Supplement: Supplementary Material*

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Supplement Table: Summary of Evidence on Colorectal Cancer Screening from CTFPHC and USPSTF Guidelines and Evidence Reviews

* This supplementary material was provided by the authors to give readers further details on their article. The material was reviewed but not copyedited.

Supplement Table: Summary of Evidence on Colorectal Cancer Screening from CTFPHC and USPSTF Guidelines and Evidence Reviews

(Blue shading = data from CTFPHC and Green shading = data from USPSTF)

Screening Modalities/Frequency/ Follow-up	Sensitivity/ Specificity	CRC-specific Mortality	CRC-specific Mortality by Age Group	All-cause mortality	Harms	Other Considerations
gFOBT Hemoccult II 4 RCTs: n=313,180 (156,737 [I]; 156,443[C]); 1 RCT: 2-3 screens in 21-24 mo, f/u 9 yr; 1 RCT: 9 biennial screens; f/u 17 yr; 1 RCT 4-6 biennial screens; f/u 19.5 yr; 1 RCT annual or biennial screening; f/u 30 yr; Overall f/u: 9 to 30 yr 5 RCTs: n=419,966 217,966[I];202,000[C]; 5 RCTs: 2 to 9 biennial screens; f/u 30 yr; 1 RCT: 11 rounds of annual screens; f/u 30 yr	Median sensitivity: 47.1% (range 12.9%-75.0%) Median specificity: 96.1% (range 90.1%-98.1%);	RR, 0.82 (95% CI, 0.73 to 0.92, I^2=67%); ARR: 2,654/million (95%CI, 1,128-4,010 fewer) Number needed to screen (NNS): 377 (95% CI, 249-887), 1 modeling study: 55% reduction GRADE: Moderate 1 RCT: Annual RR, 0.68 (95% CI, 0.56-0.82) Biennial: RR, 0.78 (95% CI,0.65-0.93) Quality: good	1 RCT: Age <60y Annual: RR, 0.82 (95%CI, 0.59 to 1.14) Biennial: RR, 0.90 (95%CI, 0.65 to1.24) Ages 60-69y Annual: RR, 0.58 (95%CI,0.43 to 0.78 Biennial: RR, 0.67 (95%CI, 0.51 to 0.89) Ages >70y Annual: RR, 0.47 (95%CI, 0.26 to 0.84). Biennial: RR, 0.66 (95% CI 0.35 to 1.26) 1 RCT (Biennial): Age <60y:	4 RCTs RR, 1.00 (95% CI, 1.00 to 1.01, I^2=0%) ARR: 901/million (2,371 fewer to 4,172 more) GRADE: Low	False positives: 2 uncontrolled studies: 12.2 per 1,000 (95%CI, 10.7 to 13.7); False negatives: 3 uncontrolled studies: 5.5 per 1,000 (95%CI, 2.8 to 8.2) GRADE: Very low Overdiagnosis/Overtreatment: Not available	Benefits: Non-invasive procedure, simplicity, comfort, lack of invasiveness, ease, convenience, time, cost, and privacy Harms: Confusing instructions, discomfort, embarrassment and adverse effects associated with the FOBT Benefits: No bowel preparation, anesthesia, or transportation to a facility required 3 Modeling studies: Benefits: Life-years gained per 1000 individuals screened: HS gFOBT every year: 247 CRC deaths averted per 1000 individuals screened: 22 Harms: Complications (GI and CV events) of CRC screening and follow-up testing per 1000 individuals screened:11 Burden: Lifetime No. of colonoscopies per 1000 individuals screened: 2253

Screening Modalities/Frequency/ Follow-up	Sensitivity/ Specificity	CRC-specific Mortality	CRC-specific Mortality by Age Group	All-cause mortality	Harms	Other Considerations
			RR, 0.96 (95% CI, 0.85 to 1.10) Age 60-69 y: (Mortality Rate, 0.87 (95% CI, 0.79 to 0.97)			
FIT 1 RCT: n=192,261 (94,423 [I]; 97,838 [C]) f/u 8 yr	Median sensitivity: 81.5% (range, 53.3%-100%) Median specificity: 95.0% (range, 87.2%-96.9%) Sensitivity (range, 73%-88%); specificity (range, 91%-96%); single stool specimen; 18 FIT families; Prospective diagnostic accuracy: 6 Qualitative (n=36,808); 7 Quantitative (n=40, 134) Quality: Fair to good	RR, 0.88 (95% CI, 0.72 to 1.07); ARR, 277/million (95%CI, 631 fewer to 151 more), NNS 209 (95%CI, 41-430); 1 modeling study (Markov): 74% reduction GRADE: Moderate	NA		False-Positives: 2 uncontrolled studies: cut-point 50 ng/ml: 128.9 per 1,000 (95%CI, 124.6 to 133.2) 2 uncontrolled studies; cut-point 70-75 ng/ml: 93.7 per 1,000 (95% CI, 72.0 to 115.4) 3 uncontrolled studies; cut-point 100 ng/ml: 55.5 per 1,000 (95% CI, 22.0 to 88.9) Overall: 87.9 per 1,000 (95%CI, 52.4, 123.4); Grade: Very Low False Negatives: 1 uncontrolled study, cut-point 50 ng/ml: 1.3 per 1,000 (95%CI, 0.2 to 7.3) 2 uncontrolled studies; cut-point 70-75 ng/ml: 0.2 per 1,000 (95%CI, 0.1 to 0.2)	Harms**:** Lack of awareness; embarrassment; false positives leading to unnecessary additional follow-up tests, such as colonoscopy Benefits: No bowel preparation, anesthesia, or transportation to a facility required 3 Modeling studies: Benefits: Life-years gained per 1000 individuals screened: FIT every year: 244; CRC deaths averted per 1000 individuals screened: 22 Harms: Complications (GI and CV events) of CRC screening and follow-up testing per 1000 individuals screened: 10; Burden: Lifetime No. of colonoscopies per 1000 individuals screened: 1757

Screening Modalities/Frequency/ Follow-up	Sensitivity/ Specificity	CRC-specific Mortality	CRC-specific Mortality by Age Group	All-cause mortality	Harms	Other Considerations
					2 uncontrolled studies; cut-point 100 ng/ml: 0.83 per 1,000 (95%CI, 0.0 to 1.67) Overall: 0.69 per 1,000 (-0.02 to 1.41) Grade: Very Low	
Flexible Sigmoidoscopy 4 RCTs: 413,955 (165,333 [I]; 248,622 [C]); 3 RCTs: once only screen; 1 RCT: one screening at baseline then one at 3 or 5 yr; f/u: 6 to 11.9 yr. 4 RCTs: n=458,002; 1 or 2-time flex sig; f/u: 11 to 12 yr.	NA	RR, 0.72 (95% CI; 0.65 to 0.81) ARR, 1,176 per million (95% CI; 830 to 1,486 fewer); NNS: 850 (95% CI, 673-1205); GRADE: Moderate IRR (4 RCTs), 0.73; 95% CI, 0.66 to 0.82). Mortality benefit was limited to distal CRC (f, 0.63; 95% CI, 0.49-0.84; I^2 = 44%); GRADE: Fair (USPSTF)	55-64 y (1 RCT), RR, 0.84 (95% CI,0.67, 1.06) 65-74 y, RR, 0.65 (95% CI, 0.52 to 0.82)	4 RCTs: RR, 0.99 (95% CI, 0.97 to 1.01, I^2=35%) ARR:1,838/million (95% CI, 4,704 fewer to 1,095 more) GRADE: Low	Death: 1 uncontrolled study; No. of tests: 0.15 per 1,000 (95%CI, 0.07 to 0.32) Perforation: 3 uncontrolled studies; No. of tests: 0.03 per 1,000 (95%CI, 0.0 to 0.07) 4 uncontrolled studies: No. of patients: 0.01 per 1,000 (95%CI, 0.0 to 0.03) Overall: 0.02 per 1,000 (95%CI, -0.00 to 0.04) 16 observational studies: (n = 137, 987) pooled point estimate, 1 perforation in 10,000 procedures (95% CI, 0.4-1.4 in 10,000) Event Rate per 10,000: 0.74 (0.40-1.35) Major Bleeding (requiring hospitalization): 2 uncontrolled studies; No. of patients: 0.09 per 1,000 (95%CI, 0.04 to 0.15) 10 observational studies; 2 major bleeds in 10,000 procedures	Benefits: Physician recommendation, greater screening readiness, confidence in completing a test, and perceived pros of screening Harms: Perforation anxiety 3 Modeling studies: Benefits: Life-years gained per 1000 individuals screened: Flexible sigmoidoscopy every 5 y: 221; CRC deaths averted per 1000 individuals screened: 20; Harms: Complications (GI and CV events) of CRC screening and follow-up testing per 1000 individuals screened: 10 Burden: Lifetime No. of colonoscopies per 1000 individuals screened: 1820 Test availability has declined in the United States.

Screening Modalities/Frequency/ Follow-up	Sensitivity/ Specificity	CRC-specific Mortality	CRC-specific Mortality by Age Group	All-cause mortality	Harms	Other Considerations
					Event Rate per 10,000 Procedures: 1.8 (95% CI 0.70-4.4) Minor Bleeding (not requiring hospitalization): 2 uncontrolled studies No. tests: 0.0 per 1,000 (95%CI, 0.0 to 0.3) 5 uncontrolled studies: No. Patients: 0.50 per 1,000 (95%CI, 0.25 to 0.74) Overall: 0.36 per 1,000 (95%CI, 0.16 to 0.56) GRADE: Very Low Other SAE from 13 prospective and 5 retrospective studies: hospitalization, ED, CVD, hernia, severe pain, hypotension, syncope, PE, MI, colitis, seizure, severe diarrhea, diverticulitis, long term complications, GI issues	
Screening colonoscopy 4 prospective diagnostic accuracy studies; n= 4,821:	Sensitivity ≥10 mm adenomas: 89% (95% CI, 78%-96%) to 98% (95% CI, 74%-100%); ≥6 mm adenomas: 75% (95% CI, 63%-84%) to 93% (95% CI, 88%-96%).	Data from modeling studies only. Markov modeling study: 83% reduction MISCAN modeling study: 51.9% reduction	NA	NA	Death: 1 uncontrolled study; No. of tests: 0.3 per 1,000 (95%CI, 0.2 to 0.6) 2 uncontrolled studies; No. of patients: 0.02 per 1,000 (95%CI, 0.0 to 0.1); Overall: 0.2 per 1,000 (95%CI, -0.1 to 0.4) Perforation: 3 uncontrolled studies; No. of tests: 0.41 per 1,000 (95%CI, 0.19 to 0.62)	

Screening Modalities/Frequency/ Follow-up	Sensitivity/ Specificity	CRC-specific Mortality	CRC-specific Mortality by Age Group	All-cause mortality	Harms	Other Considerations
		SimCRC modeling study: 80.6% reduction			5 uncontrolled studies; No. per patients: 0.53 per 1,000 (95%CI, 0.37 to 0.69) Overall: 0.49 per 1,000 (95%CI, 0.36 to 0.62). GRADE: Very Low 26 observational studies; (n = 3,414,108); Event Rate per 10,000 procedures: 3.6 (95%CI, 2.4-5.4); 4 perforations/10,000 procedures (95% CI, 2-5/10,000) Major Bleeding (requiring hospitalization): 1 uncontrolled study; No. of tests: 0.0 per 1,000 (95%CI, 0.0 to 11.7) 3 uncontrolled studies: No. of patients: 1.08 per 1,000 (95%CI, 0.85 to 1.32) Overall: 1.08 per 1,000 (95%CI, 0.8 to 1.3) 22 studies: Event Rate per 10,000 procedures, 8.2 (95% CI, 5.0-13.5) 8 major bleeds/10, 000 procedures (95% CI, 5-14/10 000) 29 Prospective studies: 8,389 SAEs, more invasive, procedural complications, harms of overdiagnosis and overtreatment of smaller lesions (ie, <10 mm), operator dependent, aggressive bowel preparation Minor Bleeding (not requiring hospitalization): 1 uncontrolled	

Screening Modalities/Frequency/ Follow-up	Sensitivity/ Specificity	CRC-specific Mortality	CRC-specific Mortality by Age Group	All-cause mortality	Harms	Other Considerations
					study: No. of tests: 2.68 per 1,000 (95%CI, 2.21 to 3.25) 4 uncontrolled studies; No. of patients: 0.84 per 1,000 (95%CI, 0.0 to 2.0) Overall: 1.65 per 1,000 (95%CI, -0.05 to 3.3) GRADE: Very Low	
Screening CT Colonoscopy (CTC) 9 Prospective diagnostic accuracy studies; n=6,497	Sensitivity ≥10 mm adenomas 67% (95% CI, 45%-84%) to 94% (95% CI, 84%-98%), and specificity ranged from 98% (95% CI, 96%-99%) to 96% (95% CI, 95%-97%). Sensitivity ≥ 6 mm adenomas 73% (95% CI, 58%-84%) to 98% (95% CI, 91%-100%); Specificity from 89% (95% CI, 84%-93%) to 91% (95% CI, 88%-93%)	NA	NA	NA	**Perforation:** 1 uncontrolled study; No. of patients: 0.0 per 1,000 (95%CI, 0.0 to 0.3). GRADE: Very Low 15 observational studies: (n= 75 354); Risk of perforation for screening CTC <2/10,000 examinations **Ionizing radiation:** 4 diagnostic accuracy studies Exposure to low-dose ionizing radiation 1-7 mSv Incidental extracolonic findings, SAEs: 21 Prospective and retrospective studies: (n = 38,293);identification in 27% to 69% of examinations; 5%-37% necessitate diagnostic follow-up; ≤3% required any type of definitive treatment 15 observational studies: 104 SAEs, low rate of bowel perforation from insufflation, operator dependent, unclear evidence about cumulative	Benefits: Non-invasiveness, avoidance of sedation/anesthesia, ability to drive after the test, avoidance of normal colonoscopy, risks, identifying abnormalities outside the colon, and mild or no discomfort Harms: Abdominal pain, discomfort, diarrhea, flatulence, CO2 insufflation, the breath hold, loss of dignity, pain, feelings of disrespect, mild bloating and moderate cramping

Screening Modalities/Frequency/ Follow-up	Sensitivity/ Specificity	CRC-specific Mortality	CRC-specific Mortality by Age Group	All-cause mortality	Harms	Other Considerations
					radiation exposure to small excess risk of cancer Overall quality: fair Harms: There is insufficient evidence about the potential harms of associated extracolonic findings, which are common. Serious events: Prospective Studies (11);Retrospective Studies (4): Collapse (1/982); MI (1/982); CVA (1/982); Hospitalizations (2/2531); Severe nausea and vomiting (1/2531); Major bleeding events (4); Self-limiting vasovagal episodes: (63) Extra-colonic findings: additional diagnostic evaluation; surgical resection; additional diagnostic imaging; cancers etc. 3 Modeling studies: Benefits: Life-years gained per 1000 individuals screened: CT colonography every 5 y : 248 Colorectal cancer deaths averted per 1000 individuals screened: 22 Harms: Complications (gastrointestinal and cardiovascular events) of colorectal cancer screening and follow-up testing per 1000 individuals screened: 10 Burden: Lifetime No. of colonoscopies per 1000 individuals screened: 1743	

ARR: Absolute risk reduction; CT: Computed tomography; CV: Cardiovascular; CVA: Cerebrovascular accident; ED: Emergency department; FIT: Fecal immunochemical test; FP: False positive; FN: False negative; FS: Flexible sigmoidoscopy; F/U: Follow-up; gFOBT: Guaiac Fecal Occult Blood Test; GI: gastroinstential; HSgFOBT: High-sensitivity Guaiac Fecal Occult Blood Test; IRR: Incidence rate ratio; MI: myocardial infarction; NNS: Number needed to screen; PE: Pulmonary embolism; RCT: Randomized controlled trial; RR: Relative risk; SAE: Serious adverse event