectal cancer screening test.

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Colorectal cancer ranks third in incidence and second in cause of cancer death for both men and women (1). Most cases of colorectal cancer occur in average-risk individuals (those without a family or predisposing medical history), and increasing age, male sex, and black race are associated with increased incidence (2). Black persons have the highest incidence of and mortality rates from colorectal cancer among all racial and ethnic subgroups (3–7) and

nearly double the colorectal cancer–related mortality rate compared with other ethnic minorities (8).

Colorectal cancer screening has been recommended by the U.S. Preventive Services Task Force (USPSTF) and many other organizations for more than 10 years (9). On the basis of evidence from multiple randomized, controlled trials (RCTs), a screening program with repeated annual or biennial guaiac fecal occult blood tests (FOBTs) and endoscopic follow-up of positive test results reduces colorectal cancer mortality; according to a recent update, colorectal cancer mortality was reduced 16% (CI, 10% to 22%) after 12 to 18 years (10). Extrapolating from trial evidence, clinical studies of test accuracy, and other supporting evidence, the USPSTF recognized flexible sigmoidoscopy (with or without FOBTs), colonoscopy, and double-contrast barium enema as other colorectal cancer screening options in 2002 (11, 12). However, because colorectal cancer screening tests have potential harms, limited accessibility, or imperfect acceptability to patients, and no tests could be identified as superior in cost-effectiveness analysis (13), the USPSTF also recommended that choice among recommended methods for colorectal cancer screening to be individualized to patients or practice settings (14).

Despite strong recommendations from the USPSTF and many others, serial national surveys document inade-

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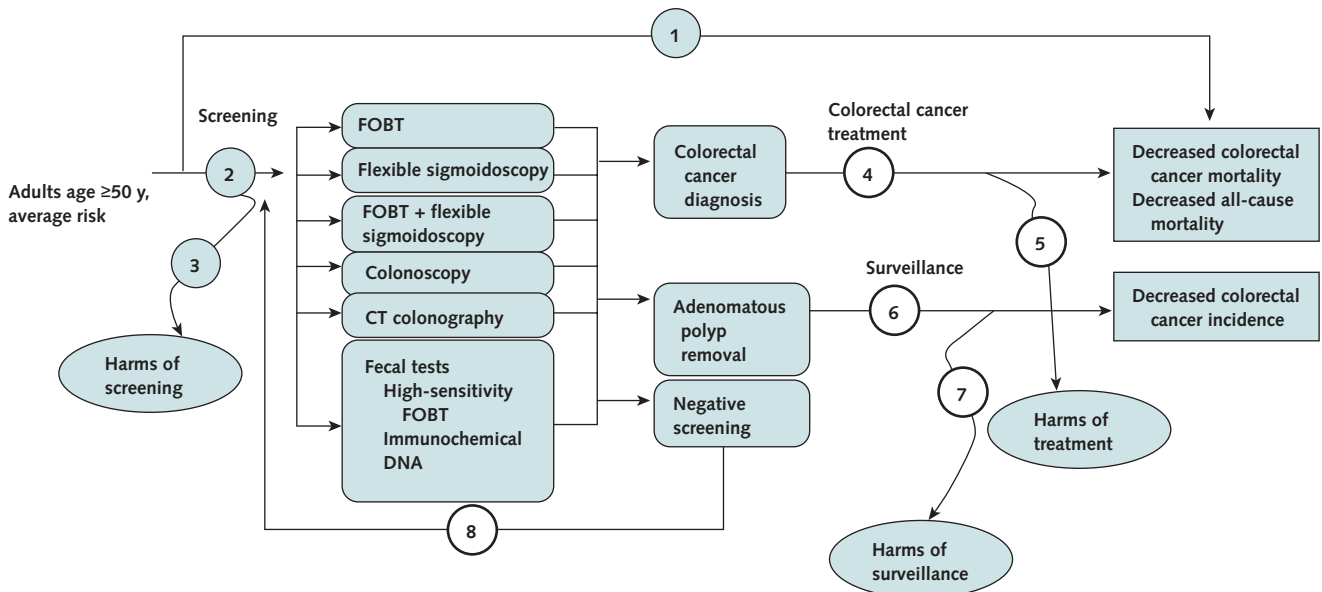
Print

Editorial comment	680
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Appendix
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Appendix Figures
Conversion of graphics into slides
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Audio summary

Figure 1. Analytic framework and key questions (KQs).



KQ1: What is the effectiveness of the following screening methods (alone or in combination) in reducing mortality from colorectal cancer? a. Flexible sigmoidoscopy, b. Colonoscopy, c. Computed tomographic (CT) colonography, d. Fecal screening tests: i. High-sensitivity guaiac fecal occult blood test (FOBTs); ii. Fecal immunochemical test; iii. Fecal DNA test.

KQ2a: What are the sensitivity and specificity of 1) colonoscopy and 2) flexible sigmoidoscopy when used to screen for colorectal cancer in the community practice setting?

KQ2b: What are the test performance characteristics of 1) CT colonography and 2) fecal screening tests (as listed in KQ1d) for colorectal cancer screening, as compared to an acceptable reference standard?

KQ3a: What are age-specific rates of harm from colonoscopy and flexible sigmoidoscopy in the community practice setting?

KQ3b: What are the adverse effects of newer tests, including 1) CT colonography and 2) fecal screening tests (as listed in KQ1d)?

quate, slowly improving rates of colorectal cancer screening in the United States (15–20). In 2006, 60.8% of adults 50 years of age or older reported recent colorectal screening (20). Disparities in colorectal cancer screening exist, with lower rates of colorectal cancer screening in nonwhite and Hispanic populations (16, 21, 22) and in areas with higher poverty rates (23).

To increase the uptake of and benefits from recommended colorectal cancer screening, researchers have sought to improve the accuracy, acceptability, or accessibility of screening by introducing new tests or enhancing existing tests. However, the availability of additional options for colorectal cancer screening—including highly sensitive guaiac FOBT; fecal immunochemical testing; fecal DNA testing; and “virtual colonoscopy” approaches, such as computed tomographic (CT) colonography—has created uncertainty about what methods should be used for colorectal cancer screening in the general population.

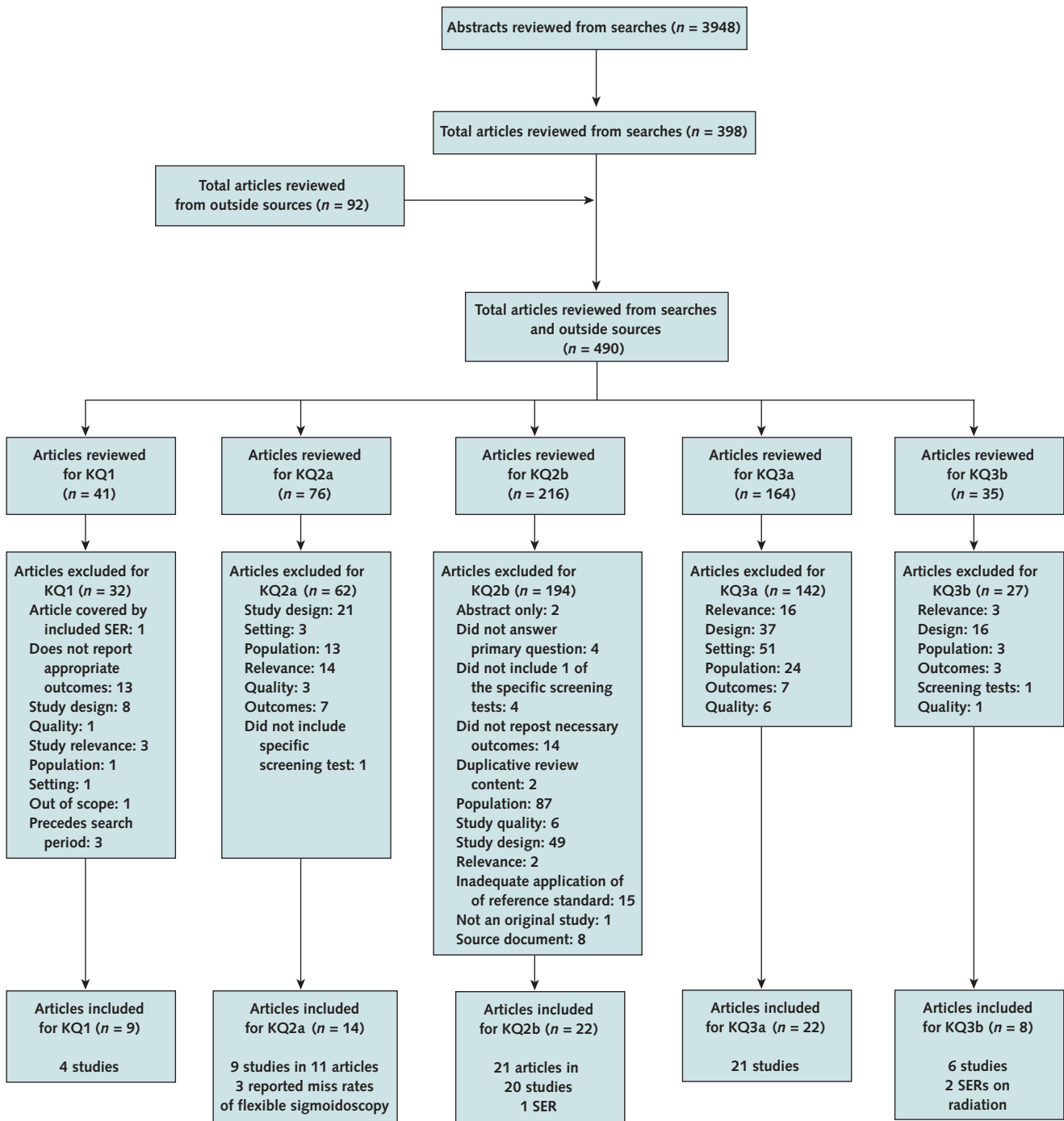
To assist the USPSTF in updating its 2002 recommendation for colorectal cancer screening in average-risk adults age 50 years or older, we conducted a targeted systematic review primarily focused on evidence gaps or new evidence since the previous review. This approach updated what the USPSTF judged was the most important evidence for newer colorectal cancer screening tests and community-

performed endoscopies, and it was supplemented by a companion decision analysis examining screening program performance and life-years gained by using different colorectal cancer screening tests, test intervals, and starting and stopping ages (24).

METHODS

Under guidance from the USPSTF, this targeted review addressed only the first 3 questions of the full evidence chain in the analytic framework (Figure 1). From our larger report (25), we report here the accuracy (one-time test performance characteristics) and potential harms of newer colorectal cancer screening tests (high-sensitivity FOBTs, fecal immunochemical tests, fecal DNA testing, and CT colonography) in screening populations (key questions 2b and 3b) and the accuracy and harms of screening colonoscopy and flexible sigmoidoscopy in the community setting (key questions 2a and 3a). In the full report, we discuss lack of new data on the mortality benefits of colorectal cancer screening beyond FOBT programs (key question 1); race-, sex-, and age-related issues in colorectal cancer screening; considerations of targeted screening recommendations; and suggested future research. Detailed methods are provided in the Appendix and Appendix Tables 1,

Figure 2. Study selection.



KQ = key question; SER = standardized evidence review. For list of key questions, see legend for Figure 1.

2, and 3 (available at www.annals.org) and in the full report (25).

Searches and Selection Process

In brief, we searched PubMed; Database of Abstracts of Reviews of Effects; Cochrane Database of Systematic Reviews; and the Institute of Medicine, National Institute

for Health and Clinical Effectiveness, and Health Technology Assessment databases for recent systematic reviews (1999–2006) to support our review of all key questions (26). We found 11 existing systematic reviews for newer colorectal cancer screening tests (key question 2b). Using methods detailed in the **Appendix**, we selected 3 good-

quality reviews of CT colonography (27, 28) or fecal DNA testing (29) to locate relevant primary studies; we supplemented these with additional MEDLINE and Cochrane Library searches from January 2006 through January 2008 to locate additional studies published after the end date of the searches. Because there were no good-quality relevant systematic reviews for reports on fecal immunochemical tests (key questions 2b and 3b), we searched MEDLINE and the Cochrane Library (1990–2008) and from 2000 to 2008 to locate studies of the harms of screening tests (key questions 3a and 3b) since the 2002 report.

Abstracts and articles were dual-reviewed against inclusion criteria (**Appendix**) and required agreement of 2 reviewers. Eligible studies reported on the sensitivity and specificity of colorectal cancer screening tests or on health outcomes. We excluded studies that did not address average-risk populations for colorectal cancer screening, unless an average-risk subgroup was reported. We excluded case-control studies of screening accuracy because these may overestimate sensitivity as a design-related source of bias (30), as recently demonstrated for FOBTs (31). To avoid biases related to reference standards, we excluded studies of test accuracy that incompletely applied a valid reference standard or used an inadequate reference standard (32). For CT colonography, we considered only technologies that were compared with colonoscopy in average-risk populations, used a multidetector scanner (27), and reported per-patient sensitivity and specificity. In all, we evaluated 3948 abstracts and 490 full-text articles (**Figure 2**).

Quality Assessment and Data Abstraction

Two investigators critically appraised and quality-rated all eligible studies by using design-specific USPSTF criteria (33) supplemented by other criteria (**Appendix**). Poor-quality studies were excluded. One investigator abstracted key elements of included studies into standardized evidence tables. A second reviewer verified these data. We resolved disagreements about data abstraction or quality appraisal by consensus. Evidence tables and tables of excluded studies for each key question are available in the full report (25).

Data Synthesis and Analysis

We report qualitative synthesis of the results for most key questions because of study heterogeneity. The performance of screening tests is preferentially described per person (sensitivity and specificity), supplemented by per-polyp analyses (miss rates). Sensitivity for large adenomas from 2 similar studies of CT colonography screening was combined by using the inverse variance fixed-effects model because no heterogeneity was detected on the basis of the Cochran Q test and the I^2 statistic (34). Because of the stringency of our inclusion criteria for studies to estimate rates of endoscopy harms in the community practice setting (key question 3a), included studies were clinically homogeneous enough to pool. A random-effects logistic model was used to evaluate statistical heterogeneity, esti-

mate pooled rates, and explore potential sources of variation for complications from study-level characteristics (35, 36). Model details and SAS PROC NL MIXED code are provided in the **Appendix**. Total serious adverse events required hospital admission (for example, perforation, major bleeding, severe abdominal symptoms, and cardiovascular events) or resulted in death. Results of exploratory analyses for potential sources of variation for pooled estimates are discussed in the full report, along with pooled estimates for individual complications, such as perforations (25).

Role of the Funding Source

The Agency for Healthcare Research and Quality funded this work, provided project oversight, and assisted with internal and external review of the draft evidence synthesis but had no role in the design, conduct, or reporting of the review. The authors worked with 4 USPSTF members to develop the analytic framework, set the review scope, and resolve methodologic issues during the conduct of the review. The draft systematic review was reviewed by 8 external peer reviewers and was revised for the final version.

RESULTS

Our results are organized by screening method rather than key question, with newer tests discussed first. More detailed results, including evidence tables for each key question, are available in the full report (25).

Fecal Immunochemical Tests, Hemocult SENSAs, Fecal DNA, and CT Colonography (Key Questions 2b and 3b)

We evaluated 3 categories of newer fecal colorectal cancer screening tests (fecal immunochemical testing, high-sensitivity guaiac FOBT, and fecal DNA testing) and CT colonography. Among these, the largest body of fair- or good-quality evidence with which to evaluate performance of colorectal cancer screening tests in average-risk screening populations was for several different fecal immunochemical tests, followed by Hemocult SENSAs (Beckman Coulter, Fullerton, California), CT colonography, and fecal DNA testing.

Accuracy of Newer FOBTs

Although we found 9 fair- or good-quality cohort studies evaluating fecal immunochemical tests in 86 498 average-risk persons, these tests cannot be clearly analyzed as a class (37). Therefore, we grouped results by test type for 4 different tests (**Table 1**). Limited data suggest better detection of colorectal cancer and large adenomas with 2 to 3 days of sample collection for FOBTs than with 1 day of sample collection. With few exceptions, studies did not directly compare fecal immunochemical tests with each other or with regular or high-sensitivity Hemocult testing.

Overall, fecal immunochemical tests had higher sensitivity for colorectal cancer (61% to 91%) (38–46) than

Table 1. Summary of Newer Fecal Test Studies

Study, Year (Reference); Patients, n; Study Quality	Gold Standard	Additional FOBT Tested or Threshold for Occult Blood Detection, ng/mL	Duration of Fecal Sample Collection, d
Magstream (Fujirebio, Tokyo)			
Morikawa et al., 2005 (44); 21 805; fair	Colonoscopy for all patients	20	1
Launoy et al., 2005 (42); 7421; fair	Registry follow-up for screen-negative patients; colonoscopy for screen-positive patients	>20	2
		>50	
		>75	
Allison et al., 1996 (39); 8104; fair	Registry follow-up for screen-negative patients; colonoscopy for screen-positive patients	HemeSelect (Magstream)	3
		Hemoccult SENA	
		Hemoccult SENA/HemeSelect	
		Hemoccult II	
OC-Hemodia (Eiken Chemical Co., Tokyo)			
Cheng et al., 2002 (40); 7411; fair	Colonoscopy for all patients		3
Itoh et al., 1996 (41); 27 860; fair	Registry follow-up for screen-negative patients; colonoscopy for screen-positive patients		1
Levi et al., 2007 (43); fair	Colonoscopy for all patients		3
FlexSure OBT (Hemoccult ICT, Beckman Coulter, Fullerton, California)			
Allison et al., 2007* (38); 5841; good	Colonoscopy for screen-positive patients or flexible sigmoidoscopy for screen-negative patients	FlexSure	3
		Hemoccult SENA	
		FlexSure/Hemoccult SENA	
MonoHaem (Millipore, Billerica, Massachusetts)			
Nakama et al., 1999 (45); 4611; fair	Colonoscopy for all patients		1
			2
			3
Nakama et al., 1996 (46)†; 3365; fair	Registry follow-up for screen-negative patients; colonoscopy for screen-positive patients	1-y follow-up 2-y follow-up 3-y follow-up	1
Fecal DNA			
Imperiale et al., 2004 (47); 4404; fair	Colonoscopy for all patients, but test accuracy limited to those selected for fecal DNA testing	Fecal DNA testing done only in subsample based on histopathologic and colonoscopic results (n = 2507)	Whole-stool (30-g) sample
		Hemoccult II	3

CRC = colorectal cancer; FDA = U.S. Food and Drug Administration; FOBT = fecal occult blood testing; NR = not reported.

* Left-sided tumors only.

† Sensitivity and specificity of small adenomas or polyps of unknown size are found in the full evidence table (25).

was reported for nonrehydrated Hemoccult II (25% to 38%) in another recent systematic review (31) and in the only study of fecal immunochemical testing that also eval-

uated Hemoccult II (39). Estimated specificity varied across fecal immunochemical tests (91% to 98%), and, in most studies, specificity appears lower than the reported

Table 1—Continued

Test Positivity Rate, %	Sensitivity (95% CI), %	Specificity, %	FDA Approved	Available in U.S. Market
5.6	CRC: 65.8 Advanced neoplasia: 27.1 Adenoma \geq 10 mm: 20.0	CRC: 94.6 Advanced neoplasia: 95.1 Adenoma \geq 10 mm: NR	No	No
5.8	CRC: 85 Advanced neoplasia: NR	CRC: 94 Advanced neoplasia: NR	No	No
3.1	CRC: 67.8 Advanced neoplasia: NR	CRC: 97 Advanced neoplasia: NR		
2.0	CRC: 61 Advanced neoplasia: NR	CRC: 98 Advanced neoplasia: NR		
5.9	CRC: 68.8 Polyp \geq 10 mm: 66.7	CRC: 94.4 Polyp \geq 10 mm: 95.2	Yes	No
13.6	CRC: 79.4 Polyp \geq 10 mm: 68.6	CRC: 86.7 Polyp \geq 10 mm: 87.5	Yes	Yes
3.0	CRC: 65.6 Polyp \geq 10 mm: 50.0	CRC: 97.3 Polyp \geq 10 mm: 97.9		
2.5	CRC: 37.1 Polyp \geq 10 mm: 30.8	CRC: 97.7 Polyp \geq 10 mm: 98.1	Yes	Yes
9.2	CRC: 87.5 Advanced neoplasia: 48.4	CRC: 91.0 Advanced neoplasia: 91.3	Yes (OC-Auto Micro 80, Polymedco, Cortlandt Manor, NY)	Yes
5.3	CRC: 86.5	CRC: 94.9	No	No
18.8	CRC: 66.7 Advanced neoplasia: 55.6	CRC: 83.1 Advanced neoplasia: 91.9	No	No
3.2	CRC: 81.8 Adenoma \geq 10 mm: 29.5	CRC: 96.9 Adenoma \geq 10 mm: 97.3	Yes	Yes
10.1	CRC: 64.3 Adenoma \geq 10 mm: 41.3	CRC: 90.1 Adenoma \geq 10 mm: 90.6	Yes	Yes
2.1	CRC: 64.3 Adenoma \geq 10 mm: 22.8	CRC: 98.1 Adenoma \geq 10 mm: 98.4		
NR	CRC: 55.6 Adenoma: 30.1	CRC and adenoma: 97.1	Yes	No
NR	CRC: 83.3 Adenoma: 50.7	CRC and adenoma: 96.0		
NR	CRC: 88.9 Adenoma: 54.8	CRC and adenoma: 93.9		
4.7	CRC: 90.9 CRC: 83.3 CRC: 71.4	CRC: 95.6	Yes	No
8.2	CRC: 51.6 (34.8–68.0) Advanced adenoma: 15.1 (12.0–19.0)	Minor polyps: 92.4 No polyps: 94.4	No	Yes
5.8	CRC: 12.9 (5.1–28.9) Advanced adenoma: 10.7 (8.0–14.0)	Minor polyps: 95.2 No polyps: 95.2	Yes	Yes

specificity of nonhydrated Hemoccult II (98% to 99%) (39). Sensitivity for advanced neoplasia or large adenomas was less commonly reported but ranged from 27% to

67% for fecal immunochemical tests (39, 40, 43–45). The sensitivity of nonhydrated Hemoccult II for large adenomas has been estimated at 16% to 31% (31). The single

study directly comparing HemeSelect and nonrehydrated Hemocult II reported twice the sensitivity for polyps 10 mm or greater for HemeSelect (SmithKline Diagnostics, San Jose, California) (67% vs. 31%) (39). Currently, U.S. Food and Drug Administration (FDA)–approved fecal immunochemical tests with fair- or good-quality studies of screening test performance are largely not available on the U.S. market. Of the 4 fecal immunochemical tests discussed here, few were both FDA approved and on the U.S. market at the time this article was written.

Hemocult SENSE had higher sensitivity for colorectal cancer (64% to 80%) than would be expected for Hemocult II but lower specificity (87% to 90%) (38, 39) (Table 1). In direct comparisons, Hemocult SENSE was less sensitive for colorectal cancer (64%) than was FlexSure OBT/Hemocult ICT (82%) but more sensitive for large adenomas (41% vs. 30%). Hemocult SENSE was more sensitive for colorectal cancer (79%) than HemeSelect (69%) but had similar sensitivity for large adenomas (69% vs. 67%, respectively). Hemocult SENSE was less specific for colorectal cancer and for adenomas compared with both fecal immunochemical tests (38). More people would be referred for colonoscopy with Hemocult SENSE than with fecal immunochemical tests because of 2- to 3-fold higher rates of positive test results with the former. A combination Hemocult SENSE/FlexSure screening approach, in which the fecal immunochemical test was developed only if the guaiac-based test result was positive, had identical sensitivity and better specificity compared with Hemocult SENSE alone (98.1% vs. 90.1%). These estimates provide relative rather than absolute sensitivity or specificity because patients with negative results underwent flexible sigmoidoscopy (or registry follow-up) only.

Accuracy of Fecal DNA Testing

Eligible fecal DNA screening studies were limited to a fair-quality large cohort study that used a multitarget fecal DNA panel test (the precommercial version of PreGen Plus, version 1 [Exact Sciences, Marlborough, Massachusetts], which tests for 21 DNA mutations in the *K-ras*, *APC*, and *p53* genes, along with markers for microsatellite instability and long DNA) in average-risk patients undergoing colonoscopy (47) and a smaller cohort study that tested a single mutation of the *K-ras* gene (48). We will not further discuss the test for the single *K-ras* gene mutation because it showed zero sensitivity: It was positive in none of the 31 participants with advanced colorectal neoplasia, including 7 patients with invasive colorectal cancer.

Researchers compared a one-time application of PreGen Plus (version 1.0) with 3-card nonrehydrated Hemocult II in a study that enrolled 5486 average-risk asymptomatic patients who were all to undergo colonoscopy (47) (Table 1). Among the 4404 that adhered to all 3 tests, a subset ($n = 2507$; mean age, 69.5 years; 45% male; 87% white; 14% with a positive family history) was selected for

fecal DNA testing on the basis of colonoscopic and histopathologic results.

Test performance for fecal DNA was compared with that for Hemocult II in the selected subgroup; among these patients, 8.2% had positive results on the fecal DNA panel and 5.8% had positive Hemocult II results. One-time fecal DNA testing was more sensitive for adenocarcinoma than was Hemocult II (sensitivities of 51% [CI, 34.8% to 68.0%] and 12.9% [CI, 5.1% to 28.9%], respectively). Both fecal DNA testing and Hemocult II had poor sensitivity for advanced carcinoma. Although specificity for minor polyps or no polyps did not differ between fecal DNA and Hemocult II, power to detect a difference may have been limited because the full sample was not tested.

Serious Harms of Fecal Colorectal Cancer Screening

We found no studies addressing serious adverse effects from any type of fecal colorectal cancer screening tests. Risks are most likely related to false-positive test results and the associated risks from unnecessary colonoscopy screening.

Accuracy of CT Colonography

Although we located 7 fair- or good-quality cross-sectional studies (49–55) examining a total of 4468 average-risk patients screened for colorectal cancer with both CT colonography and same-day colonoscopy, 3 of these (50–52) did not contribute to our estimates of CT colonography test performance because of study limitations described in our larger report (25). The 4 remaining studies discussed here examined CT colonography screening in 4312 average-risk patients (Table 2); 3 of these studies also estimated colonoscopy sensitivity (49, 53, 54).

The 2 largest and most comparable and applicable studies were conducted by Pickhardt and colleagues (49) and the American College of Radiology Imaging Network (ACRIN) (55) and together represent 87% of patients. These 2 studies found that CT colonography was comparable to colonoscopy for detecting large adenomas (≥ 10 mm), but not necessarily for smaller adenomas (≥ 6 mm). Pooled sensitivity for large adenomas in these 2 studies was 92% (CI, 87% to 96%), with no statistical heterogeneity detected between the studies ($I^2 = 0\%$; $P = 0.42$). Point estimates for the sensitivity of CT colonography for smaller adenomas in ACRIN (78% [CI, 71% to 85%]) were 11% lower than for Pickhardt and colleagues' study (88.7% [CI, 82.9% to 93.1%]) and significantly lower than estimates for optical colonoscopy obtained by using an enhanced reference standard of segmental unblinding (49). In addition, although CIs for sensitivity for detecting smaller adenomas overlap with those for the sensitivity for larger adenomas within both studies, intervals are wide. We did not pool sensitivity estimates for smaller adenomas because the 2 studies had quite different results, which were also statistically heterogeneous. This finding suggests uncertainty about the

true sensitivity of CT colonography for smaller adenomas. Of note, the sensitivity of CT colonography for at least 1 of the studies (55) is predicated on CT colonography–detected lesions that were 5 mm or greater, although these would not be the basis for referral for colonoscopy. The authors report that using a radiologic threshold of 6 mm for CT colonography–detected lesions reduced the sensitivity for large adenomas to 88%; similar data to estimate the change in sensitivity for smaller lesions are not provided. Sensitivity estimates for large adenomas or tumors for the 5-mm threshold varied among radiologists (from 67% to 100%), with fewer than half of radiologists detecting 100% of the 1 to 13 large adenomas in the cases they read. One of 7 colorectal tumors was missed on CT colonography in 1 study (55), whereas both colorectal tumors were detected by CT colonography in the other (49).

Per-patient specificity of CT colonography for small or large adenomas varied between the 2 largest studies. One study that used segmental unblinding to clearly distinguish false-positive CT colonography findings from false-negative colonoscopy findings had statistically significantly worse specificity (79.6% [CI, 77.0% to 82.0%]) for lesions 6 mm or greater, compared with 96% specificity for lesions 10 mm or greater (49). In contrast, ACRIN reported similar specificity for lesions regardless of size, with better specificity (88% [CI, 84% to 92%]) for lesions 6 mm or greater than reported by Pickhardt and colleagues (55). We did not pool specificity estimates because between-study results were too different and were statistically heterogeneous. In the ACRIN study, 40% (CI, 33.5% to 46.3%) of patients with lesions 6 mm or greater detected on CT colonography had lesions 6 mm or greater detected on colonoscopy.

Sensitivity and specificity estimates from 2 smaller fair-quality studies comparing CT colonography with colonoscopy are less informative because these studies detected relatively few lesions and their primary purposes were 1) to examine the relative accuracy of 2-dimensional vs. 3-dimensional methods for displaying and reviewing CT colonography images and 2) to compare radiologist performance (53, 54). Thus, these studies do not provide overall results for the population but rather report subsets of data to compare readers or technologies. Results are generally consistent, with better sensitivity for larger (compared with smaller) lesions, no clear differences between 2- and 3-dimensional approaches (which was confirmed by ACRIN), and some degree of interreader variability (which seems exaggerated in these studies because of small numbers of lesions).

The pooled sensitivity estimates for large adenomas provided here might be considered best-case estimates because the studies had very low (<1%) rates of inadequate examinations, used standardized CT technologies, used fecal tagging and contrast-based luminal fluid opacification, and used a limited number of very experienced radiologists for all readings. In addition, we know little about the sensitivity of CT colonography for flat adenomas from these

studies. In a related report from the study by Pickhardt and colleagues (56), the per-lesion sensitivity for flat adenomas 6 mm or greater (82.8%) was reported to be similar to the sensitivity for polypoid adenomas 6 mm or greater (86.2%). This determination, however, was based on a total of 29 flat adenomas 6 mm or greater, with flat polyps found in 52 of 1233 persons (4.9%) (56).

On the basis of a referral threshold of any polyp 6 mm or greater, these studies suggest that 1 in 3 to 1 in 8 persons screened with CT colonography would be referred for colonoscopy.

Serious Harms of CT Colonography

Few serious, procedure-related harms (for example, perforation, major events requiring medical attention) have been reported in 6 fair-quality cohort studies that addressed potential adverse effects with CT colonography screening (49, 54, 55, 57–59). Overall, the risk for perforation with screening CT colonography in asymptomatic persons seems very low, with no perforations reported in 2 studies of 14 238 screening CT colonographies (55, 57) or in a study of 3120 CT colonographies (54). In 1 study, however, 1 person among 2531 persons undergoing both CT colonography and colonoscopy was hospitalized for bacteremia (55). Among 11 870 screening and diagnostic CT colonography examinations, researchers reported just 1 perforation in the subgroup of persons undergoing screening CT colonography, compared with 6 in the subgroup undergoing diagnostic CT colonography (59). Two small studies ($n = 1587$) did not report on perforation rates but did report that no major adverse events occurred (49, 58).

Harms related to bowel preparations required for CT colonography, colonoscopy, or flexible sigmoidoscopy are considered in the larger report (25).

Uncertain Effects of CT Colonography Screening

Uncertainties associated with CT colonography screening include potential long-term harms from CT colonography–related radiation exposure. In addition, because CT colonography produces images of structures outside the colon, the implications of extracolonic findings that occur with CT colonography screening—including potential benefits from early disease detection as well as harms from unnecessary medical testing and anxiety—are unclear.

We identified no studies that directly measured harms caused by low-dose radiation exposure from CT. However, existing models can indirectly estimate potential adverse effects for lifetime attributable risk for cancer by extrapolating the cancer-related risks at the range of effective radiation doses reported for CT colonography from existing risk models based on much higher radiation exposure. On the basis of 2 reviews, total radiation exposure with CT colonography ranges from 1.6 to 24.4 mSv for dual positioning (both supine and prone), with a median dose estimate of 8.8 mSv or 10.2 mSv per examination (60, 61).

Table 2. Accuracy of Computed Tomographic Colonography and Estimated Rates of Referral to Colonoscopy

Variable	Colonoscopy: Pickhardt et al., 2003 (49)		CT Colonography	
			Pickhardt et al., 2003 (49)	Johnson et al., 2008 (55)
Study aim	To evaluate performance characteristics of CT colonography screening			To assess the accuracy of CT colonography in multicenter screening setting
Patients, <i>n</i>	1233			2531
Population	50–79 y; 41% female			≥50 y; 54% female
CT colonography	–	Flythrough 3D imaging with 2D correlation of abnormality (Viatronix V3D 1.2, Stony Brook, New York); stool tagging; luminal fluid tagging; 6 trained radiologists		Randomly assigned primary 2D or 3D flythrough analysis (5 software packages used); stool tagging; luminal fluid tagging; 15 trained and certified radiologists
Reference standard	Same-day colonoscopy by 1 of 17 experienced colonoscopists using segmental unblinding	–		Same-day blinded colonoscopy conducted or supervised by unspecified number of experienced endoscopists, with unblinded second colonoscopy for CT-detected lesions ≥10 mm not detected on initial colonoscopy
Study quality	Good: Use of enhanced reference standard allows distinguishing false-positive CT colonography results from false-negative optical colonoscopy results; interobserver agreement checked on subset of cases			Fair: Colonoscopy reference standard by community operators without clear quality guidelines; incomplete follow-through on second-look colonoscopies (15 of 27); test performance based on 5-mm CT colonography threshold
Applicability	Predominantly average-risk screening population, 3% with family history; may represent best-case estimates because of technology used and limited number of experienced readers			Multicenter study of primarily average-risk participants (9% with family history; 2% with personal history of polyps or cancer); use of 15 trained, qualified readers, with range of sensitivity (67%–100%) for large adenomas and CRC
Sensitivity (per patient) (95% CI), %				
CRC	1 of 2 CRC cases detected	2 of 2 CRC cases detected		6 of 7 CRC cases detected
Adenoma ≥10 mm	87.5 (74.8–95.3)	93.8 (82.8–98.7)		90 (84–96) [†]
Adenoma ≥6 mm	92.3 (87.1–95.8)	88.7 (82.9–93.1)		78, (71–85) [†]
Specificity (per patient) (95% CI), %				
Lesions ≥10 mm	NA	96.0 (94.8–97.1)		86 (81.3–90.0)
Lesions ≥6 mm	NA	79.6 (77.0–82.0)		88 (84.0–92.0)
Referral for colonoscopy				
Lesions ≥10 mm	NA	1 in 13		NR
Lesions ≥6 mm	NA	1 in 3		1 in 6–8

2D = 2-dimensional; 3D = 3-dimensional; CRC = colorectal cancer; CT = computed tomography; NA = not applicable; NR = not reported.

* Point estimates and CIs are calculated from multiple measurements provided in the studies. Methods can be found in reference 25.

[†] Detection of adenoma or cancer in Johnson et al. (55) on CT colonography–detected lesions 5 mm or greater.

[‡] Detection of polyp in Kim et al. (54).

[§] Polyp prevalence significantly different from those reported in other similar studies.

^{||} Range of estimates: 1 in 6 referred for colonoscopy is based on the referral threshold for 5-mm lesions on which sensitivity and specificity calculations are based; 1 in 8 is based on a colonoscopy referral threshold for lesions ≥6 mm.

On the basis of the National Research Council’s Biological Effects of Ionizing Radiation (BEIR) VII phase 2 report findings (62), the National Research Council predicts that approximately 1 additional individual per 1000 would develop cancer (solid cancer or leukemia) from exposure to 10 mSv above background (according to the linear no-threshold model). Because of limitations in the data used to develop this model, these risk estimates are uncertain and could vary by a factor of 2 or 3 (62). In addition, some organizations believe that the linear no-threshold model is

an oversimplification that may overestimate the risk for malignancy (63).

Extracolonic findings detected by CT colonography are common, occurring in 27% to 69% of persons screened with CT colonography (Appendix Table 4, available at www.annals.org). We identified 9 studies (*n* = 12 557) that reported estimates of extracolonic findings in asymptomatic persons (49, 55, 64–70). In these studies, classification of extracolonic findings varied but generally considered 3 types of clinical significance: high (findings

Table 2—Continued

CT Colonography (continued)	
Kim et al., 2007 (54)*	Johnson et al., 2007 (53)*
To compare 3D vs. 2D interpretation of CT colonography	To compare 3D vs. 2D interpretation of CT colonography using 2.5-mm and 1.25-mm slice thickness
96	452
40–76 y; 42% female	41–82 y; 44% female
3D virtual colon dissection (Perspective Filet View) and 2D display (Rapidia); intravenous contrast agent for extracolonic findings; 2 very experienced radiologists	3D virtual dissection (Voxtool 5.4.46, GE Healthcare, Milwaukee, Wisconsin); no contrast agent; 3 very experienced radiologists
Same-day colonoscopy by 1 of 5 experienced gastroenterologists using segmental unblinding	Same-day videotaped colonoscopy conducted or supervised by 1 of 50 experienced endoscopists; repeat colonoscopy in 6 cases of large lesion on CT colonography
Fair: Retrospective analysis comparing types of CT colonography and reader reliability	Fair: Limited power because of multiple analyses comparing readers, displays, and collimation thicknesses; colonoscopy reference standard not high quality
Uncertain because of setting, small study size, limited number of very experienced radiologists compared with endoscopists	Small number of more skilled radiologists; unusually high yield of CRC and low prevalence of polyps compared with other screening populations, possibly due to not excluding patients with previous colonic resections
Range of 3D and 2D	Range of 3D and 2D
None detected	5 of 5 CRC cases detected
100‡	50–83
59–77‡	NR
99–100	97–99
89–99	NR
1 in 10	Not calculated§
1 in 5	Not calculated§

that require surgical treatment, medical intervention, or further investigation), moderate (findings that would not require immediate medical attention but would probably require recognition, investigation, or future treatment), and low (findings that would not require further investigation or treatment). These 3 categories generally map to the CT Colonography Report and Data System (C-RADS) (71), as described elsewhere (25). Extracolonic findings of high clinical significance (for example, indeterminate solid organ masses or chest nodules, abdominal aortic aneu-

rysms ≥ 3 cm, aneurysms of the splenic or renal arteries, or adenopathy > 1 cm) occurred in 4.5% to 11% of asymptomatic populations (49, 65–67, 69, 70). Extracolonic findings of moderate clinical significance (such as renal calculi and small adrenal masses) were equally or more common and occurred in up to 27% (49, 64, 65, 67–70). Because all extracolonic findings of high significance, along with some moderate findings, would require medical follow-up, these have the potential for additional morbidity and cost, as well as potential benefit. Across studies, approximately 7% to 16% of persons undergoing CT colonography were recommended to have additional diagnostic evaluation for extracolonic findings (55, 64, 65, 67, 68, 70). Only a minority of these findings ultimately warranted definitive treatment (for example, repair of abdominal aortic aneurysm, resection of malignant lesions, or chemotherapy for metastatic lesions) (64, 65, 68–70). Although these estimates provide important contextual information, they are limited by the available studies, which varied greatly in their ability to accurately assess follow-up and in the duration of follow-up, the longest of which was 2 years.

Colonoscopy and Flexible Sigmoidoscopy in Community Settings (Key Questions 2a and 3a)

Accuracy of Colonoscopy

Evaluating the accuracy of screening colonoscopy in average-risk participants, particularly in community settings, is challenging because of the lack of an independent gold standard and very few applicable studies. As detailed in the full report (25), we found no studies of miss rates after tandem screening colonoscopy in average-risk patients to fairly represent performance of community endoscopists, and no studies of repeated colonoscopy within 3 years after screening colonoscopy in a representative sample of average-risk community-based patients.

Researchers have used CT colonography screening studies already discussed (49, 53, 54) to estimate the sensitivity of colonoscopy for colorectal cancer and for adenomas of various sizes detected using either CT colonography or colonoscopy. Two of these studies conducted CT colonography followed by colonoscopy with segmental unblinding to recheck CT colonography–located lesions not seen on first-pass colonoscopy (49, 53); 1 of these provides the single best estimate for community performance of colonoscopy (49) (Table 2). In this good-quality study of 1233 average-risk persons, colonoscopy by 1 of 17 experienced colonoscopists missed 10% of adenomas 6 mm or greater and 12% of adenomas 10 mm or greater. Sensitivity (per-person detection rate) of colonoscopy for adenomas 6, 8, or 10 mm or greater did not statistically significantly differ from sensitivity of CT colonography. Colonoscopy missed 1 of 2 colorectal lesions detected, whereas CT colonography detected both. In the second study using segmental unblinding, no colorectal cancer was detected in 96 average-risk patients using either test, and

colonoscopy by 1 of 5 gastroenterologists missed 10% of polyps 6 mm or greater but no polyps 10 mm or greater. Colonoscopy was much less accurate in the third study of 452 asymptomatic, average-risk patients, detecting only 77% (20 of 26) of neoplasms 10 mm or greater and just 1 of 5 colorectal lesions detected by CT colonography (53). This study, however, evaluated the performance of more than 50 experienced endoscopists, whereas CT colonography was conducted by 3 very experienced radiologists.

Taken together, these data are insufficient to provide precise estimates of the sensitivity of colonoscopy in community settings, particularly for colorectal cancer detection, because of the small number of patients studied ($n = 1781$) and the relatively few lesions (7 total colorectal lesions). They do, however, confirm that colonoscopy misses some polyps and may also miss colorectal cancer.

Serious Harms from Colonoscopy

We found 17 fair- or good-quality, primarily prospective, studies evaluating clinically significant adverse events from screening colonoscopy conducted in predominantly asymptomatic persons (49, 55, 67, 72–85). Only 1 of these studies (81) was included in the 2002 systematic review for the USPSTF. Seven of these 16 studies were conducted in community settings (55, 73, 75, 77, 79, 81–83). Using a random-effects logistic model to pool data from the 12 studies ($n = 57\,742$) (49, 55, 73–76, 79, 80, 82–85) reporting this outcome, we found 2.8 total serious complications (including perforations, hemorrhage, diverticulitis, cardiovascular events, severe abdominal pain, and death) per 1000 procedures (CI, 1.5 to 5.2 per 1000 procedures; test for heterogeneity; $P = 0.13$) (Appendix Figure 1, available at www.annals.org). When we limited the model to the 7 studies conducted in the United States, serious complications were nonsignificantly reduced (2.5 per 1000 procedures [CI, 1.0 to 6.1 per 1000 procedures]). Because of reporting limitations, complication rates could not be calculated for colonoscopies with and without polypectomy. Only 3 of these 11 studies reported the proportion of colonoscopies in which polypectomies were performed—the proportions ranged from 41% to 68% (79, 80, 82). In these 3 studies, more than 85% of serious complications, perforations, and major bleeding incidents occurred during colonoscopies that required polypectomies. We could not estimate complications by age because of limitations in study reporting.

Accuracy of Flexible Sigmoidoscopy

We found no studies that estimated accuracy of flexible sigmoidoscopy in average-risk patients undergoing screening with both flexible sigmoidoscopy and colonoscopy. We report here the accuracy of screening with simulated flexible sigmoidoscopy reported in 6 large cohort studies of screening colonoscopy in a total of 14 938 average-risk patients (86–91). Elsewhere (25), we describe 3 studies—1 tandem flexible sigmoidoscopy study

that reported adenoma miss rates (92) and 2 prospective studies that reported distal advanced neoplasia or colorectal cancer on flexible sigmoidoscopy repeated 3 years after negative results on screening flexible sigmoidoscopy (93, 94)—that do not provide any greater precision than these estimates.

The estimated sensitivity of flexible sigmoidoscopy (using either biopsy or visual inspection to determine colonoscopy referral) for colorectal cancer throughout the entire colon was 58% to 75%, based on small numbers of colorectal lesions, with an estimated sensitivity of 72% to 86% for advanced neoplasia. Variations in these estimates are probably due to differences in examiner skill and the patient's risks for proximal lesions in the unexamined colon. These estimates are further limited because they simulate flexible sigmoidoscopy results by using colonoscopy examinations. This approach presumes that all lesions are detected if they are within the insertion depth for flexible sigmoidoscopy and ignores differences introduced through the more thorough bowel preparation used for colonoscopy or through colonoscopists' skill. The community performance of flexible sigmoidoscopy screening and its effect on health outcomes, including mortality from colorectal cancer, will become clearer after current RCTs are reported.

Serious Harms from Flexible Sigmoidoscopy

We found 8 fair- or good-quality studies that evaluated clinically significant adverse events from flexible sigmoidoscopy for colorectal cancer screening in an average-risk population (72, 74, 84, 85, 95–98). Only 1 of these studies was included in the 2002 review (72).

Using a random-effects logistic model to pool data from the 6 studies (72, 74, 84, 85, 95, 96) reporting this outcome ($n = 126\,985$), we found 0.34 serious complication per 1000 procedures (CI, 0.06 to 1.9 per 1000 procedures; test for heterogeneity, $P = 0.26$) (Appendix Figure 2, available at www.annals.org). Serious complications were defined the same as for screening colonoscopy but excluded complications from follow-up colonoscopy. Per protocol, all of these studies performed polypectomy during flexible sigmoidoscopy; based on 2 studies, polypectomies were conducted in 20% to 22% of flexible sigmoidoscopy examinations (72, 74). We could not estimate complications by age because of limitations in study reporting.

DISCUSSION

Since 2002, research on colorectal cancer screening has grown substantially as researchers have investigated the accuracy of novel screening approaches and have continued examining already recommended approaches. As discussed in our full report (25), we found no new reports of the mortality impact of colorectal cancer screening (besides FOBT programs); however, results from several trials of

flexible sigmoidoscopy that will report mortality effects are pending (84, 99–101). In addition, although we found many studies addressing test performance of newer FOBTs, fecal DNA screening tests, or CT colonography (25), relatively few addressed average-risk screening populations and used minimally acceptable study designs and methods. **Table 3** summarizes review findings about the performance and harms of new fecal screening tests, CT colonography, colonoscopy, and flexible sigmoidoscopy by key question, with newer tests reported first.

Recent guidance articulates evidence requirements to justify replacing a currently recommended diagnostic (or screening) test with a newer test in the absence of RCTs showing benefit (102, 103); this pertains to replacing existing colorectal cancer screening tests with newer ones. Accordingly, researchers should evaluate the comparative accuracy of newer and older tests by using the same reference standard as trials that showed treatment benefit in the same (or similar) patients representing the appropriate disease spectrum (103). If the newer test has increased sensitivity—with similar specificity and patient safety—or similar sensitivity but other advantages (for example, improved specificity, acceptability, or accessibility), studies of test accuracy alone may support substituting this test in the absence of trial data (103). However, when new tests offer tradeoffs between desirable and undesirable attributes (for example, improved sensitivity but reduced specificity), a decision analytic model or new research may be needed. When data on new tests are incomplete or uncertain, and the costs or consequences of making assumptions from such data are potentially severe, clinicians may require further research before acting (103).

Fecal Screening Tests

As determined primarily through indirect comparisons, several fecal immunochemical tests had superior single-test sensitivity for colorectal cancer and possibly for advanced neoplasia compared with Hemoccult II. Fecal immunochemical tests had similar or somewhat lower specificity, suggesting that test choice might be important when considering substituting fecal immunochemical tests in a fecal screening program. For one quantitative fecal immunochemical test (Magstream, Fujirebio Inc., Tokyo, Japan), choice of positive cutoff values would allow programs to determine the appropriate tradeoff between improved sensitivity and specificity. Limited evidence suggested better test performance with 2- or 3-day sample collection than with 1-day collection. Ease of administration may work in favor of some fecal immunochemical tests (31), although their increased costs may reduce acceptability for payers. The relatively small increase in Medicare reimbursement for fecal immunochemical tests (exceeding those for Hemoccult II) (104) may be affecting market availability. Not all well-studied fecal immunochemical tests were both FDA approved and on the U.S. market at the time this article was written.

On the basis of fewer data and less precise estimates, Hemoccult SENSE also had increased sensitivity for colorectal cancer compared with Hemoccult II but reduced specificity. Direct comparisons with fecal immunochemical tests were few, with mixed results for sensitivity and consistently lower specificity for Hemoccult SENSE. The tradeoffs from improved sensitivity with reduced specificity in a screening program of repeated testing is best evaluated through modeling (24).

One study on screening test performance of the pre-commercial version of a multitarget fecal DNA test (PreGen Plus) showed improved sensitivity for colorectal cancer but not adenomas, similar or slightly reduced specificity, and higher positive rates compared with Hemoccult II (47). Test accuracy estimates for colorectal cancer were imprecise for both tests because of power, and sensitivity and specificity of Hemoccult II in this study were lower than generally reported in higher-quality studies (31, 105). In addition, this study's findings may not be generalizable to population screening because participants were relatively older (three quarters were >65 years of age, compared with screening beginning at age 50 years) and the version of PreGen Plus tested has been supplanted by other versions (1.1 and higher) for which there are no screening population studies (**Table 3**). Commercial availability of fecal DNA tests may be further affected by the recent FDA requirement for premarket review of this test, which was previously considered to be outside FDA jurisdiction (106, 107). Furthermore, in the absence of trial data or modeling, fecal DNA could be considered only as a substitute for an annual or biennial FOBT in established screening programs. This could be cost-prohibitive given the relative cost for fecal DNA compared with guaiac or immunochemical tests (104). Cost concerns may underlie recommendations by the manufacturer to repeat fecal DNA screening at 5-year intervals (108). Data on health outcomes are insufficient, however, to support this interval recommendation (109).

Accuracy, Harms, and Uncertainties with CT Colonography

Computed tomographic colonography has been studied as a diagnostic test (for patients with symptoms) and, less frequently, as a screening test in average-risk asymptomatic patients. Recent publication of the ACRIN study has more than doubled the number of average-risk patients studied to determine the accuracy of CT colonography for colorectal cancer screening (55), with only 1 smaller screening study ($n = 300$) still pending (110). On the basis of published studies in 4312 average-risk screening patients, CT colonography screening by trained and experienced radiologists had sensitivity similar to that of colonoscopy for colorectal cancer and large adenomas (≥ 10 mm). However, estimates of sensitivity of CT colonography for smaller adenomas (≥ 6 mm) was more variable between studies (with point estimates of 78% and 88.7% and wide

Table 3. Summary of Results*

Key Question and Test	Number of Studies and Study Design	Limitations	Consistency
What are the test performance characteristics of CT colonography and fecal screening tests (e.g., high-sensitivity guaiac FOBT, FIT, or fecal DNA tests) for CRC screening as compared to an acceptable reference standard? (Key question 2b)			
Fecal tests	11 total studies		
FIT	9 cohort studies of test accuracy	Cannot clearly be analyzed as a class; many different tests, with few studies per test. Performance for all but 1 FIT was reported qualitatively at a single cut-point rather than quantitatively (i.e., across multiple cut-points). Several studies used registry follow-up for screen-negative patients, probably overestimating sensitivity.	Estimates of sensitivity and specificity show variability within each test, possibly because of different collection methods or reference standard applied.
High-sensitivity guaiac	2 cohort studies of test accuracy	2 comparative studies, 1 using different reference standards for different tests.	1 study provides estimates for left-sided lesions only.
Fecal DNA	2 cohort studies of test accuracy	1 study for each of 2 approaches. Only fecal DNA panel had any sensitivity for CRC; this test has been replaced by another, presumably upgraded test.	Not applicable.
CT colonography	4 cohort studies of test accuracy	Variability between readers limits studies' ability to provide precise estimates of CT colonography sensitivity for lesions <10 mm. Specificity estimates are somewhat uncertain. Health implications of uncertainties in test performance are unclear.	1 study (n = 1233) using 3D flythrough endoluminal imaging and 1 study (n = 2531) using 3D flythrough or 2D imaging represent most (87%) patients studied and use comparable approaches, including oral contrast agents for fecal tagging and luminal fluid opacification.
What are the adverse effects of CT colonography and/or fecal screening tests (high-sensitivity FOBTs, FIT, and fecal DNA)? (Key question 3b)			
Fecal tests	–	–	–
CT colonography	4 prospective cohort studies, 2 retrospective cohort studies	Unclear clinical significance of asymptomatic perforations visualized on CT. No direct evidence of harms from low-dose ionizing radiation from CT studies. Uncertain impact of possibly clinically significant extracolonic findings found in 5%–27% of CT colonography examinations, based on 9 studies (n = 12 557).	4 prospective studies included predominantly asymptomatic, average-risk populations. 2 large retrospective studies included both symptomatic and asymptomatic persons. Risk for perforations from CT colonography seems higher in symptomatic persons.

Table 3—Continued

Validity	Summary of Findings	Comment
<i>Internal</i> —Fair. <i>External</i> —Fair. Most studies evaluated non-FDA-approved tests or those not on the U.S. market.	Studies ($n = 86\,498$) provided estimates for Magstream (3 studies; $n = 37\,330$), OC-Hemodia (3 studies; $n = 35\,351$), FlexSure OB T (now Hemocult ICT) (1 study; $n = 5841$), and MonoHaem (2 studies; $n = 7976$). Across tests, sensitivity for CRC ranged from 61% to 91%; specificity ranged from 91% to 98%; rates of positive test results ranged from 2.0% to 5.9%.	In a recent systematic review, sensitivity of nonrehydrated Hemocult II for CRC ranged from 25% to 38% (except 1 outlier study with 60% sensitivity), and specificity was 98%–99%. Results from NCT00025025 (“Colorectal Cancer Screening: Fecal Blood vs. DNA.” David Ahlquist, MD, Mayo Clinic Cancer Center, protocol chair), a randomized multicenter study of 2000 patients (age 50–80 y) undergoing FOBT, a newer-generation multitarget DNA-based panel testing of blood and of stool, and colonoscopy were recently published (Ahlquist DA, et al. <i>Ann Intern Med</i> . 2008;149:441-50) and answer some but not all questions.
<i>Internal</i> —Fair. <i>External</i> —Good.	In 1 study ($n = 8104$), Hemocult SENA (13.6% with positive test results) was more sensitive for CRC (79.4%) than Hemocult II was (37.1%), but with lower specificity (86.7% vs. 97.7%). A second study ($n = 5841$) of left-sided CRC found that Hemocult SENA (10.1% with positive test results) had a sensitivity of 64.3% and specificity of 90.1%.	
<i>Internal</i> —Fair to poor. Test accuracy limited to selected subgroup ($n = 2507$) with CRC, advanced adenomas or tumors ($n = 436$), and a randomly selected group with minor ($n = 648$) or no ($n = 1423$) detected polyps. <i>External</i> —Fair to poor. Population was older (75% >65 y) than usual CRC screening population; panel test evaluated has been replaced and now requires premarket review by FDA.	For PreGenPlus fecal DNA panel, sensitivity for CRC was 51.6%; specificity was 94.4%; rate of positive test results was 8.2%. In comparison, sensitivity of Hemocult II for CRC was 12.9%; specificity was 94.3%; and rate of positive test results was 5.8%. Among all participants ($n = 5486$), more (11.7%) did not adhere to fecal DNA tests than to Hemocult II (7.8%).	
<i>Internal</i> —Fair to good. One study used segmental unblinding to separate false-positive CT colonography findings from false-negative colonoscopy findings, and the other used second-look colonoscopy for discrepant large-lesion findings. <i>External</i> —Fair to poor. Best data from studies using CT technologies and experienced readers with uncertain generalizability to community CT colonography practices; uncertainty around reader variability.	Among 1233 average-risk patients, per-patient sensitivity of 3D CT colonography was 93.8% for large (≥ 10 mm) adenomas and 88.7% for adenomas ≥ 6 mm; sensitivity estimates were not significantly different based on polyp size and were not significantly different from sensitivity estimates for colonoscopy. CIs are very wide. Specificity was significantly lower for lesions ≥ 6 mm (79.6%) than for lesions ≥ 8 mm (92.2%) or ≥ 10 mm (96%). Among 2531 average-risk patients, per-patient sensitivity of 3D or 2D CT colonography was 90% for large (≥ 10 mm) adenomas and 78% for adenomas ≥ 6 mm; sensitivity estimates were not significantly different based on polyp size, with very wide CIs. Specificity was 86% for lesions ≥ 10 mm and 88% for lesions ≥ 6 mm. Data could not be pooled for sensitivity and specificity estimates from the 2 largest studies because of statistically significant heterogeneity, except for sensitivity for adenomas ≥ 10 mm; pooled sensitivity was 92% (95% CI, 87%–96%; $Q = 0.652$; $P = 0.42$). In 2 other studies ($n = 548$), ranges of test performance for different readers for 3D CT colonography reported as follows: lesions ≥ 10 mm—sensitivity, 73%–100%, specificity, 98%–100%; lesions ≥ 6 mm—sensitivity, 60%–75%, specificity, 89%–99%. Sensitivity and specificity estimates for 3D imaging did not clearly differ from estimates for 2D imaging. Estimates for the proportion who would be referred for colonoscopy after CT colonography vary from 1 in 3 to 1 in 13, depending on referral size.	Uncertainties remain about the performance of CT colonography screening in community settings. Available data support the need for quality standards for CT colonography screening.
<i>Internal</i> —Fair. <i>External</i> —Fair. Evidence for harms from CT colonography among asymptomatic persons not in community settings.	In 3 prospective studies ($n = 4707$) and the asymptomatic subgroup of 1 large retrospective study ($n = 11\,707$), there were no serious complications, including perforation. In 1 study ($n = 2531$), 1 person was hospitalized for bacteremia after undergoing same-day CT colonography and colonoscopy. In the other large retrospective study ($n = 11\,870$), which included both symptomatic and asymptomatic patients, 7 perforations occurred. However, only 1 perforation occurred in the asymptomatic population (the number of screening CT colonography procedures was not reported).	No studies identified Uncertainties remain about the implications of extracolonic findings, which require additional diagnostic tests or surgery in 7%–16% of cases. Uncertainties remain about about radiation-related risks. Indirect evidence estimates excess lifetime risk for cancer from low-dose (10 mSv) ionizing radiation to be 1 of 1000.

Continued on following page

Table 3—Continued

Key Question and Test	Number of Studies and Study Design	Limitations	Consistency
What are the sensitivity and specificity of colonoscopy and flexible sigmoidoscopy when used to screen for CRC in the community practice setting? (Key question 2a)			
Colonoscopy	3 cohort studies of accuracy of colonoscopy compared with CT colonography; "enhanced" reference standard of second-look colonoscopy for discrepancies between CT colonography and colonoscopy	Small number ($n = 1781$) of patients studied with very few lesions. Number of colonoscopists varied from 5 to 50 per study, which complicates estimates of test accuracy with considerations of training and experience. Estimates of colonoscopy test performance are hampered by lack of a true gold standard.	Variability in CT technology (e.g., use of contrast agent vs. no contrast agent, 2D vs. 3D). All studies conducted in average-risk screening populations.
Flexible sigmoidoscopy	6 cohort studies of screening colonoscopies	Using screening colonoscopy to estimate flexible sigmoidoscopy results probably overestimates sensitivity because studies considered all neoplasia distal to the splenic flexure as detected by flexible sigmoidoscopy and the colonoscopy bowel preparation is superior to that for flexible sigmoidoscopy. Examiner skill may also vary from flexible sigmoidoscopy. Small number of CRC cases (20 total) limits precision of accuracy estimates.	6 screening colonoscopy studies ($n = 14\,938$) simulate the flexible sigmoidoscopy screening with biopsy and colonoscopy referral for adenomas of any size; 2 of these screening colonoscopy studies ($n = 6146$) also simulate the flexible sigmoidoscopy screening without biopsy and colonoscopy referral for any lesion.
What are age-specific rates of harm from colonoscopy and flexible sigmoidoscopy in the community practice setting? (Key question 3a)			
Colonoscopy	3 retrospective cohort studies, 14 prospective cohort studies	Not all studies were conducted in a community setting. Duration of follow-up and methods for determining adverse events varied. Available data precluded determination of harms for colonoscopies with and without associated polypectomies. Age-specific harm rates could not be determined.	No significant statistical heterogeneity in pooling estimates of serious adverse events. In meta-regression, only study setting by country was significantly associated with complications, but stratified analyses by country did not produce clinically significantly different harms estimates.
Flexible sigmoidoscopy	2 retrospective cohort studies, 6 prospective cohort studies	5 studies were not conducted in the United States, and 3 of 5 studies did not report endoscopist characteristics. Duration of follow-up and methods for determining adverse events varied. Age-specific harm rates could not be determined.	No significant statistical heterogeneity in pooling estimates of serious adverse events. In meta-regression, only study setting by country was significantly associated with complications, but stratified analyses by country did not produce clinically significantly different harms estimates.

2D = 2-dimensional; 3D = 3-dimensional; CRC = colorectal cancer; CT = computed tomography; FDA = Food and Drug Administration; FIT = fecal immunochemical test; FOBT = fecal occult blood test; RCT = randomized, controlled trial.

* Results reported in this table are limited to those reported in the article, which is derived from a larger, more detailed report available at www.ahrq.gov (25).

CI) and was not clearly comparable to the sensitivity of colonoscopy for smaller adenomas. The health impact of potentially reduced sensitivity for smaller polyps is unclear (111). Specificity estimates for CT colonography were also quite variable between studies; for lesions 6 mm or greater, point estimates ranged from 79.6% to 88%.

Beyond issues of test accuracy, other uncertainties may affect considerations of whether this test is ready for widespread population screening. These include questions about potential harms from radiation exposure, uncertainty about extracolonic findings, uncertainty about test referral thresholds and repeat test intervals, and judgments about how the test performance seen in clinical studies will translate to the conduct of CT colonography screening examinations in community settings. Most important is how clinicians and policymakers value these remaining uncertainties and whether the costs or consequences of making

assumptions from incomplete data are viewed as potentially severe, thus requiring further research before acting (103).

Immediate procedure-related harms with CT colonography appear to be minimal. The risk for perforation with air insufflation is very low, particularly in asymptomatic persons undergoing screening. Uncertainty remains about delayed harms associated with CT-related radiation exposure, an area of growing concern with more widespread use of CT for diagnostics and screening (112). The estimate of 1/1000 excess lifetime tumors in a 50-year-old after a single CT colonography examination is uncertain and could vary 2- to 3-fold. Radiation-related cancer risks could decrease if newer technologies reduce average radiation exposure (that is, from 10 mSv to about 5 mSv) (113). A recent survey of 22 institutions conducting CT colonography found a total median radiation dose per screening protocol

Table 3—Continued

Validity	Summary of Findings	Comment
<i>Internal</i> —Fair. <i>External</i> —Fair to poor. Estimates are not precise and are not clearly applicable to the community endoscopists.	Sensitivity of colonoscopy for CRC varied widely (20%–50%), largely because of small numbers of tumors (7 total CRC cases detected in all 3 studies). Sensitivity for large adenomas (≥ 10 mm) ranged from 77% to 100%. Sensitivity for smaller polyps is harder to estimate because of inconsistent reporting but suggests about a 10% miss rate.	These data reinforce the need for performance standards for community colonoscopy, particularly for screening.
<i>Internal</i> —Fair. <i>External</i> —Fair. Estimates taken from studies conducted in average-risk screening populations but simulated from cohorts undergoing screening colonoscopy.	In 3982 average-risk adults, the sensitivity of simulated flexible sigmoidoscopy with biopsy for CRC throughout the colon ranged from 58.3% to 62.5%. Among 14 938 predominantly average-risk adults age 40–79 years, estimated sensitivity of flexible sigmoidoscopy with biopsy for advanced neoplasia throughout the colon generally ranged from 70% to 86%. The sensitivity of simulated flexible sigmoidoscopy without biopsy for CRC was 75%, based on a single study ($n = 1994$), and ranged from 77% to 86% for advanced neoplasia ($n = 6146$).	Simulated estimates of test performance of flexible sigmoidoscopy with and without biopsy should be unnecessary once results are reported from 4 pending RCTs.
<i>Internal</i> —Fair. <i>External</i> —Good. All studies conducted either among asymptomatic persons or in a community setting, or both.	In 12 studies ($n = 57\,742$), serious complications occurred in 2.8 per 1000 procedures (CI, 1.5–5.2 procedures). Limiting to 7 U.S. studies, serious complications were nonsignificantly reduced to 2.5 per 1000 procedures (CI, 1.0–6.1 procedures).	—
<i>Internal</i> —Fair. <i>External</i> —Good. All studies conducted among asymptomatic, average-risk persons.	In 6 studies ($n = 126\,985$), serious complications occurred in 0.34 per 1000 procedures (CI, 0.06–1.9 procedures).	—

of 5.6 mSv (range, 2.6 to 14.7 mSv) (114). Thus, because radiation doses depend on factors associated with the technology used and with decisions by the technician (112), higher radiation exposure might persist in some settings. Even assuming a 10-fold lower risk (1/10 000 excess cancer risk), a recent modeling exercise (115) found that lifetime CT colonography screening (starting at age 50 years and repeated every 10 years) produced 36/100 000 radiation-induced cases of cancer with 8 deaths, which offset some of the modeled mortality benefits from reductions in colonoscopy-associated complications.

Extracolonic findings that may require clinical follow-up occur relatively commonly (up to 1 in 4 asymptomatic persons undergoing CT colonography screening), with 7% to 16% clearly receiving recommendations for further diagnostic imaging tests or surgery (55, 67). Whether these extracolonic findings will ultimately provide additional

benefit or harm to those undergoing CT colonography screening for colorectal cancer, and at what additional cost to the health care system, is unknown. A recent modeling study that attempted to address extracolonic findings found a net benefit (115), although the range of these findings was restricted to considering cancer and abdominal aortic aneurysms (reducing the estimated prevalence of extracolonic findings from <1% to at most 5% of the screened population). Other limitations and concerns about the assumptions underpinning this modeling exercise have been noted elsewhere (116).

The referral threshold for colonoscopy (size of lesions detected by CT colonography) is largely based on expert opinion rather than clinical outcomes. Most, but not all (109), experts currently suggest colonoscopy referral for a polyp 6 mm or greater. This makes referral to colonoscopy relatively common, with as many as 1 in 3 persons, to as

few as 1 in 8, referred after CT colonography (Table 2). An ongoing nonrandomized comparative study of colonoscopy and CT colonography screening is offering patients with only 1 or 2 polyps 6 to 9 mm in size on CT colonography the option of CT colonography surveillance instead of immediate colonoscopy, under an institutional review board–approved protocol (67, 117). Under this protocol, fewer patients (1 in 13) have been referred to colonoscopy, compared with referring all those with polyps 6 mm or greater (1 in 8). The safety of this approach is still being determined. Variability in polyp measurement due to differences among readers, CT measurement approaches, and viewing displays further complicates considerations of appropriate polyp size for colonoscopy referral after CT colonography examination (118–120).

An important question for those considering implementing population colorectal cancer screening using CT colonography is whether test accuracy for this technology-dependent, operator-dependent test will be the same in nonresearch settings as in clinical studies. Studies on the accuracy of CT colonography have generally used an enhanced reference standard, which allows the separation of false-positive CT colonography results from false-negative colonoscopy results by reconciling differences with second-look colonoscopy. These studies have confirmed that colonoscopy and CT colonography miss adenomas and colorectal cancer, although reliable estimates of colonoscopy accuracy are limited by very small numbers of lesions. When considering the comparative accuracy between 2 operator-dependent technologies (CT colonography and colonoscopy), current studies are further limited by using designs that compared a larger number of experienced colonoscopists (5 to 50) to a much smaller number of experienced or very experienced radiologists (2 to 15).

As others have stated, “Accurate CT colonography with high sensitivity and specificity for polyps \geq 6 mm in size depends on meticulous technique” (67). Differences in the experience and training of radiologist readers has been cited as the major factor underlying discrepant test accuracy estimates for CT colonography in nonscreening populations (121). Radiologists in nonacademic settings who read a validated set of 15 CT colonographies exhibited considerable individual variability in accuracy (53% to 93%) (122), consistent with our findings from 2 smaller CT screening studies comparing readers (53, 54), as well as from ACRIN, which used trained and certified readers (55). The challenges of adequately ensuring high-quality CT colonography readings are further illustrated by reports from ACRIN that half of the radiologists did not pass the initial certifying examination (after either 1.5 days of training or experience with \geq 500 cases), although all did pass after further training (123). Clearly, specification, implementation, and monitoring of quality standards will be needed before widespread population screening with CT colonography. Activities are reported to be under way to

upgrade quality metrics and training for CT colonography through the American College of Radiology (109).

Little is known about relative patient preferences for CT colonography compared with colonoscopy in average-risk screening populations, and preferences may differ from those of high-risk or symptomatic patients undergoing diagnostic CT colonography. Some data suggest that average-risk patients may prefer CT colonography for convenience, and slightly more (49.8%) would prefer CT colonography for future screening compared with those preferring colonoscopy (41.1%) (49). Issues about patient preferences will become particularly important once considerations of benefits, harms, and community accuracy are resolved. At that point, patient acceptability should also consider the 2-step process (CT colonography followed by referral colonoscopy as needed), with a second bowel preparation for colonoscopy potentially required. Same-day colonoscopy may make repeated bowel preparation unnecessary but requires coordination between radiology and gastroenterology services (124).

Availability of accurate CT colonography screening examinations that do not require any (or full) bowel preparation could greatly influence patient preferences and willingness to be screened (125, 126).

Accuracy and Harms with Colonoscopy and Flexible Sigmoidoscopy in Community Settings

Colonoscopy has presumed accuracy given its position in the diagnostic evaluation of patients screened by other colorectal cancer methods, although gastroenterologists have explicitly recognized that accuracy is highly dependent on the quality of the bowel preparation and endoscopic examination (127). Recent CT colonography studies using an enhanced standard of repeating colonoscopy examination for discordant colonoscopy–CT colonography findings have confirmed that screening colonoscopy can miss colorectal tumors as well as adenomas. Related data from tandem colonoscopy in diagnostic or high-risk screening populations suggest reasonably low miss rates for large adenomas (2.1% [CI, 0.3% to 7.3%]) (128); similarly, new or missed colorectal tumors occurred in 3.4% of a population-based cohort ($n = 12\,487$) who had previously undergone colonoscopy for any reason up to 3 years before a new diagnosis of colorectal cancer (129). Although available studies do not precisely estimate the risk for missed lesions with screening colonoscopy, all underscore the importance of quality initiatives for the performance of colonoscopy or any operator-dependent technological screening tool (127).

Colonoscopy presents a higher risk for immediate harms than do other tests. Serious harms from community endoscopies are about 10 times more common with colonoscopy (2.8 per 1000 procedures) than with flexible sigmoidoscopy (3.4 per 10 000 procedures). The estimates for harms from flexible sigmoidoscopy, however, have

much wider CIs. Age-specific harm rates were sought but could not be determined.

Limitations

We reviewed the accuracy and harms of newer colorectal cancer screening tests as potential replacements for currently recommended tests. The USPSTF commissioned a separate, simultaneous decision analysis comparing different colorectal cancer screening programs to consider tradeoffs in test accuracy, repeated screening, and starting and stopping ages. Because of the targeted nature of this review, we did not formally update or address test acceptability (preferences, costs, adherence) issues; however, the importance of these issues for new technologies, such as CT colonography, may be considered as secondary to establishing the accuracy, harms, and community performance of the screening tests.

Conclusion

Some newer fecal screening tests with better sensitivity and similar specificity are reasonable substitutes for Hemoccult II testing to improve annual or biennial fecal screening programs for colorectal cancer. Modeling can help determine tradeoffs in fecal tests with improved sensitivity but reduced specificity and to compare results from screening programs. Colorectal cancer screening with CT colonography in average-risk populations is likely to detect larger adenomas and colorectal cancers as well as colonoscopy does, but it is not clear that CT colonography is as sensitive for smaller adenomas (≥ 6 mm) or what proportion of positive CT colonography results will be false positive. We did not evaluate the clinical benefit of detecting smaller polyps in this report. In addition, uncertainties about potential radiation-related harms, the effect of extracolonic findings, and test performance in community settings still remain. Given potential harms and observed variability in test accuracy, emphasis on quality standards for implementation of any operator-dependent colorectal cancer screening tests appears prudent. Considerations about colorectal cancer screening are affected by its rapidly evolving clinical science base, by the ongoing evolution of colorectal cancer screening technologies, and by a marketplace that continues to change. Thus, frequent reconsideration of available evidence and updating of recommendations is warranted.

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APPENDIX: DETAILED METHODS

Under guidance from the USPSTF, we created and received USPSTF approval for an analytic framework and key questions adapted from the 2002 USPSTF report (130). The scope of this targeted review differed from the 2002 USPSTF report in several ways:

1. We did not update the direct evidence that standard FOBT screening is effective in improving health outcomes, except in addressing longer-term follow-up from the original trials included in the 2002 report; this evidence was considered established for the 2002 and was foundational for the last recommendation.

2. We did not update evidence on colorectal cancer screening methods not recommended after the last review (such as digital rectal examination) or omitted from this review at the workplan stage by the USPSTF because of poor test performance characteristics (such as double-contrast barium enema). A single study ($n = 580$) from the previous 2002 evidence report found that double-contrast barium enema used as a surveillance method after adenomatous polypectomy (with comparison to colonoscopy as the gold standard) showed a sensitivity of only 48% (CI, 24% to 67%) for polyps larger than 10 mm. A more recent study in a high-risk screening and diagnostic evaluation population comparing double-contrast barium enema with both optical and CT colonoscopy showed similarly low sensitivity estimates for

large polyps (131). Given its confirmed low sensitivity for the targets of screening (lesions ≥ 10 mm), double-contrast barium enema as a primary colorectal cancer screening test was removed from the review.

3. Systematic review of the adherence, acceptability, and feasibility the screening tests was not part of this updated report. Similarly, the USPSTF judged that a thorough review of cost-effectiveness analyses was beyond the scope of our review, particularly because the USPSTF was conducting a simultaneous decision analysis (24). The decision analysis focused on projected benefits to a cohort that began colorectal cancer screening at age 40 years or later for different screening strategies, different beginning and ending ages, and different intervals for rescreening after a normal test result, with varying screening test adherence (24). These 2 reports were used together by the USPSTF to make its updated recommendation on colorectal cancer screening, and they affected the scope of our updated evidence review.

Data Sources and Searches

We first searched PubMed, Database of Abstracts of Reviews of Effects, the Cochrane Database of Systematic Reviews, Institute of Medicine, National Institute for Health and Clinical Excellence, and Health Technology Assessment databases for recent systematic reviews (1999–2006) for all key questions. We also searched the National Guideline Clearinghouse, Institute of Medicine, and National Institute for Clinical Evidence Web sites for relevant reports.

For each key question, we used already synthesized literature to identify all appropriate primary studies to the extent possible, supplementing with new literature searches corresponding with the end-of-search windows of relevant good-quality systematic reviews and meta-analyses. We developed literature search strategies and terms for each key question (25), with search dates guided by existing systematic reviews (including the 2002 USPSTF report) and the development of screening technology.

We conducted 5 separate literature searches, 1 for each key question (except that we combined searching for harms for key questions 3 and 3b, but conducted 2 separate combined harms searches) in both MEDLINE and the Cochrane Central Register of Controlled Trials. Although the searches were specifically designed for a particular key question, all abstracts were reviewed for inclusion in all key questions. All searches covered reports published through January 2008. For all key questions, we supplemented literature searches by reviewing bibliographies of relevant articles (including systematic reviews) and considering studies recommended by experts during and after peer review.

For key question 2a (accuracy of flexible sigmoidoscopy and colonoscopy), we found no systematic reviews conforming to our inclusion and exclusion criteria more recent than the 2002 USPSTF review and therefore searched MEDLINE and the Cochrane Library from January 2000 through January 2008 for primary literature.

Key question 2b (test performance characteristics of newer screening tests) covered 3 tests: CT colonography, fecal immunochemical tests, and fecal DNA tests. We found 11 systematic reviews relevant to newer colorectal cancer screening tests: 6 of

CT colonography screening (27, 28, 132–135), 3 of fecal DNA screening (29, 136, 137), and 2 of fecal immunochemical screening tests (31, 37). On the basis of their use of comprehensive search strategies, recent search dates (last search date at least within the last 3 years or no older than 2005), and use of quality assessment of articles as quality indicators, we selected 3 reviews (2 of CT colonography (27, 28) and 1 of fecal DNA testing (29) to substitute for a portion of the comprehensive search strategy necessary to locate primary studies for key question 2b (26). We searched MEDLINE and the Cochrane Library for additional primary studies of CT colonography and fecal DNA testing (January 2006 through January 2008) beginning after the latest systematic review search date. We considered all studies examining CT colonography screening in average-risk patients from the selected reviews (27, 28), supplemented by studies in average-risk patients located through our literature search; as a final check, we examined the included studies in other relevant systematic reviews of CT colonography. No additional eligible studies were identified. Although we found several reviews of fecal immunochemical tests (key questions 2 and 3b), none met our standards for methods and reporting. We therefore searched MEDLINE and the Cochrane Library from 1990, when these tests began to be described, through January 2008. We checked our search results against 2 systematic reviews located during our review process to supplement with any potentially relevant studies not already identified (31, 37).

For key questions 3a and 3b (harms of screening tests), we found no systematic reviews more recent than the 2002 USPSTF review and therefore searched MEDLINE and the Cochrane Library from January 2000 through January 2008 and coded abstracts from both approaches.

Study Selection

In total, we evaluated 3948 abstracts and 490 full-text articles. Abstracts and articles were reviewed against specified inclusion criteria (see below) and required agreement of 2 reviewers. Eligible studies reported on the performance of colorectal cancer screening tests (sensitivity and specificity) or health outcomes. We excluded studies that did not address average-risk populations for colorectal cancer screening, unless an average-risk subgroup was reported. We excluded case-control studies of screening accuracy because these may overestimate sensitivity as a design-related source of bias (30), a problem recently demonstrated clearly for FOBTs (31). To avoid biases related to reference standards, we excluded studies of test accuracy that incompletely applied a valid reference standard or used an inadequate reference standard (32). For CT colonography, we considered only technologies that were compared against colonoscopy in average-risk populations, used a multidetector (not single-detector) scanner (27), and reported per-patient sensitivity and specificity.

Quality Assessment and Data Abstraction

Two investigators critically appraised and quality-rated all eligible studies by using design-specific USPSTF criteria (see below) (33) supplemented by National Institute for Clinical Excel-

lence (138) and Oxman and Guyatt (139) criteria for systematic reviews and QUADAS criteria for diagnostic accuracy studies (140). Only good-quality systematic reviews were used as sources for primary articles, and all poor-quality studies were excluded from the review. One investigator abstracted key elements of all included studies into standardized evidence tables. A second reviewer verified these data. Disagreements about data abstraction or quality appraisal were resolved by consensus. Evidence tables and excluded studies tables for each key question are available in the full report (25).

Data Synthesis and Analysis

We primarily report qualitative synthesis of the results for most key questions because of study heterogeneity. Results of key questions 2b and 3b were judged to be too heterogeneous in terms of populations, settings, and study designs for meta-analysis and were therefore qualitatively synthesized. The performance of screening tests is preferentially described per person (sensitivity and specificity), supplemented by per-polyp analysis (miss rates). Ninety-five percent CIs are reported when available.

Because of the stringency of our inclusion criteria for key question 3a (complications of endoscopy), which focused on estimates of harms in the community practice setting, the studies we included were thought to be clinically homogenous enough to allow pooling of complication rates. Meta-analysis was performed to estimate combined complication rates for major or serious bleeding, perforation, and total serious adverse events that require hospital admission or result in death, including perforation, major bleeding, severe abdominal symptoms, and cardiovascular events. Several studies reported that their patients experienced no adverse events, and therefore we used a logistic random-effects model (35, 36) to include studies without any adverse events and estimate the combined complication rates. The model was described briefly as follows.

Suppose that there are $i = 1, \dots, n$ studies and number of complications and total procedures are x_i and n_i for study i . Denote that the complication rate from each study is p_i , then we have

$$x_i \sim \text{binomial}(n_i, p_i) \quad (1)$$

$$\log\left(\frac{p_i}{1-p_i}\right) = \beta_0 + \mu_i \quad (2)$$

$$\mu_i \sim N(0, \tau^2) \quad (3)$$

where μ_i is the random effects across studies and τ^2 estimates the heterogeneity among studies on the logit scale. The combined complication rate, p_{com} , would be estimated by

$$p_{com} = \frac{\exp(\beta_0)}{1 + \exp(\beta_0)} \quad (4)$$

This model allows inclusion of studies with no adverse events, and the random effects incorporate variation among studies into the combined estimate. A P value less than 0.05 for τ^2 is considered to represent statistically significant heterogeneity.

Exploratory meta-regressions were conducted by using logistic random-effects models to examine the association of important study-level characteristics: study design; study setting by

country; and population characteristics, including age range, and indication for endoscopy with complication rate. To do this, we need to add only one more term to equation (2) of the logistic random-effects model:

$$\log\left(\frac{p_i}{1-p_i}\right) = \beta_0 + \beta_1 z_i + \mu_i \quad (5)$$

where z_i represents any study-level characteristics from study i , and the association of this study characteristic with complication rate is investigated through β_1 .

The analysis was performed by using the NLMIXED procedure in SAS software, version 9.1 (SAS Institute, Cary, North Carolina), with the code listed in **Appendix Table 3**.

Review Oversight and Peer Review

The Agency for Healthcare Research and Quality funded this work, provided project oversight, and assisted with internal and external review of the draft evidence synthesis but had no role in the design, conduct, or reporting of the review. The authors worked with 4 USPSTF liaisons at key points throughout the review process to develop and refine the analytic framework questions, set the review scope, and resolve methodologic issues during the conduct of the review. A draft of the evidence synthesis was reviewed by 8 experts, including experts in the fields of gastroenterology and radiology, and several experts who have written systematic evidence reviews on one or more aspects of colorectal cancer screening.

Appendix Table 1. Eligibility Criteria for Studies, by Key Question

Key Question	Population	Study Design	Setting	Outcomes	Other
KQ1: Impact of screening on mortality (for any screening test)	Age ≥ 40 y, average risk; recruited from primary care or primary care-comparable population	Systematic evidence review; RCT; cluster RCT; or well-designed CCT, cohort, and case-control studies	Primary care or other setting with primary care-comparable population	Mortality (all-cause or CRC-specific)	For guaiac FOBT, only updates for the trials included in the previous review were considered
KQ2a: Accuracy of flexible sigmoidoscopy and colonoscopy (community setting)	Age ≥ 40 y, average risk; recruited from primary care or primary care-comparable population	Systematic evidence review; RCT; cohort studies; systematically selected case series; screening registry	Community primary care or other setting with primary care-comparable population	Sensitivity and specificity (per person) or miss rates (per polyp); yield for CRC, advanced neoplasia, or adenomas by size	Colonoscopy as reference standard; full spectrum of disease represented; indeterminate results not excluded
KQ2b: Accuracy of newer screening tests (CT colonography, high-sensitivity FOBT, FIT, fecal DNA)	Age ≥ 40 y, average risk; recruited from primary care or primary care-comparable population	Systematic evidence review; RCT; diagnostic cohort studies; systematically selected case series; screening registry	Any	Sensitivity and specificity (per person) or miss rates (per polyp); yield for CRC, advanced neoplasia, or adenomas by size	Colonoscopy (or registry follow-up) as reference standard; full spectrum of disease represented; indeterminate results not excluded
KQ3a: Harms of flexible sigmoidoscopy and colonoscopy (community setting)	Age ≥ 40 y, average risk; recruited from primary care or primary care-comparable population	Systematic evidence review; RCT/CCT; registries; large-database observational studies, cohort studies; cross-sectional studies; systematically selected case series	Community primary care or other setting with primary care-comparable population	Adverse events requiring hospitalization, including perforation, major bleeding, severe abdominal symptoms, cardiovascular events, and/or resulting in death	Harms due to bowel preparation and sedation considered separate from serious adverse events
KQ3b: Harms of newer screening tests (CT colonography, high-sensitivity FOBT, FIT, fecal DNA)	Age ≥ 40 y, average risk	Systematic evidence review; RCT/CCT; registries; large-database observational studies, cohort studies; cross-sectional studies; systematically selected case series	Any	Adverse events requiring hospitalization, including perforation, major bleeding, severe abdominal symptoms, cardiovascular events, and/or resulting in death	Potential harms due to radiation and extracolonic findings considered separate from serious adverse events

CCT = controlled clinical trial; CRC = colorectal cancer; CT = computed tomography; FIT = fecal immunochemical test; FOBT = fecal occult blood test; KQ = key question; RCT = randomized, controlled trial.

Appendix Table 2. U.S. Preventive Services Task Force Design-Specific Quality Rating Criteria

Systematic reviews

- Criteria
 Comprehensiveness of sources considered/search strategy used
 Standard appraisal of included studies
 Validity of conclusions
 Recency and relevance are especially important for systematic reviews

RCTs and cohort studies

- Criteria
 Initial assembly of comparable groups
 For RCTs: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
 For cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
 Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)
 Important differential loss to follow-up or overall high loss to follow-up
 Measurements: equal, reliable, and valid (includes masking of outcome assessment)
 Clear definition of the interventions
 All important outcomes considered

Case-control studies

- Criteria
 Accurate ascertainment of cases
 Nonbiased selection of case-patients/controls with exclusion criteria applied equally to both
 Response rate
 Diagnostic testing procedures applied equally to each group
 Measurement of exposure accurate and applied equally to each group
 Appropriate attention to potential confounding variables

Diagnostic accuracy studies

- Criteria
 Screening test relevant, available for primary care, adequately described
 Credible reference standard used, performed regardless of test results
 Reference standard interpreted independently of screening test
 Indeterminate result handled in a reasonable manner
 Adequate spectrum of patients included in study
 Adequate sample size
 Administration of reliable screening test

RCT = randomized, controlled trial.

Appendix Table 3. SAS Code for the Meta-Analysis of Serious Complications

The following SAS code shows how to calculate the combined rate of total serious complications and examines the impact of Community_setting (1 = Yes, 0 = No) on total serious complication rate using a logistic random-effects model with PROC NL MIXED.

```
data totalSC;
input Study$      n_proc    n_serious_tot    Community_setting;
/* Community_setting = 1 if the study was conducted in a community
   setting; 0, otherwise */
datalines;
Kewenter_1996           190           3           0
Robinson_1999           1474          7           1
Thiis_1999              521           1           0
Nelson_2002             3196          18          0
Segnan_2002             775           2           0
Pickhardt_2003          1233           1           0
Cotterill_2005          324            0           1
Ko_2006                 502            8           0
Levin_2006              16318         44          1
Rathgaber_2006         12407          14          1
Ko_2007                 18271         45          1
Johnson_2008           2531           2           1
;
```

/** To obtain a combined rate of total serious complication rate */

```
proc nlmixed data = totalSC;
parms beta0 = -7.0 s2u = 0.5; /* Specify the initial value */
eta = beta0 + u;
/* Specify the model on logit scale where
beta0 will be used to estimate combined complication rate, and
u is the random-effects term across studies */
```

```
expeta = exp(eta);
p = expeta/(1+expeta);
model n_serious_tot ~ binomial(n_proc,p);
/* Specify the distribution for the number of complications */
```

```
random u ~ normal(0,s2u) subject=study;
/* Specify the distribution of random effects */
```

```
estimate "Complication Rate" exp(beta0)/(1+exp(beta0));
/* Obtain the combined complication rate using beta0 */
run;
```

/** To examine the impact of community setting on the total serious complication rate */

```
proc nlmixed data = totalSC;
parms beta0 = -7.0 s2u = 0.5 beta1 = 0.5; /* Specify the initial values */
eta = beta0 + beta1 * Community_setting + u;
/* Impact of community setting is investigated by beta1*/
```

```
expeta = exp(eta);
p = expeta/(1+expeta);
model n_serious_tot ~ binomial(n_proc,p);
/* Specify the distribution for the number of complications */
```

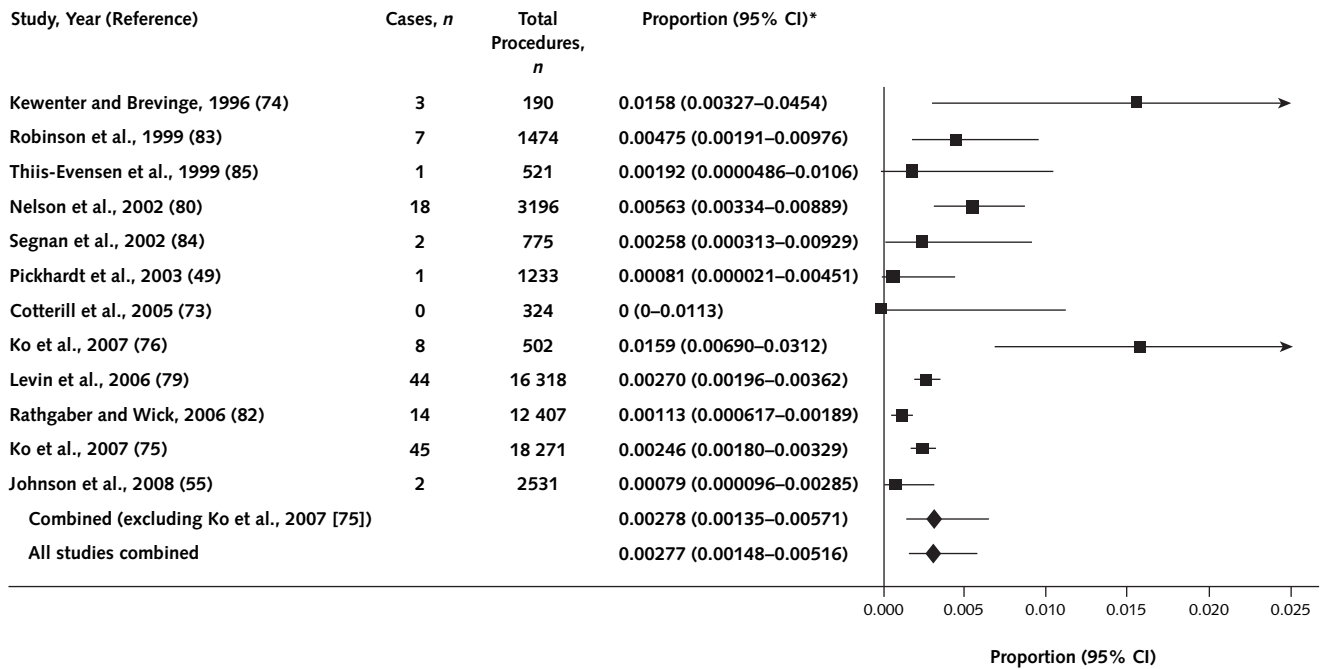
```
random u ~ normal(0,s2u) subject=study;
/* Specify the distribution of random effects */
run;
```

Appendix Table 4. Extracolonic Findings in Asymptomatic Persons Undergoing Computed Tomographic Colonography

Study, Year (Reference)	Study Design	Population, n	Follow-Up	Description of Extracolonic Findings (as Reported in Study)	Work-up of Extracolonic Findings (with Final Disposition at End of Study)
"Average-risk" populations					
Johnson et al., 2008 (55)	Prospective cohort study	2531, asymptomatic	NR	66% persons with any extracolonic finding, 16% persons had extracolonic findings that were considered to require additional evaluation or urgent care	Subsequent evaluation NR
Pickhardt et al., 2008 (70)	Prospective cohort study	2195, asymptomatic	Chart review, up to 18 mo	9.3% (204 of 2195) at least "moderate" or "high" clinical significance	7.2% (157 of 2195) recommended to have additional diagnostic evaluation, 6.1% (133 of 2195) had additional diagnostic evaluation, 2.5% (55 of 2195) with confirmed diagnosis of an unsuspected condition of at least "moderate" importance, 1.0% (22 of 2195) required surgical procedures as follow-up
Kim et al., 2007 (67)	Prospective cohort study	3120, 98% asymptomatic	NR	2.2% (70 of 3120) persons with potentially important finding (C-RADS E4), 8.5% (265 of 3120) persons with probably unimportant finding (C-RADS E3), 47.8% (1490 of 3120) persons with clinically unimportant finding (C-RADS E2)	7.7% (241 of 3120) recommended to have additional diagnostic evaluation, 0.3% (8 of 3120) persons with extracolonic cancer (treatment NR)
Pickhardt et al., 2007 (66)	Prospective cohort study	2014, presumed asymptomatic	Chart review, unclear duration	Only evaluated extracolonic GI tumors, 0.5% (10 of 2014) persons with focal extracolonic GI tumors	0.5% (10 of 2014) had further diagnostic evaluation, 0.3% (7 of 2014) required surgical resection, 0.05% (1 of 2014) required endoscopic resection; all GI tumors found to be benign
Chin et al., 2005 (68)	Prospective cohort study	432, asymptomatic	Through general practitioner, 2 y	27.3% (118 of 432) persons with any extracolonic findings, 7.4% (32 of 432) persons with clinically relevant extracolonic findings	7.4% (32 of 432) required further diagnostic evaluation: 1.8% (8 of 432) cancer or aneurysms, 5.5% (24 of 432) benign lesions; 1.4% (6 of 432) ongoing follow-up at 2 y, none required treatment at 2 y
Gluecker et al., 2003 (69)	Prospective cohort study	681, asymptomatic	Chart review, at least 12 mo	69% (469 of 681) persons with any extracolonic finding, 10% (71 of 681) persons with findings of "high" clinical importance, 27% (183 of 681) persons with findings of "moderate" clinical importance	Total 94 follow-up diagnostic procedures, 15 follow-up diagnostic procedures in 183 persons with "moderate" findings, 1% (9 of 681) needed treatment
Pickhardt et al., 2003 (49)	Prospective cohort study	1245, asymptomatic	NR	4.5% (56 of 1245) persons with findings of "high" clinical importance, >13% (169 of 1245) persons with findings of "moderate" clinical importance	0.4% (5 of 1245) extracolonic cancer (treatment NR)
Asymptomatic surveillance populations					
Ginnerup Pedersen et al., 2003 (64)	Prospective cohort study	75, asymptomatic, undergoing surveillance	Chart review, 6 mo	65% (49 of 75) persons with any extracolonic finding, 12% (9 of 75) persons with extracolonic findings warranting additional work-up	11% (8 of 75) had further diagnostic evaluation, 3% (2 of 75) had surgery because of findings or complications of work-up
Hara et al., 2000 (65)	Prospective cohort study	264, asymptomatic but 162 undergoing surveillance	Chart review, 7–22 mo	41% (109 of 264) with any extracolonic findings, 11% (30 of 264) persons with extracolonic findings of "high" clinical importance, 17% (46 of 264) persons with extracolonic findings of "moderate" clinical importance	6.8% (18 of 264) had further diagnostic evaluation, 1.9% (5 of 264) had surgery because of malignant or nonmalignant findings, 1.5% (4 of 264) required ongoing follow-up

C-RADS = Colonography Reporting and Data System; GI = gastrointestinal; NR = not reported.

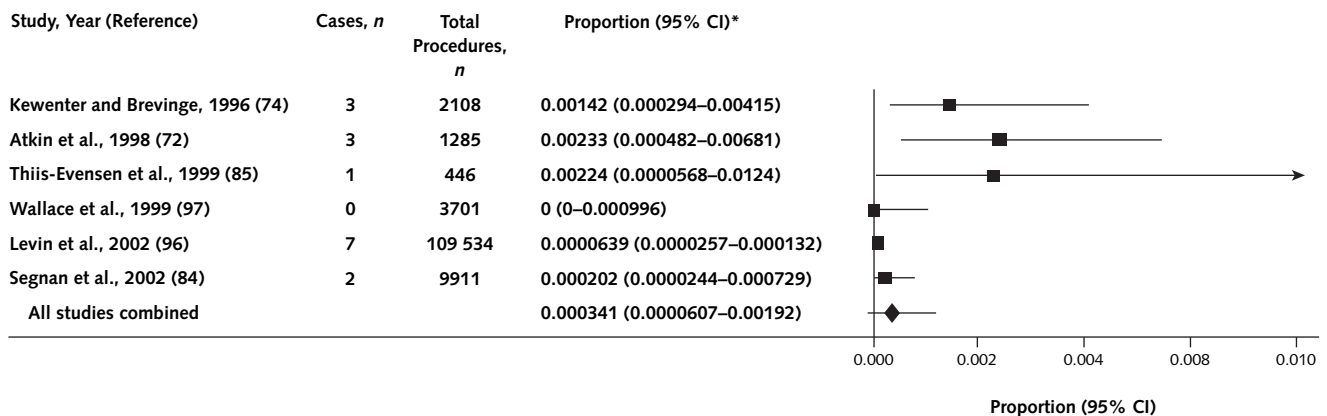
Appendix Figure 1. Proportion of total serious complications in colonoscopy studies.



Test for heterogeneity for all studies based on logit of proportions using a random-effects model ($P = 0.13$).

* 95% CIs are exact confidence intervals.

Appendix Figure 2. Proportion of total serious complications in flexible sigmoidoscopy studies.



Test for heterogeneity for all studies based on logit of proportions using a random-effects model ($P = 0.26$).

* 95% CIs are exact confidence intervals.