

Screening for Colorectal Cancer

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Section I. Purpose and Background

Colorectal cancer is the second most common cause of cancer mortality and is the third most common diagnosed cancer affecting both men and women.¹ The burden of colorectal cancer varies across Canada² and overall, 9200 deaths were estimated in Canada for 2012, representing 12% of all cancer deaths.¹ In 2012, 23,300 new cases of colorectal cancer were estimated (49/100,000).

Organized screening programs have been implemented in some Canadian provinces and others are undergoing pilot programs. (Appendix I) The programs screen using guaiac fecal occult blood testing (gFOBT) or immunochemical fecal occult blood testing (iFOBT or FIT [fecal immunochemical test]) with colonoscopy follow-up for positive screening results. Other tests used for screening include flexible sigmoidoscopy and colonoscopy. Each of the screening tests has limitations, such as the possibility of false positives and negatives or sedation and bowel preparation requirements.³ While the sensitivity of colonoscopy is higher than FOBT, colonoscopy can result in serious harms such as bowel perforation.⁴

This protocol describes the process the Canadian Task Force on Preventive Health Care (CTFPHC) will use to develop a systematic review to inform guidance on screening for colorectal cancer. The lack of current Canadian guidance, the variability in the provincial screening programs (such as tests used and frequency), and the recent publication of RCTs on screening with flexible sigmoidoscopy were the basis for selecting this topic for guideline development. A CTFPHC guideline will include recommendations on what populations are appropriate for screening, which screening test is most appropriate, and the interval and age to start and stop screening.

Section II. Previous CTFPHC Recommendations and Recommendations from Other Guideline Developers

The previous recommendations on colorectal cancer screening from the CTFPHC were published in 2001⁵ and recommended screening for asymptomatic adults over 50 years of age with flexible sigmoidoscopy or FOBT. The US Preventive Services Task Force (USPSTF) 2008 guidelines recommended screening for adults 50 to 70 years of age with FOBT, sigmoidoscopy, or colonoscopy.⁶ The 2011 Scottish International Guidelines Network (SIGN) guidelines recommended population screening with gFOBT.⁷ A summary of these recommendations is provided in Appendix II. Provincial screening guidelines are summarized in Appendix I. These programs vary in the population eligible for screening (including age range), the screening test, and the screening interval, although the majority recommends screening using FOBT every 2 years for ages 50 to 74 years.

Section III. Scan of New Evidence since Previous Recommendation

Since the previous CTFPHC and USPSTF recommendations were published, randomized controlled trials on the effects of screening with FOBT and flexible sigmoidoscopy on mortality have been published. In addition, there may be information published on newer screening tests such as CT colonography and fecal DNA testing.

Section IV. Review Approach

This review will be conducted by the Evidence Review and Synthesis Centre (ERSC) at McMaster University who will conduct a systematic literature search for randomized controlled trials to address

screening effectiveness, all study types to address test characteristics and harms of screening, and a search to address the contextual questions. Screening studies for possible inclusion will be done by two people independently. At the title and abstract level, any citation that is selected for inclusion by either reviewer will move to full text review. At that level any disagreement will be discussed between reviewers and a third party will resolve further disagreements. Risk of bias will be assessed using the Cochrane risk of bias framework with decisions made by one reviewer and a second reviewer verifying those decisions. In the case of a disagreement that cannot be resolved a third party will be asked to make a decision. The GRADE system will be used to assess the strength and the quality of evidence using GRADEPro software. Individual study quality will be assessed for risk of bias due to limitations in design, indirectness, inconsistency of findings, imprecision, publication bias and other potential bias such as industry funding. Meta-analysis will be conducted where appropriate. The evidence review and recommendation statement will be peer reviewed by individual reviewers as well as relevant organizations. In the absence of mortality data for any of the screening tests, the data identified for key question 2 may influence the recommendations.

Population and Subgroups

This guideline will focus on adults who are not at high risk for colorectal cancer. Populations at high risk of colorectal cancer (Table 1) will be excluded, such as those with prior colorectal cancer or polyps, with symptoms suggesting underlying colorectal cancer, or familial adenomatous polyposis and hereditary non-polyposis colorectal cancer.

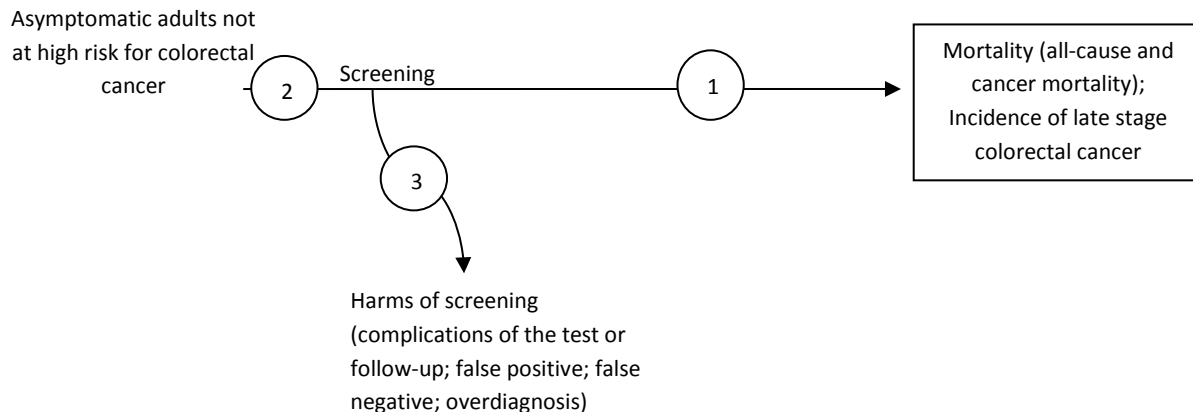
Within the population covered by the guideline, separate recommendations may be developed for those at lower and higher risk, if results of the literature search suggest that this is necessary.

Characteristics that may increase risk within the population covered by the guideline include older age (age range for screening to be assessed), family history of colorectal cancer, obesity (BMI $\geq 30\text{kg/m}^2$), high alcohol consumption (>2 drinks/day for men and >1 /day for women⁸⁻¹⁰), Ashkenazi Jewish ethnicity^{8,9,11,12}, physical inactivity,^{8,10-12} smoking,^{1,8-10,12} and low fibre diet.^{8-10,12} Other such characteristics identified during the literature search will be included.

Subgroup analysis will be conducted on the various risk populations if appropriate. In addition, subgroup analysis may be conducted based on the quality of the evidence and those studies assessed at higher quality of evidence will be used to develop the recommendation statement.

Analytic Framework and Key Questions

The following key and contextual questions and analytical framework will be addressed in the review and will be used to develop recommendations for screening for colorectal cancer.



KEY QUESTIONS

1. What is the effectiveness of each colorectal cancer screening testⁱ to reduce colorectal cancer-specific mortality, all-cause mortality, or incidence of late stage colorectal cancer in asymptomatic adults who are not at high risk for colorectal cancerⁱⁱ?
 - a. What is the optimal age to start and stop screening and the optimal screening interval of asymptomatic adults not at high risk for colorectal cancer?
 - b. What is the evidence that the clinical benefits of screening differ for the various screening tests, or by subgroups that may influence the underlying risk of colorectal cancerⁱⁱⁱ?
2. What is the sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios of the colorectal cancer screening tests to detect colorectal cancer?
3. What is the incidence of harms^{iv} of screening for colorectal cancer in adults not at high risk for colorectal cancer? What is the evidence that the harms of screening differ for the various screening tests or by subgroups that may influence the underlying risk of colorectal cancer?

CONTEXTUAL QUESTIONS

1. What are the patient preferences and values for screening for colorectal cancer?
2. What is the evidence for a higher burden of disease, a differential treatment response, differential performance, or barriers to implementation of colorectal cancer screening in the Aboriginal population, other ethnic populations, rural or remote populations, women, or the elderly?
3. What risk assessment tools are identified in the literature to assess the risk of colorectal cancer?
4. What are the cost-effectiveness and resource implications of screening for colorectal cancer?

ⁱ Screening tests include colonoscopy, flexible sigmoidoscopy, CT colonography, gFOBT, FIT, fecal DNA testing, and other screening tests currently in use identified in the literature search

ⁱⁱ Populations at high risk of colorectal cancer (Table 1) will be excluded, such as those with prior colorectal cancer or polyps, signs/symptoms suggesting underlying colorectal cancer, familial adenomatous polyposis, or hereditary non-polyposis colorectal cancer.

ⁱⁱⁱ Characteristics that may increase risk within the population covered by the guideline include older age, obesity, Ashkenazi Jewish ethnicity, high alcohol consumption, physical inactivity, smoking, and low fibre diet

^{iv} Complications of the screening test or follow-up test, false positive, false negative, overdiagnosis

Literature Search

The previous CTFPHC guidelines from 1994¹³ and 2001⁵ searched from 1966 and the earliest RCT identified was from 1980. The USPSTF guideline from 2008 included studies from 1996. The USPSTF guidelines from 2008 were based on a partial update of their 2002 guidelines. In particular, they did not update the direct evidence on standard FOBT screening except for studies included in 2002. In addition, they did not update evidence on screening methods not recommended by the 2002 review. With that in mind, in this review MEDLINE, the Cochrane Library, and EMBASE will be searched for relevant English and French language articles from September 2000 (the end date of the USPSTF search for the 2002 guidelines) to present in order to capture any relevant studies not included in the 2008 guidelines. The detailed search strategy is reported in Appendix III.

Inclusion and Exclusion Criteria

Table 1 reports the inclusion and exclusion criteria that will be used to select studies for this review. The incidence of polyps is excluded as an outcome. It is not a good surrogate outcome for the following reasons: (1) many polyps will never develop into cancer and it may take years for other polyps to become cancerous;¹⁴ (2) there are different types and sizes of polyps; and (3) the number, type, and size of polyps are all factors in progression to cancer.^{14,15} We also excluded the overall incidence of colorectal cancer as a relevant outcome, since simply detecting cancer (without considering the associated outcomes) may not be clinically relevant. However, given the burden of morbidity associated with advanced cancer, reduction in incidence of late stage (Stage III or IV or Duke's C or D¹⁶) colorectal cancer was included as a clinically relevant outcome for key question 1. All stages are included for key question 2 examining test characteristics.

TABLE 1. INCLUSION AND EXCLUSION CRITERIA		
	Inclusion	Exclusion
P	Asymptomatic adults 18 years and older who are not at high risk of colorectal cancer. (Leave in: first degree relatives, obesity, HPV , HIV, CKD, diabetes)	High risk adults, defined as those with with FAP, HNPCC, history of IBD, colitis, Crohn's, personal history of polyps (any polyp) or colorectal cancer; patients with symptoms suggesting underlying colorectal cancer (such as rectal bleeding or iron deficiency anemia), known genetic mutations associated with colorectal cancer risk

TABLE 1. INCLUSION AND EXCLUSION CRITERIA

	Inclusion	Exclusion
I	Screening with colonoscopy, CT colonography, gFOBT, iFOBT, FS, BE, DRE, fecal DNA, serum DNA, other identified tests currently being used for screening in Canada Such as: peptide binding, phage display, tests for genetic mutations as screening tests	Surveillance, follow-up, case-finding Tests under development or in research phase Risk calculators – who is at risk for CRC and should be screened (is contextual question and will be picked up later) Strategies to improve uptake (in HCPs and in public) Patient risk factors and patient factors re who gets screened Bowel prep Air versus water insufflation Nurse versus gastroenterologists; Florescence/staining versus no florescence/staining Different types of equipment for colonoscopy- cap, flexible versus fixed head, computer assisted read
C	Compare between the tests, no screening	
O	Mortality (all-cause and colorectal cancer-specific) Incidence of late stage colorectal cancer (stage III or IV; or Duke's C or D) Sensitivity, specificity, negative and positive predictive value for detection of any stage colorectal cancer for those tests with evidence for screening effectiveness or those in use in Canada Harms: complications (bleeding [not requiring hospitalization and requiring hospitalization], perforation, death) of the test or follow-up test, false positive, false negative, overdiagnosis	Incidence or prevalence of polyps, adenomatous polyps, adenomas Exclude treatment of harms of test (eg treatment of perforation).
S	Primary care, including referrals for tests by primary care practitioners	Specialist settings
Study design	RCTs for KQ1; RCTs, cohort studies and case controlled studies KQ2 and KQ3	Uncontrolled observational studies, ecological studies

FAP = familial adenomatous polyposis; HNPCC = hereditary nonpolyposis colorectal cancer; IBD = inflammatory bowel disease; CT = computed tomography; gFOBT = guaiac fecal occult blood testing; iFOBT = immunochemical FOBT; FS = flexible sigmoidoscopy; BE = barium enema; DRE = digital rectal exam; RCTs = randomized controlled trial; KQ = key question

Section V. Planned Schedule and Timeline

Timelines

- Draft protocol: March 2013
- Final protocol: May 2013
- Draft evidence review: March 2014

- Final evidence review: July 2014
- Draft recommendation statement: July 2014
- Published recommendation statement: February 2015

A targeted literature search will be conducted six to eight weeks prior to publication for relevant randomized controlled trials to ensure that the recommendations include all relevant data. In addition, authors of key studies will be contacted to determine if they are planning to release new data from their trials in the immediate future.

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Appendix I: Provincial Screening Guidelines¹⁷

Province	Program launch date	Population	Screening test	Follow up test
NS	Colon Cancer Prevention Program ¹⁸	50-74y; no family history or symptoms	FIT every two years	Colonoscopy
NB	Planning phase ¹⁷	N/A	FIT every 2 years	Colonoscopy
PE	Launched April 2011 ¹⁹	50-74y with no significant family history (no first degree relatives with CRC diagnosed less than 60 years old, or two or more second degree relatives with CRC) or personal history of CRC. No family history of FAP or HNPCC. No history of IBD; no FOBT in the last two years or CS in the last 10 years.	FIT every two years	Colonoscopy
NL	Program launched July 2012 in one region; phased launch planned ²⁰	50-74y	FIT every two years	Colonoscopy
QC	Planning stages ²¹	50-74y	FIT every 2 years	Colonoscopy
ON	ColonCancerCheck program 2008 ²²	50-74y; average risk	gFOBT every two years	Colonoscopy
MB	ColonCheck ²³	Asymptomatic adults 50-74y no symptoms or personal history	gFOBT every two years	Colonoscopy
SK	Screening Program for Colorectal Cancer ²⁴	50-74y	FIT every two years	Colonoscopy
AB	TOP guidelines, 2008 ²⁵	Average risk (50-74); No screening for low risk (under 50 years)	gFOBT every 1-2 yrs OR FS every 5 yrs OR DCBE every 5 yrs OR CS every 10 years	Colonoscopy
BC	Colon Check 2012 ²⁶	50-74y; asymptomatic (include those with family history)	FIT every two years	Colonoscopy
YK	No organized program ¹⁷	N/A	N/A	N/A
NT	No organized program	FIT offered to average risk adults	N/A	N/A
NU	No organized program ¹⁷	N/A	N/A	N/A

N/A = not applicable; FOBT = fecal occult blood test; FIT = fecal immunochemical test (immunochemical FOBT); FS = flexible sigmoidoscopy; CS = colonoscopy; DCBE = double contrast barium enema

Appendix II: Details of relevant recommendations for general population screening

Organization (year) Guideline title	Screening test	Age of screening	Screening interval
SIGN (2011) ⁷ Diagnosis and management of colorectal cancer: A national clinical guideline	gFOBT	Not specified	Not specified
USPSTF (2008) ^{4,6} Screening for colorectal cancer	FOBT or sigmoidoscopy or colonoscopy	50-75 y	Annual FOBT; sigmoidoscopy every 5 years; colonoscopy every 10 years
CTFPHC (2001) ^{5,27} Colorectal cancer screening: recommendation statement from the Canadian Task Force on Preventive Health Care	FOBT or flexible sigmoidoscopy	> 50 years	Annual or biennial FOBT; interval not specified for sigmoidoscopy

gFOBT = guaiac fecal occult blood test

Appendix III: Detailed search strategy

Colorectal Cancer Screening Main Search - MEDLINE

1. Colonoscopy/
2. Colonoscop\$.ti, ab
3. Sigmoidoscopy/
4. Sigmoidoscop\$.ti, ab
5. Colonography, Computed Tomographic/
6. Colonograph\$.ti, ab
7. Virtual colonoscop\$.ti, ab
8. CT colonograph\$.ti, ab
9. Computed tomographic colonograph\$.ti, ab
10. Occult blood/
11. fobt\$.ti, ab
12. ifobt\$.ti, ab
13. Fecal occult blood.ti, ab
14. Faecal occult blood.ti, ab
15. ((fecal or faecal) and immunochemical).ti, ab
16. ((fecal or faecal) and dna).ti, ab
17. Instant-view.ti, ab
18. FlexSure OBT.ti, ab
19. immoCARE.ti, ab
20. HemeSelect.ti, ab
21. MonoHaem.ti, ab
22. Hemoccult.ti, ab
23. ColoScreen.ti, ab
24. Seracult.ti, ab
25. HM-Jack.ti, ab
26. OcculTech.ti, ab
27. PreGen-Plus.ti, ab
28. QuickVue.ti, ab
29. HemoQuant.ti, ab
30. Guaiac/du
31. Stool screening.ti, ab
32. Stool test\$.ti, ab
33. Stool based test\$.ti, ab
34. Feces/
35. Or/1-34 **Colorectal screening tests**
36. Mass Screening/
37. (Screen\$ or diagnos\$).ti, ab
38. 36 or 37 **Screening hedge**
39. Randomized controlled trial.pt

40. randomized.pt
41. placebo.mp
42. Or/39-41 **RCT Hedge**
43. Colorectal neoplasms/
44. Colonic neoplasms/
45. Sigmoid neoplasms
46. Anus neoplasms
47. Anal Gland neoplasms/
48. Rectal neoplasms/
49. Adenomatous polyps/
50. Intestinal polyps/
51. Colonic polyps/
52. Colorectal cancer.ti, ab
53. Colorectal neoplas\$.ti, ab
54. Colon cancer.ti, ab
55. Colon neoplas\$.ti, ab
56. Or/43-55 **colorectal cancer**
57. 38 and 56 **screening and colorectal cancer**
58. 35 or 57 **colorectal cancer AND screening OR colorectal cancer screening tests**
59. 58 and 42 **all = colorectal cancer AND screening OR colorectal cancer tests AND RCT KQ1**
60. Sensitiv:.mp
61. Predictive value:.mp
62. Accurac:.tw
63. Or/60-62 **Diagnostic filter**
64. 58 and 63 **all and diagnostic filter KQ2**
65. Colonoscopy/ae
66. Colonoscopy/mo
67. Sigmoidoscopy/ae
68. Sigmoidoscopy/mo
69. Colonography, computed tomographic/ae
70. Colonography, computed tomographic/mo
71. (adverse effects or mortality).fs
72. Complication\$.ti
73. Adverse\$.ti
74. Harm\$.ti
75. Harm.ti, ab
76. Harms.ti, ab
77. Harmed.ti, ab
78. Harmful.ti, ab
79. Adverse effects.fs
80. Complication\$.ti, ab
81. Side effect\$.ti, ab

82. Adverse effect\$.ti, ab
83. Adverse event\$.ti, ab
84. Adverse reaction\$.ti, ab
85. Death
86. Death\$.ti, ab
87. Mortality.fs
88. Mortalit\$.ti, ab
89. Perforat\$.ti, ab
90. Intestinal perforation
91. Chemical colitis.ti, ab
92. Colitis/ci
93. Or/65-92 **harms**
94. 58 and 93 **colorectal cancer AND screening OR screening tests and harms KQ3**
95. Exp cohort studies
96. (cohort adj (study or studies)).tw
97. Cohort analy\$.tw
98. Epidemiologic studies
99. (observational adj (study or studies)).tw
100. Longitudinal.tw
101. Cross-sectional.tw
102. Cross-sectional studies/
103. Or/95-102 **Cohort hedge**
104. 42 or 103 **RCT and Cohort**
105. 94 and 104 **KQ3**
106. Animals
107. Humans
108. 106 not (106 and 107)
109. 59 or 64 or 105 **KQ1,2,3**
110. 109 not 108 **no animal studies**
111. Limit 110 to (English or French)
112. Limit 111 to yr="2000-Current"

Contextual Question Hedges – to be added to Line 58 (In OVID, the RCT Hedge is removed)

CQ1

70. *"patient acceptance of health care"/ or *patient compliance/ or *patient participation/ or patient satisfaction/ or patient preference/ or *treatment refusal/
71. (consumer? adj3 (acceptance or preference? or satisfaction or experience?)).tw
72. (patient? adj3 (acceptance or preference? or satisfaction or experience?)).tw
73. willingness to pay.tw
74. ((conjoint or contingent) adj3 (valuation or analysis)).tw
75. Or/70-74

CQ2

- 76. "Process Assessment (Health Care)"/ or Quality Indicators, Health Care/ or Quality Assurance, Health Care/
- 77. Benchmarking/
- 78. (performance adj2 (indicators or measures)).tw.
- 79. Or/76-78

CQ3

- 80. exp continental population groups/
- 81. exp Ethnic Groups/
- 82. indians, north american/ or inuits/
- 83. first nations.tw.
- 84. (aboriginal? and canada).tw.
- 85. native canadians.tw.
- 86. (immigran* or new canadians).tw.
- 87. ((African or Asian or Indo or Columbian or Spanish or Chinese) adj2 Canadian?).mp.
- 88. Rural Population/
- 89. (rural adj (population? or area? or region?)).tw.
- 90. Rural Health/ or Rural Health Services/
- 91. Healthcare Disparities/
- 92. Social Class/
- 93. poverty/
- 94. socioeconomic.tw.
- 95. Socioeconomic Factors/
- 96. (poor or disadvantaged or poverty or social status).tw.
- 97. exp homeless persons/ or vulnerable populations/
- 98. exp "Costs and Cost Analysis"/
- 99. (cost or costs).tw.
- 100. *"patient acceptance of health care"/ or *patient compliance/ or *patient participation/ or patient satisfaction/ or patient preference/ or *treatment refusal/
- 101. (women? adj3 (acceptance or preference? or satisfaction or experience?)).tw.
- 102. (consumer? adj3 (acceptance or preference? or satisfaction or experience?)).tw.
- 103. (patient? adj3 (acceptance or preference? or satisfaction or experience?)).tw.
- 104. willingness to pay.tw.
- 105. ((conjoint or contingent) adj3 (valuation or analysis)).tw.
- 106. exp Canada/
- 107. (Canada or Canadian or Ontario or British Columbia or Alberta or Saskatchewan or Manitoba or Quebec or Nova Scotia or Prince Edward Island or Newfoundland or New Brunswick or Yukon or Northwest Territories or Nunavut).tw.
- 108. Or/80-107

CQ4

- 109. Risk prediction tool*.mp
- 110. *risk assessment
- 111. (risk assessment or risk stratification or risk prediction).tw
- 112. (risk adj3 (prediction or tool Or score Or scale)).tw
- 113. Or/109-112

CQ5

- 114. Exp *"Costs and Cost Analysis"/
- 115. (cost or econom*).ti
- 116. Or/114-115
- 117. Comment.pt
- 118. Editorial.pt
- 119. Letter.pt
- 120. Or/117-119
- 121. 58 and 75 **CQ1**
- 122. 58 and 79 **CQ2**
- 123. 58 and 108 **CQ3**
- 124. 58 and 113 **CQ4**
- 125. 58 and 120 **CQ5**
- 126. 121 or 122 or 123 or 124 or 125 **ALL CQ**
- 127. 126 not 120 **without comments, editorials, or letters**
- 128. Animals
- 129. Humans
- 130. 128 not (128 and 129)
- 131. 127 not 130 **without animals**
- 132. Limit 131 to (English or French)