

# CLINICAL PRACTICE GUIDELINE

## Clinical Practice Guideline on Screening for Colorectal Cancer in Individuals With a Family History of Nonhereditary Colorectal Cancer or Adenoma: The Canadian Association of Gastroenterology Banff Consensus



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**BACKGROUND & AIMS:** A family history (FH) of colorectal cancer (CRC) increases the risk of developing CRC. These consensus recommendations developed by the Canadian Association of Gastroenterology and endorsed by the American Gastroenterological Association, aim to provide guidance on screening these high-risk individuals. **METHODS:** Multiple parallel systematic review streams, informed by 10 literature searches, assembled evidence on 5 principal questions around the effect of an FH of CRC or adenomas on the risk of CRC, the age to initiate screening, and the optimal tests and testing intervals. The GRADE (Grading of Recommendation Assessment, Development and Evaluation) approach was used to develop the recommendations. **RESULTS:** Based on the evidence, the Consensus Group was able to strongly recommend CRC screening for all individuals with an FH of CRC or documented adenoma. However, because most of the evidence was very-low quality, the majority of the remaining statements were conditional (“we suggest”). Colonoscopy is suggested (recommended in individuals with  $\geq 2$  first-degree relatives [FDRs]), with fecal immunochemical test as an alternative. The elevated risk associated with an FH of  $\geq 1$  FDRs with CRC or documented advanced adenoma suggests initiating screening at a younger age (eg, 40–50 years or 10 years younger than age of diagnosis of FDR). In addition, a shorter interval of every 5 years between screening tests was suggested for individuals with  $\geq 2$  FDRs, and every 5–10 years for those with FH of 1 FDR with CRC or documented advanced adenoma compared to average-risk individuals. Choosing screening parameters for an individual patient should consider the age of the affected FDR and local resources. It is suggested that individuals with an FH of  $\geq 1$  second-degree relatives only, or of nonadvanced adenoma or polyp of unknown histology, be screened according to average-risk guidelines. **CONCLUSIONS:** The increased risk of CRC associated with an FH of CRC or advanced adenoma warrants

more intense screening for CRC. Well-designed prospective studies are needed in order to make definitive evidence-based recommendations about the age to commence screening and appropriate interval between screening tests.

**Keywords:** Adenoma; Cancer; Colonoscopy; Colorectal; FOBT; Neoplasms; Polyp; Screening.

### Executive Summary

Colorectal cancer (CRC) is the second leading cause of cancer deaths in Canada and the United States. A positive family history (FH) significantly increases the risk of developing CRC, and screening programs can substantially reduce CRC incidence and mortality. These consensus recommendations were developed by the Canadian Association of Gastroenterology (CAG), with US and Canadian experts, and endorsed by the American Gastroenterological Association. The purpose was to systematically and critically review the literature and provide specific recommendations

\*Authors share co-first authorship.

**Abbreviations used in this paper:** CAG, Canadian Association of Gastroenterology; CI, confidence interval; CPG, clinical practice guideline; CRC, colorectal cancer; EtD, Evidence-to-Decision; FDR, first-degree relative; FH, family history; FIT, fecal immunochemical test; FS, flexible sigmoidoscopy; gFOBT, guaiac fecal occult blood test; GRADE, Grading of Recommendation Assessment, Development and Evaluation; HR, hazard ratio; MA, meta-analysis; OR, odds ratio; QoE, quality of evidence; RCT, randomized controlled trial; RR, relative risk; SDR, second-degree relative; SR, systematic review.

Most current article

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0016-5085/\$36.00

<https://doi.org/10.1053/j.gastro.2018.08.017>

for CRC screening of individuals with an FH of nonhereditary CRC or adenoma.

This is the first guideline to use systematic reviews and the GRADE (Grading of Recommendation Assessment, Development and Evaluation) approach to make recommendations for screening for CRC in this high-risk population. Multiple parallel systematic review streams, informed by 10 literature searches, assembled evidence on 5 principal questions: (1) effect of an FH of CRC on an individual's risk of CRC, (2) effect of an FH of adenoma on an individual's risk of CRC, (3) age at which screening should begin, (4) optimal screening tests, and (5) optimal testing intervals for individuals with an FH of CRC or adenoma. The GRADE approach was used to assess the quality of evidence. Questions were developed through an iterative online platform, and then statements were developed and voted on by a group of specialists.

Consensus was reached on 19 statements addressing 5 main patient risk categories, including individuals with 2 or more first-degree relative (FDRs) with CRC, 1 FDR with CRC, 1 or more FDRs with advanced adenoma, 1 or more second-degree relatives (SDRs) with CRC, and 1 or more FDR with any non-advanced adenoma (Table 1).

Because of the lack of high-quality data, the majority of statements are conditional recommendations ("we suggest"). However, based on moderate-quality evidence, the Consensus Group is able to strongly recommend CRC screening over no screening for all individuals with an FH of CRC or documented adenoma. In addition, despite very-low-quality evidence, colonoscopy is recommended in individuals with 2 or more FDRs with CRC, because of the high-risk of life-threatening negative consequences of missed lesions.

Based on available data and consensus, Table 2 provides a concise summary of the preferred and second-choice screening tests, the age at which screening should begin, and the interval for screening according to the level of elevated CRC risk for each patient subgroup. For individual at highest risk (2 or more FDRs with a history of CRC), we recommend screening with colonoscopy, which we suggest begin at age 40–50 years or 10 years younger than the age of diagnosis of the FDR (whichever is earlier), at an interval of every 5 years. For individuals with 1 FDR with a history of CRC or advanced adenoma, we suggest commencing CRC screening at age 40–50 years or 10 years younger than the age of diagnosis of the FDR (whichever is earlier), at an interval of every 5–10 years. For those with an FH of CRC, colonoscopy is suggested with fecal immunochemical test (FIT) as an alternative, while both tests are suggested options for those with an FH of advanced adenoma. Finally, it is suggested that individuals with an FH of 1 or more SDRs only, or of nonadvanced adenoma or polyp of unknown histology be screened according to average-risk guidelines.

Except for the statements for those at the highest risk, age ranges are provided. The relationship between the age at which an affected FDR was diagnosed with CRC and an individual's risk of developing CRC is difficult to define. The evidence shows that the risk falls on a continuum, and that there is no clearly defined age above or below which a clear

inflection in risk can be recognized. The Consensus Group carefully considered the issue of recommending a range of years, acknowledging that some clinicians and programs may wish for greater precision. However, the evidence in cases where a range was recommended does not support a specific age point. Definitive statements in these circumstances are misleading and imply a degree of certainty that does not currently exist. Furthermore, specifying a range allows some flexibility, including consideration of the age of the affected FDR and local resources, and underscores the need for further data, which will hopefully lead to greater clarity in the future.

The Consensus Group acknowledged that heritable cancers tend to occur at an earlier age and that this heritable risk decreases with advancing age of the diagnosis of the CRC in the FDR. That being the case, the age of the affected relative should be considered when making clinical decisions regarding screening. For example, having an FDR diagnosed at 75–90 years of age is unlikely to seriously impact an individual's risk of CRC, while an FDR diagnosed at age 35 years is probably highly relevant. Therefore, we acknowledge that national or provincial programs may wish to set specific FDR age cutoffs for screening, based on additional factors, including feasibility, cost, and cost-effectiveness. From an evidence perspective, we are, unfortunately, not able to provide clear guidance at this time. Future research should prioritize prospective studies that assess the optimal time to initiate screening and appropriate intervals between screening tests.

This guideline should help to optimize the use of the resources available for screening programs, and potentially improve early detection and outcomes of CRC or adenomas for patients at elevated risk due to an FH of CRC or advanced adenoma. Counseling and shared decision making are critical to maximize uptake of CRC screening.

## Introduction

Colorectal cancer (CRC) is the second leading cause of cancer in Canada, and the fourth leading cause in the United States.<sup>1,2</sup> It is the second leading cause of cancer deaths in both countries, with approximately 9400 Canadians, and 50,260 Americans dying of the disease annually. The 2017 estimated incidence of new cases CRC was 26,800 Canadians, and 135,430 Americans, and the prevalence of individuals living with CRC was 105,195 Canadians (2009) and 1.3 million Americans (2014).<sup>1,2</sup>

A systematic review (SR) estimated the prevalence of an individual having 1 or more first-degree relatives (FDRs) with CRC to be 3%–10%, and of having 2 or more FDRs with CRC to be about 0.3%.<sup>3</sup> Many of these individuals with a positive family history (FH) are at an increased risk of developing CRC. However, the magnitude of the individual's increased risk appears to be dependent on the degree of relationship to the affected relative, age of the affected relative at time of diagnosis, and the age of the individual. Overall CRC burden in a family (ie, total number of individuals with CRC on the same side of the family) also increases the magnitude of the individual's CRC risk. This may be a red flag for an inherited CRC syndrome.<sup>4</sup>

**Table 1.** Summary of Consensus Recommendations for Screening for Colorectal Cancer in Individuals With a Family History of Nonhereditary Colorectal Cancer or Adenoma<sup>a</sup>

Recommendations
<p><b>1 or more FDR with CRC</b></p> <p>1. For an individual with 1 or more FDR with a history of CRC, we recommend screening over no screening. GRADE: Strong recommendation, moderate-quality evidence. Vote: strongly agree, 100%</p>
<p><b>1 FDR with CRC</b></p> <p>2. For an individual with 1 FDR with a history of CRC, we suggest colonoscopy as the preferred screening test over no screening or all other screening modalities. GRADE: Conditional recommendation, very-low-quality evidence. Vote: strongly agree, 88%; agree, 13%</p> <p>3. For an individual with 1 FDR with a history of CRC, we suggest FIT as a second-line screening option. GRADE: Conditional recommendation, moderate-quality evidence. Vote: strongly agree, 50%; agree, 38%; uncertain, 13%</p> <p>4. For an individual with 1 FDR with a history of CRC undergoing screening colonoscopy, we suggest commencing CRC screening at age 40–50 y or 10 y younger than the age of diagnosis of the FDR, whichever is earlier. GRADE: Conditional recommendation, very-low-quality evidence. Vote: strongly agree, 50%; agree, 50%</p> <p>5. For an individual with 1 FDR with a history of CRC undergoing screening with FIT, we suggest commencing CRC screening at age 40–50 y or 10 y younger than the age of diagnosis of FDR, whichever is earlier. GRADE: Conditional recommendation, very-low-quality evidence. Vote: strongly agree, 25%; agree, 75%</p> <p>6. For an individual with 1 FDR with a history of CRC undergoing screening with colonoscopy, we suggest 5–10 y as screening intervals. GRADE: Conditional recommendation, very-low-quality evidence. Vote: strongly agree, 25%; agree, 63%; uncertain, 13%</p> <p>7. For an individual with 1 FDR with a history of CRC undergoing screening with FIT, we suggest 1–2 y as screening intervals. GRADE: Conditional recommendation, very-low-quality evidence. Vote: strongly agree, 38%; agree, 63%</p>
<p><b>2 or more FDRs with CRC</b></p> <p>8. For an individual with 2 or more FDR with a history of CRC, we recommend colonoscopy as the preferred screening test over no screening or all other screening modalities. GRADE: Strong recommendation, very-low-quality evidence. Vote: strongly agree, 63%; agree, 38%</p> <p>9. For an individual with 2 or more FDR with a history of CRC undergoing colonoscopy, we suggest commencing CRC screening at age 40 y or 10 y younger than the age of diagnosis of the earliest diagnosed FDR, whichever is earlier. GRADE: Conditional recommendation, very-low-quality evidence. Vote: strongly agree, 63%; agree, 38%</p> <p>10. For an individual with 2 or more FDR with a history of CRC undergoing screening with colonoscopy, we suggest 5 y as screening intervals. GRADE: Conditional recommendation, very-low-quality evidence. Vote: strongly agree, 38%; agree, 63%</p>
<p><b>1 or more SDR with CRC</b></p> <p>11. For an individual with 1 or more SDR with a history of CRC, we recommend screening over no screening. GRADE: Strong recommendation, moderate-quality evidence. Vote: strongly agree, 88%; agree, 13%</p> <p>12. For an individual with 1 or more SDR with a history of CRC, we suggest commencing CRC screening at age 50 y. GRADE: Conditional recommendation, low-quality evidence. Vote: strongly agree, 50%; agree, 50%</p> <p>13. For an individual with 1 or more SDR with a history of CRC, we suggest screening tests and intervals in accordance with average-risk guidelines. GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 38%; agree, 63%</p>
<p><b>1 or more FDR with advanced adenoma</b></p> <p>14. For an individual with 1 or more FDR with a history of a documented advanced adenoma, we recommend screening over no screening. GRADE: Strong recommendation, moderate-quality evidence. Vote: strongly agree, 63%; agree, 38%</p> <p>No recommendation. For an individual with 1 or more FDR with a history of a documented advanced adenoma the Consensus Group was not able to make a recommendation (neither for nor against) on the use colonoscopy as the preferred screening test over no screening or all other screening modalities.</p> <p>15. For an individual with 1 or more FDR with a history of a documented advanced adenoma, we suggest colonoscopy or FIT over no screening or all other screening modalities. GRADE: Conditional recommendation, very-low-quality evidence. Vote: strongly agree, 63%; agree, 38%</p>

Table 1. Continued

	Recommendations
16.	For an individual with 1 or more FDR with a history of a documented advanced adenoma undergoing screening with colonoscopy or FIT, we suggest commencing CRC screening at age 40-50 y or 10 y younger than the age of diagnosis of the earliest diagnosed FDR, whichever is earlier. GRADE: Conditional recommendation, very-low-quality evidence. Vote: strongly agree, 38%; agree, 38%; uncertain, 25%
17.	For an individual with 1 or more FDR with a history of a documented advanced adenoma undergoing screening with colonoscopy, we suggest 5-10 y as screening intervals. GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 13%; agree, 75%; uncertain, 13%
18.	For an individual with 1 or more FDR with a history of a documented advanced adenoma undergoing screening with FIT, we suggest 1-2 y as screening intervals. GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 38%; agree, 63%
<b>1 or more FDR with any non-advanced adenoma</b>	
19.	For an individual with 1 or more FDR with a history of a non-advanced adenoma or polyp of unknown histology, we suggest screening in accordance with average-risk guidelines. GRADE: Conditional recommendation, low-quality evidence. Vote: strongly agree, 63%; agree, 38%

<sup>a</sup>The strength of each recommendation was assigned by the Consensus Group, per the GRADE system, as strong (“we recommend...”) or conditional (“we suggest...”).

CRC usually develops from premalignant polyps, and CRC screening can be used to detect and remove these polyps or localized cancer. Evidence from studies conducted in individuals primarily at “average risk” for CRC shows that screening (with endoscopy or occult blood tests) can reduce CRC mortality and incidence.<sup>5-7</sup>

Guidelines and the introduction of population-based screening programs have led to substantially increased uptake of CRC screening. Rates in the United States and Canada were about 25%-35% before 2003, but have increased to 55%-60% in 2012-2013 surveys.<sup>8,9</sup> Individuals with an FH of CRC are more likely to adhere to CRC screening recommendations compared to those with no FH.<sup>3</sup> But even among this higher-risk population, participation rates remain less than optimal.<sup>3,10-12</sup>

While a variety of guidelines for screening individuals for CRC are available, the majority apply to patients at average risk,<sup>13-22</sup> or those at highest risk due to inherited germline mutations associated with CRC and polyposis.<sup>4,23,24</sup> The few guidelines that make detailed recommendations for screening individuals with an FH of CRC or adenoma have not systematically reviewed the literature in this specific population.<sup>17,19,20</sup> Recent guidelines from the US Multi-Society Task Force on CRC screening used a modified process to systematically review published literature on this topic, however, systematic assessments of the methodological quality of the individual studies were not presented, and the paper was published after our consensus meeting.<sup>22</sup> For this guideline, systematic literature searches were conducted and the quality of evidence (QoE) and strength of recommendations were rated using the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) approach.<sup>25</sup>

This guideline specifically excludes individuals with hereditary syndromes, such as Lynch syndrome, familial

adenomatous polyposis, attenuated familial adenomatous polyposis, MUTYH-associated polyposis, Peutz-Jeghers syndrome, juvenile polyposis syndrome, Cowden syndrome, serrated (hyperplastic) polyposis syndrome, hereditary pancreatic cancer, and hereditary gastric cancer. However, hereditary CRCs occurring due to mutations and defects in certain genes account for about 5% of all CRC.<sup>4</sup> Given the substantial risk of CRC and extracolonic cancers warranting specific screening strategies, it is important to identify these patients with hereditary syndromes. The National Comprehensive Cancer Network proposed 9 recommendations (summarized in Table 3) for patients who should be referred to a genetics provider for further assessment of a hereditary cancer syndrome. In addition, many jurisdictions and hospitals have implemented universal screening programs for CRC and endometrial cancers that include microsatellite instability or immunohistochemistry to identify patients at risk of Lynch syndrome. These individuals should be managed according to appropriate guidelines for individuals with hereditary gastrointestinal cancer syndromes.<sup>4,23,24</sup>

The purpose of this guideline was to systematically and critically review the literature and provide specific recommendations for CRC screening of individuals with an FH of nonhereditary CRC or adenoma.

## Methods

### Scope and Purpose

Questions around screening for CRC in individuals with an FH of nonhereditary CRC or adenomas were identified and discussed by the participants, aided by evidence derived from review of the literature on CRC screening. Specifically, the processes focused on 5 principal questions.

**Table 2.** Summary of Recommendations for Screening for Colorectal Cancer in Individuals With a Family History According to Decreasing Level of Elevated Risk of Colorectal Cancer<sup>a</sup>

		FH according to decreasing level of elevated risk of CRC				
		Highest risk		Lowest risk		
		2 or more FDRs with CRC	1 FDR with CRC	1 or more FDR with documented advanced adenoma	1 or more SDR with CRC	1 or more FDR with any non-advanced adenoma
Screening over no screening	Yes		Yes	Yes	Yes	According to average-risk guidelines
Preferred test	Colonoscopy	Colonoscopy	Colonoscopy	No recommendation for a preferred test. Colonoscopy or FIT are both options	According to average-risk guidelines	
Second-line option			FIT	40–50 y or 10 y younger than age of diagnosis of earliest FDR, whichever is earlier <sup>b</sup>	50 y	
Age	40 y or 10 y younger than age of diagnosis of earliest diagnosed FDR, whichever is earlier <sup>b</sup>	40–50 y or 10 y younger than age of diagnosis of earliest FDR, whichever is earlier <sup>b</sup>	Colonoscopy: 5–10 y FIT: 1–2 y	Colonoscopy: 5–10 y FIT: 1–2 y	Colonoscopy: 5–10 y FIT: 1–2 y	
Interval	Colonoscopy: 5 y	Colonoscopy: 5–10 y FIT: 1–2 y	Colonoscopy: 5–10 y FIT: 1–2 y	Colonoscopy: 5–10 y FIT: 1–2 y	According to average-risk guidelines	

<sup>a</sup>The age of the affected relative should be considered when making clinical decisions regarding screening.

1. For an individual, what is the effect of an FH of CRC (including the number and family connection of affected relatives) on his/her own risk of CRC?
2. For an individual, what is the effect of an FH of adenoma (including advanced and nonadvanced adenoma) on his/her own risk of CRC or adenoma?
3. For an individual with an FH of CRC or adenoma, at what age should screening begin?
4. For an individual with an FH of CRC or adenoma, what screening tests are recommended?
5. For an individual with an FH of CRC or adenoma, what are the recommended testing intervals?

The development of this clinical practice guideline began in June 2016, with the full Consensus Group participating in a 2-day face-to-face meeting in March 2017. A final manuscript was submitted for publication in March 2018.

### Sources, Literature Searches, and Systematic Reviews

Evidence for these consensus guidelines was gathered via multiple parallel SR streams. The SRs were informed by a series of 10 literature searches. The scope, search strategy, and yield of each literature search are shown in [Supplementary Table 1](#). All SRs (and the corresponding meta-analyses, where applicable) were performed by the 2 GRADE methodologists (GL and FT), with one exception, an SR of prospective studies on the risk of CRC among individuals with an FH of CRC/adenoma vs those without, which was led by Ahmed M. Abou-Setta, with the data being independently confirmed by the GRADE methodologists. All searches, data extractions, and analyses were performed by 1 investigator and double-checked by a second investigator, with any disagreements resolved by consensus. Most of the literature searches supported more than 1 of the SRs, and most SRs depended on 2 or more literature searches. The streams of evidence and the research questions they addressed are briefly summarized in [Table 4](#). The results of the SRs (along with the assessments of the QoE) were forwarded to the Consensus Group members 1 week before the face-to-face meeting.

All analyses were performed using the Cochrane Collaboration’s Review Manager (RevMan).

### Assessment of the Quality of Evidence

The GRADE approach<sup>25</sup> was used by 2 nonvoting methodologists (GL, FT) to assess the following: risk of bias (of individual studies and overall, across studies), indirectness, inconsistency, imprecision, and other aspects (including publication bias) in order to determine the overall quality (trustworthiness) of evidence for each statement. As is described in GRADE<sup>25,26</sup> and used in prior Canadian Association of Gastroenterology (CAG) consensus documents,<sup>27–30</sup> the descriptors of high, moderate, low, or very low were used to grade the QoE for each statement. One week before the face-to-face meeting, the voting members of the CRC Consensus Group had access to the GRADE assessments (including evidence profiles, the results of the SRs and meta-analyses conducted for this guideline,

**Table 3.** National Comprehensive Cancer Network Criteria for Further Genetic Risk Evaluation<sup>4</sup>

Criteria
Individuals meeting the revised Bethesda Guidelines
Individuals with a family history that meets Amsterdam Criteria
Individuals with colorectal (or endometrial) cancer with microsatellite instability or immunohistochemistry consistent with Lynch syndrome
Individuals with papillary thyroid cancer that is the cribriform-morular variant, or hepatoblastoma
Individuals with a diagnosis of CRC and >10 colorectal adenomas
Individuals with a personal history of $\geq 20$ adenomas
Individuals with multiple gastrointestinal hamartomatous polyps or serrated polyposis syndrome
Individuals from a family with a known hereditary syndrome associated with CRC with or without a known mutation
Individuals with a desmoid tumor, multifocal or bilateral CHRPE

CHRPE, congenital hypertrophy of retinal pigment epithelium.

detailed assessments of the risk of bias of all included studies, and a critical review of recent guidelines that included statements on CRC screening for individuals with FH of CRC/adenoma). These assessments were reviewed, revised as needed, and agreed upon at the face-to-face meeting. The GRADE assessments along with the results of the SRs and meta-analyses (MAs) are provided in [Supplementary Table 2](#) (relative risk of CRC in asymptomatic individuals with FH of CRC or adenoma) and [Supplementary Table 3](#) (CRC screening strategies for individuals with FH of CRC or adenoma).

### Consensus Process

The Consensus Group included 8 voting members: the meeting chair (DL), and 6 other gastroenterologists and clinical epidemiologists, as well as a family physician. The voting group included 2 participants from the United States (NJS, DAL). Non-voting members included the moderator (JKM) and 2 GRADE methodologists (GIL, FT), 1 of whom acted as a co-moderator (GIL). The meeting was observed by members of the CAG and the Canadian Partnership Against Cancer. A patient advocate provided valuable insight during the initial guideline development.

A web-based platform (ECD solutions, Atlanta, GA) was used by the CAG to facilitate the consensus process before the 2-day face-to-face meeting held in Banff, Alberta, Canada in

March 2017. Voting members used the platform to answer the principal questions to be addressed during the meeting and provided valuable comments, feedback, and suggested sources of evidence. All participants had access to the results of literature searches and relevant references.

At the meeting, the GRADE methodologists presented the data and provided the group with a review of the GRADE evaluations leading to the QoE determination for each of the questions. A modification of the Evidence-to-Decision (EtD) framework was applied to facilitate ranking of multiple screening methods for each specific population. The EtD framework is a formalized approach that enables a structured and transparent discussion on 12 criteria (is the problem a priority; how substantial are the desirable anticipated effects; how substantial are the undesirable anticipated effects; what is the overall certainty of the evidence on effects; is there important uncertainty about or variability in how much individuals value the main outcomes; do the desirable effects outweigh the undesirable effects; how large are the resource requirements; what is the certainty of evidence for the resource requirements; are the net benefits worth the incremental cost; what would be the impact on health equity; is the intervention/option acceptable to key stakeholders; and is the intervention feasible to implement).<sup>31</sup> Recommendation statements were developed that were subsequently voted on anonymously via touchpads. If  $\geq 75\%$  of participants voted 4 (agree) or 5

**Table 4.** Summary of Streams of Evidence and the Research Questions They Addressed

Evidence stream	Research question
Direct evidence	Screening test A vs test B (or vs no screening) in asymptomatic individuals with FH of CRC/adenoma Clinical outcomes: all-cause mortality, mortality from CRC, long-term ( $\geq 10$ y) incidence of CRC
Indirect evidence	Indirect outcomes: Test A vs test B (or vs no screening) in asymptomatic individuals with FH of CRC/adenoma Non-clinical outcomes: diagnostic accuracy, patient values and preferences, resource requirements Indirect population: Test A vs test B (or vs no screening) in average-risk asymptomatic individuals Clinical outcomes: all-cause mortality, mortality from CRC, long-term incidence of CRC Indirect population and indirect outcomes: Test A vs test B (or vs no screening) in average-risk asymptomatic individuals Non-clinical outcomes: diagnostic accuracy, patient values and preferences, resource requirements
Evidence used to interpret data from indirect populations	What is the relative risk of CRC in asymptomatic individuals with FH of CRC/adenoma compared to those without FH?

(strongly agree) on a scale of 1 to 5 (with 1, 2, and 3 indicating disagree strongly, disagree, and uncertain, respectively), a statement was then accepted. Once accepted, the “strength” of the recommendation (strong vs conditional) was determined based on 4 components: (1) QoE, (2) benefit-to-harm balance, (3) patients’ values/preferences, and (4) resource requirements.<sup>32</sup> When the QoE was low or very low, unless at least 1 of the other 3 factors was overwhelmingly strong, the strength of the recommendation would typically default (without a vote) to “conditional,” using the phrasing, “we suggest.” If the QoE was moderate or high, the statement’s strength was determined by an anonymous vote; if ≥75% of participants voted “strong, then the recommendation would be designated as “strong” and the phrasing was “we recommend.” The GRADE approach notes that a conditional recommendation should prompt clinicians to “. . . recognize that different choices will be appropriate for different patients and that they must help each patient to arrive at a management decision consistent with her or his values and preferences,” whereas a strong recommendation is indicative of a more broadly applicable statement (“most patients should receive the recommended course of action”).<sup>32</sup>

In accordance with CAG policy, written disclosures of any potential conflicts of interest for the 24 months before the consensus meeting were provided by all participants, reviewed by the CAG ethics committee, and made available to all group members.

**Canadian Association of Gastroenterology Approval and American Gastroenterological Association Endorsement**

The chair (DL) and 1 of the GRADE methodologists (GL) initially drafted the manuscript, which was then reviewed and revised by the remaining members of the Consensus Group, both individually and jointly during a teleconference. The manuscript was then made available to all CAG members for comments for a 2-week period before submission for publication, as per CAG policy for all clinical practice guidelines.

Finally, the recommendations were reviewed, commented on, and endorsed by the American Gastroenterological Association.

**Role of the Funding Sources**

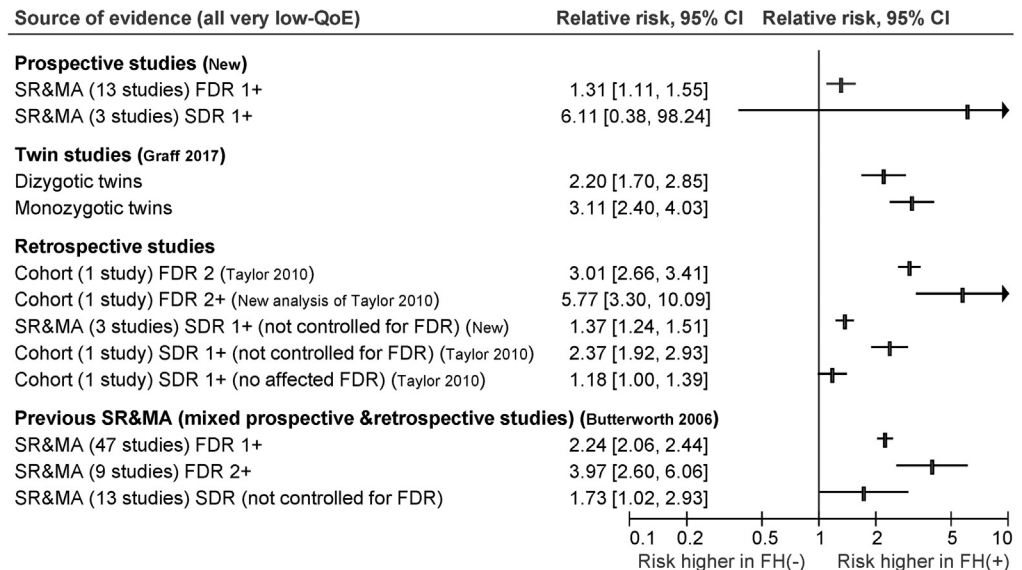
Funding for the consensus meeting was provided by an unrestricted, arms-length grant to the CAG by the Canadian Partnership Against Cancer. The CAG administered all aspects of the meeting. A member of the Canadian Partnership Against Cancer observed the meeting, but the organization had no involvement in developing the statements, conducting the SRs, drafting the manuscript, or approving this guideline.

**Principal Questions**

**Q1. For an individual, what is the effect of an FH of CRC (including the number and family connection of affected relatives, for example, 1 FDR, ≥2 FDRs, ≥1 SDRs) on his/her own risk of CRC?**

Evidence regarding this principal question was gathered via 4 streams (presented in detail in [Supplementary Table 2](#) and summarized in [Figure 1](#)): a new SR&MA of prospective studies (eligible prospective studies from previous SRs were included); an SR of published SRs (of prospective or retrospective studies); an assessment of studies on the risk of CRC among twins; and a new SR of retrospective studies (eligible retrospective studies from previous SRs were included). All studies reported relative risk (RR) of CRC (individuals with vs without FH of CRC) with a highly variable timeframe for risk reporting among studies; absolute risks (eg, 10-year risk or life-time risk) were not reported.

An SR&MA of prospective studies assessing the effect of FH on the RR of CRC (and adenomas) conducted specifically



**Figure 1.** Summary data for the relative risk of CRC among individuals with an FH of CRC vs those without (quality of evidence: very low).

for this guideline found that the risk of CRC was significantly elevated in individuals with 1 or more FDRs with CRC (13 studies; RR, 1.31; 95% confidence interval [CI], 1.11–1.55). The risk was elevated among those with 1 or more SDRs with CRC (3 studies; RR, 6.11; 95% CI, 0.38–98.00) compared to those without FH, but this was not significant. The quality of the evidence was very low (observational data with high risk of bias with/without serious imprecision). The results of this SR are presented in detail in [Supplementary Table 2](#).

Our SR of SRs included 4 SR&MAs<sup>33–36</sup> and 1 SR (without meta-analysis).<sup>37</sup> The data consistently show that individuals with 1 or more FDRs diagnosed with CRC have an approximately 2-fold increased risk of developing CRC compared to those without an FH of CRC.

Additional evidence of the risk associated with an FH comes from a study of twins.<sup>38</sup> The Nordic Twin Study, including more than 100,000 twins and more than 3000 CRCs, reported familial RRs of CRC among co-twins of 3.1 (95% CI, 2.4–3.8) for monozygotic twins and 2.2 (95% CI, 1.7–2.7) for dizygotic twins relative to the cohort risk. Given the shared DNA profile, and potentially high rates of shared environmental factors, the RR for dizygotic twins likely represents the upper plausible limit of the RR of CRC in individuals with 1 FDR with CRC.

Modeling studies suggest that results of observational studies are unlikely to be explained by confounding alone when the RR is >2, and very unlikely when the RR is >5.<sup>39</sup> Therefore, taking the data altogether, the Consensus Group agreed that an RR of 2 or more was a reasonable cutoff point to define a clinically significant increased risk of CRC, and that an individual with an FH of 1 FDR with CRC was likely at a 2-fold higher risk of CRC compared to those without ([Figure 1](#)).

In addition, an individual's CRC risk increases with an increasing number of affected FDRs.<sup>37</sup> In 1 SR&MA, the pooled RR of developing CRC was 2.24 (95% CI, 2.06–2.43) among those with 1 or more FDRs with a history of CRC, and increased to 3.97 (95% CI, 2.60–6.06) for those with 2 or more FDRs.<sup>35</sup> The large, retrospective, population-registry cohort study by Taylor et al<sup>40</sup> reported an increased risk of CRC among individuals with an FH of 2 FDRs with CRC (RR, 3.01; 95% CI, 2.66–3.38).<sup>40</sup> We conducted a pooled analysis of 4 subgroups (2, 3, 4, ≥5 FDRs) included in that study and found an even greater risk of CRC among those with 2 or more FDRs with a history of CRC (RR, 5.77; 95% CI, 3.3–10.1). The Consensus Group concluded that the risk of CRC increased with an increasing number of FDRs with CRC.

The degree of the relationship also impacts the risk of CRC, with the elevated risk being driven largely by the presence of 1 or more FDRs, rather than 1 or more SDRs. An SR&MA has reported a more modest elevated risk of CRC among individuals with 1 or more SDRs with a history of CRC (RR, 1.73; 95% CI, 1.02–2.94).<sup>35</sup> In addition, an SR&MA of large retrospective database studies that we conducted for this guideline included 3 studies (Samadder et al,<sup>41</sup> Taylor et al,<sup>40</sup> and Andrieu et al<sup>42</sup>) and revealed that the RR associated with 1 or more SDRs with a history

of CRC was 1.37 (95% CI, 1.24–1.51). However, because the studies included in both of these meta-analyses did not control for the presence of an FDR with CRC, an important confounder, we conducted a sensitivity analysis of the data reported in Taylor et al<sup>40</sup> and found that the RR associated with 1 or more SDRs and no affected FDRs was 1.18 (95% CI, 1.00–1.38), while the RR among those with 1 or more SDRs and an affected FDR was significantly higher ( $P = .03$  for subgroup differences) at 2.37 (95% CI, 1.92–2.92). These results suggest that the apparent increase in risk of CRC in individuals with an affected SDR, and the apparent additive risk associated with multiple affected SDRs are probably driven by concomitant FDRs with CRC. Therefore, the Consensus Group concluded that individuals whose FH includes only SDRs with CRC can be regarded as average-risk individuals; if they have an increased risk for CRC this would be too small to be clinically relevant. However, the Consensus Group stressed the need to take a thorough family history and the use of clinical judgment in this population. Germline genetic testing should be considered in those with a high burden of CRC among relatives.<sup>4</sup>

**Q2. For an individual, what is the effect of an FH of adenoma (including advanced and nonadvanced adenoma) on his/her own risk of CRC or adenoma?**

Data from average-risk individuals suggest that small adenomas are generally not malignant, but that malignant potential increases with increasing adenoma size (see Question 5).<sup>43,44</sup> Histology and number of adenomas also affect the risk of developing CRC.<sup>44–47</sup>

In North American adults older than 50 years of age, the overall prevalence of adenomas has been estimated to be 20%–30%, with the prevalence increasing with increasing age.<sup>48,49</sup> In contrast, the prevalence of advanced adenomas is much lower, at about 6%–7%.<sup>48,49</sup> Advanced adenomas have generally been defined as adenomas that exhibit any of the following: size ≥10 mm, or high-grade dysplasia, or villous/tubulovillous histology,<sup>45,47,50,51</sup> but, the definition can differ between countries, or even between provinces within a country. While the presence of multiple polyps also affects the risk of CRC and adenoma, we did not examine the relationship between FH, the number of adenomas, and the risk of CRC. Evidence for an increased risk of CRC in individuals with an FH of adenoma is very limited (summarized in [Table 5](#)). Most studies have assessed whether individuals with an FDR with CRC have a higher risk of adenoma, not whether individuals with an FDR with an adenoma have a higher risk for CRC.<sup>33,52</sup> One SR of studies through 2011<sup>52</sup> found only 2 studies<sup>53,54</sup> specifically addressing the latter question. However, both studies are confounded by inclusion of individuals with an FH of CRC, which may be responsible for some or all of the elevated risk of CRC when an FDR is diagnosed with adenoma. In a Japanese study, the RR of CRC in individuals who had an FDR with adenomas was 4.36 (95% CI, 1.6–10.21).<sup>53</sup> In the other study (from France), there was an increased risk for



**Table 5.** Summary Data for the Relative Risk of Colorectal Cancer Among Individuals With a Family History of Adenoma vs Those Without (Quality of Evidence: Very Low)

Source of evidence (all very-low QoE)	FH of adenoma	RR (95% CI)
<b>Prospective studies</b>		
Case-controlled (1 study) (Nakama, 2000 <sup>53</sup> )	FDR 1+ (not controlled for FH CRC)	4.36 (95% CI, 1.6–10.21)
Case-controlled (1 study) (Cottet, 2007 <sup>54</sup> )	FDR 1+ (not controlled for FH CRC)	OR 2.27 (1.01–5.09) combined outcome of adenoma + CRC
Case-controlled (1 study) (Cottet, 2007 <sup>54</sup> )	FDR 1+ (not controlled for FH CRC)	OR 3.90 (0.89–17.01) outcome of CRC
Case-controlled (1 study) (Cottet, 2007 <sup>54</sup> )	FDR 1+ (no FH CRC)	OR 2.09 (0.86–5.13) combined outcome of adenoma + CRC
Cross-sectional (1 study) (Ng, 2016 <sup>50</sup> )	FDR 1+ advanced adenoma (no FH CRC)	OR 6.05 (2.74–13.36) outcome of advanced adenoma
Cross-sectional (1 study) (Ng, 2016 <sup>50</sup> )	FDR 1+ advanced adenoma (no FH CRC)	OR 3.29 (2.16–5.03) outcome of any adenoma
<b>Retrospective study (Tuohy, 2014<sup>55</sup>)</b>		
Cohort (1 study)	FDR 1+ adenoma (not controlled for FH CRC)	1.35 (1.25–1.46) outcome of CRC
Cohort (1 study)	FDR 1+ advanced adenoma (not controlled for FH CRC)	1.68 (1.29–2.18) outcome of CRC
Cohort (1 study)	FDR 1+ adenoma (not controlled for FH CRC)	1.33 (1.26–1.40) outcome of adenoma
Cohort (1 study)	FDR 1+ advanced adenoma (not controlled for FH CRC)	1.65 (1.28–2.14) outcome of advanced adenoma

the combined outcome of CRC or advanced adenoma (odds ratio [OR], 2.27; 95% CI, 1.01–5.09), but not for CRC alone (OR, 3.90; 95% CI, 0.89–17.01).<sup>54</sup> When individuals with an FDR with CRC were excluded, the ORs were no longer significant for the combined outcome of CRC or advanced adenoma (OR, 2.09; 95% CI, 0.86–5.13) or the other outcomes; however, sample sizes were small.

A large cohort study found a 35% increase in the risk of CRC in the FDRs of individuals with adenomas (RR, 1.35; 95% CI, 1.25–1.46) and an almost 70% increase in risk of CRC in the FDRs of individuals with advanced adenomas (RR, 1.68; 95% CI, 1.29–2.18).<sup>55</sup> The risks of developing similar adenomas in FDRs of individuals with adenoma and advanced adenoma were also elevated (RR, 1.33; 95% CI, 1.26–1.40; and RR, 1.65; 95% CI, 1.28–2.14, respectively). However, similar to other studies, this analysis did not control for an FH of CRC.<sup>55</sup>

Additional evidence shows that FH of advanced adenomas is associated with increased risk of developing advanced adenomas, from a study that did exclude individuals with an FH of CRC or hereditary CRC.<sup>50</sup> Siblings of individuals with at least 1 advanced adenoma had 6-fold (OR, 6.05; 95% CI, 2.74–13.36) increased odds of advanced adenoma and 3-fold (OR, 3.29; 2.16–5.03) increased odds of any adenoma compared with individuals whose sibling did not have adenomas. The elevated risks were higher in individuals with an FDR diagnosed with the advanced adenoma at aged <60 years, but was also elevated in individuals with an FDR diagnosed at >60 years.

Over time, an FH of adenomas will become increasingly important in populations that have established effective CRC screening programs. When screening modalities that reduce the incidence of CRC are used, there will be significantly fewer diagnoses of CRC and more diagnoses of adenomas (some of which would have progressed to cancers had they not been resected as adenomas). In more recent and in future studies, the elevated risk of CRC in individuals with an FH of advanced adenoma may actually reflect the elevated risk associated with an FH of CRC observed in older studies that predate the increasing use of screening programs.

Because of the high prevalence of adenomas, having an FH of adenomas affects more individuals than having an FH of CRC. Although there are limited data available, individuals with an FH of an advanced adenoma appear to be at increased risk of CRC, regardless of the age at diagnosis of the relative. In clinical practice, given that individuals cannot reliably recall histologic information regarding their own polyps,<sup>56</sup> we recognize many will not be able to describe the polyps of a relative. However, because the evidence is for advanced adenomas, the Consensus Group agreed that the recommendations for high-risk screening of individuals with an FH of advanced adenoma should be restricted to those with an FH of “documented advanced adenoma.” Clinicians should also inquire about an FH of multiple polyps, and consider the possibility of a polyposis phenotype, especially in individuals with a high polyp burden. There is no evidence that individuals with an FH of

nonadvanced adenomas are at increased risk, and an FH of undocumented polyp/adenoma should be considered nonadvanced.

**Q3. For an individual with an FH of CRC or adenoma, at what age should screening begin? (eg, age <60 years vs age ≥60 years, contingent on age of diagnosis of relative)?**

### *Impact of the Age of the Affected Relative*

Our SR&MA of prospective studies found only 1 eligible study with extractable data that assessed the effect of the age at which the FDR was diagnosed with CRC.<sup>57</sup> Compared to individuals without an FH, the adjusted hazard ratio (HR) for CRC in individuals with an FDR diagnosed with CRC at age ≤60 years was 1.46 (95% CI, 1.17–1.81), which was not significantly different from the adjusted HR for those with FDR diagnosed at age >60 years (HR, 1.25; 95% CI, 1.07–1.45; pooled estimate from 2 age subgroups).

Evidence from retrospective studies was available from a well-conducted SR&MA, which included 3 retrospective cohort studies and 1 cross-sectional study, and reported RRs for CRC (individuals with affected FDRs vs those without FH) stratified by age of the affected FDR (within-study comparisons).<sup>35</sup> The RR for CRC for individuals with FDR diagnosed at age <50 years was 3.55 (95% CI, 1.84–6.83); this was numerically, but not significantly, higher than the RR in individuals with FDR diagnosed at age ≥50 years (2.18; 95% CI, 1.56–3.04).

Since the publication of the SR&MA mentioned, 3 large database studies have been published (Andrieu et al,<sup>42</sup> Samadder et al,<sup>41</sup> and Taylor et al, 2010<sup>40</sup>) with a possible small overlap among the populations of the latter 2 studies. We pooled these 3 studies and found that the RR (compared to individuals without FH of CRC) was 2.35 (95% CI, 1.92–2.86) for individuals with an FDR diagnosed at <60 years and 1.79 (95% CI, 1.58–2.03) for individuals with an FDR diagnosed at ≥60 years ( $P = .02$  for subgroup difference). The RR was large enough to be considered clinically important for individuals with an FDR diagnosed at younger ages, and was statistically significant in both subgroups.

The most recent of the large database studies reported detailed results on the HR for CRC according to the age of the affected FDR, and found that the HR decreased as the age at diagnosis of the FDR increased, but remained elevated among all individuals with an FDR of any age compared to those with no FH. HR point estimates ranged from 1.69 to 2.53, but the 95% CIs were widely overlapping among all FDR age groups (10-year intervals from <40 to ≥80 years).<sup>41</sup>

The Consensus Group agreed that the bulk of the evidence supports a continuum for increased RR based on the age of the CRC diagnosis for the FDR, and that a cutoff of age 50 years or 60 years is rather arbitrary. The age of the affected relative should be considered when making clinical decisions regarding screening.

### *Impact of the Age of the Individual*

Data assessing the age of the individual to be screened for CRC have clearly shown that the risk of CRC increases with age in both the average-risk and high-risk populations.<sup>58</sup> In the prospective study by Fuchs et al,<sup>58</sup> the cumulative incidence curves for CRC for individuals with and without an FH were parallel, with the individuals with an FH being at higher risk in all age groups. In fact, the CRC risk for an individual at age 40 years who had an FH was similar to the risk at age 50 years for an individual without an FH.<sup>58</sup> Similarly, in the Nordic Twin Study, the risk of CRC for the co-twin of an affected twin was elevated at every age compared to the risk in the control twin population.<sup>38</sup>

There are few prospective data assessing the effectiveness of initiating a screening program in individuals of different ages. Three SRs<sup>59–61</sup> have summarized retrospective data on the effectiveness of screening programs according to age of the screened individuals among average-risk individuals. These analyses suggest that guaiac fecal occult blood test (gFOBT) or flexible sigmoidoscopy (FS) screening programs can reduce the rate of CRC mortality both in individuals who are ≥60 years and those <60 years, but did not demonstrate significant differences in RR reductions between the age groups. In 1 large database study from Utah, the risk of CRC in individuals with 1 affected FDR was 2.28 (95% CI, 1.86–2.80) among those age <50 years, and 1.81 (95% CI, 1.71–1.92) among those ≥50 years, with no statistically significant difference among the 2 subgroups.<sup>41</sup>

The Consensus Group agreed that the bulk of the evidence supports an elevated risk of CRC for all individuals with an FH, and screening programs are likely effective in all age subgroups. However, consideration of cost and the need to prioritize resource use should be included in screening decisions. Younger individuals have lower absolute rates of CRC,<sup>58</sup> and screening in this population has a lower diagnostic yield,<sup>62,63</sup> but the potentially larger benefit in quality-adjusted life years saved for a younger individual vs an older one should also be considered.

In the Utah study, the highest RR for CRC was found in younger individuals (age <50 years) who had an FDR with early-onset CRC (age <40 years) (HR, 7.0; 95% CI, 2.86–17.09) compared to individuals aged <50 years without FH of CRC.<sup>41</sup> Initiating screening at age 40 years (or 10 years younger than the age of diagnosis of the FDR) among individuals with an FH of CRC has been associated with a low CRC miss rate of only 3%.<sup>64</sup>

### *Impact of Age in Individuals With a Family History of Adenoma*

No studies were found that assessed the age-specific risk of CRC, or the effectiveness of initiating screening programs at different starting ages in individuals with an FH of adenoma (or advanced adenoma).

### *Summary*

Therefore, the Consensus Group agreed that the clinical decision to initiate early screening should consider both the

age of the individual and the age of the affected relative, while being aware that the age-specific risk of CRC falls on a continuum and is elevated at all ages compared to those with no FH.

**Q4. For an individual with an FH of CRC or adenoma, what screening tests are recommended (eg, colonoscopy, FIT)?**

No randomized controlled trials (RCTs) or large observational studies were found that assessed the comparative efficacy of screening tests in individuals with an FH of CRC or adenomas, with the exception of 1 RCT<sup>65</sup> comparing FIT and colonoscopy. Therefore, evidence was largely extrapolated from studies in individuals at average risk or unselected populations. In general, the quality of evidence was not downgraded for indirectness of population because substantial differences in the direction of effects were not expected in individuals with FH of CRC, if it is assumed that the pathophysiology and natural history of CRC is the same in familial and sporadic cancers. If the only difference between these populations is the higher underlying risk of CRC in individuals with FH, testing strategies would be expected to have the same RRs, but larger absolute benefits with regard to CRC/adenoma detection rates and also larger absolute numbers of complications in populations with an FH compared to those at average risk. The participation rate and cost-effectiveness of a given strategy may not necessarily be the same as in average-risk populations and, in fact, evidence suggests that the importance of these considerations may be amplified in populations with FH of CRC.

The 4 main testing strategies that were considered were colonoscopy, FS, gFOBT, and FIT. The Consensus Group agreed that the most relevant outcomes were all-cause and CRC mortality, and (long-term) incidence of CRC. The evidence for the 4 testing options is summarized here and a detailed description of the quality of evidence profiles is included in [Supplementary Table 3](#) (CRC screening strategies for individuals with FH of CRC or adenoma) and a summary in [Supplementary Table 4](#) (summary of GRADE evidence profiles for CRC screening).

### Colonoscopy

No relevant studies were found assessing the efficacy of screening with colonoscopy vs no screening specifically in individuals with an FH of CRC or adenoma; therefore, evidence was extrapolated from studies in average-risk populations. An SR&MA of 6 large, observational trials found a significant reduction in the risk of CRC incidence (reported by 5 studies; RR, 0.31; 95% CI, 0.12–0.77) and, most importantly, a significant reduction in CRC mortality (reported by 3 studies; RR, 0.32; 95% CI, 0.23–0.43) with colonoscopy vs no screening.<sup>5</sup> One subsequently published large cohort study showed even stronger benefits for colonoscopy vs no screening, with a standardized mortality ratio of 0.11 (95% CI, 0.03–0.26), and a standardized incidence ratio of 0.17 (95% CI, 0.10–0.27).<sup>6</sup> The overall quality of

evidence on the benefits of screening colonoscopy compared to no screening was very low ([Supplementary Tables 3 and 4](#)).

No studies have directly compared colonoscopy vs FS for CRC screening. However, the Consensus Group agreed that the reductions in all-cause and CRC mortality with colonoscopy for individuals with FH of CRC would be expected to be similar or greater than that seen with FS (see evidence below), because of the significant reduction in the incidence of both distal and proximal CRC with colonoscopy, but only distal CRC with FS, and the likely significantly greater reduction in mortality due to proximal CRC with colonoscopy compared to FS (RR, 0.49; 95% CI, 0.29–0.85, indirect comparison from a network meta-analysis of observational studies).<sup>5</sup> However, this is very-low-quality evidence, and does not consider the potentially increased risk of harms with colonoscopy over FS.

Compared to gFOBT, there was no significant difference in participation rates between colonoscopy and gFOBT in a meta-analysis of 2 RCTs in individuals at average risk.<sup>7</sup> Meta-analysis of studies in average-risk individuals reported that one-time FIT had lower rates of colorectal neoplasia detection (RR, 0.30; 95% CI, 0.14–0.67) and higher rates of participation compared to colonoscopy (RR, 1.50; 95% CI, 1.08–2.10).<sup>7</sup> The only RCT assessing screening strategies in individuals with an FH of CRC compared single colonoscopy to annual FIT for 3 years and found no significant difference in the detection of advanced neoplasia (OR, 1.41; 95% CI, 0.88–2.26).<sup>65</sup> However, this study was at unusually high risk of bias for allocation concealment and was seriously underpowered.

Complication rates with colonoscopy screening (perforations, bleeds, or deaths) were assessed in an SR of 15 observational studies.<sup>60</sup> In 9 studies that included patients with an FH of CRC, the risk of complications was <1%, with the risk of perforations ranging from 0% to 0.22% and bleeding ranging from 0% to 0.19%.<sup>60</sup>

### Flexible Sigmoidoscopy

Three SRs comparing the use of FS vs no screening in average-risk populations<sup>7,59,66</sup> all pooled the same 4 RCTs. FS was associated with significant reductions in all-cause mortality (RR, 0.97; 95% CI, 0.96–0.99), CRC mortality (RR, 0.72; 95% CI, 0.65–0.80), and CRC incidence (RR, 0.78; 95% CI, 0.74–0.83) compared to no screening.<sup>7</sup>

An SR&MA of RCTs in average-risk individuals reported that FS had significantly higher colorectal neoplasia detection rates and no significant difference in participation rates compared to one-time FIT or one-time gFOBT.<sup>7</sup>

The rate of major complications (bleeding, perforation, or death within 30 days of screening, follow-up colonoscopy, or surgery) with screening FS was 0.08% in an SR&MA of 5 RCTs.<sup>67</sup>

### Guaic Fecal Occult Blood Test

Three SRs have assessed studies comparing the use of gFOBT (with colonoscopy offered for positive tests) vs no screening in average-risk populations.<sup>7,59,66</sup> These SRs

pooled 4 RCTs with 9 to 30 years of follow-up and showed a significant reduction in CRC mortality (RR, 0.87; 95% CI, 0.82–0.92), but not in all-cause mortality (RR, 1.00; 95% CI, 0.99–1.10) or CRC incidence (RR, 0.96; 95% CI, 0.90–1.02) with gFOBT vs no screening.<sup>7</sup> One subsequently published RCT with only a short follow-up period (median 4.5 years) reported nonsignificant differences between gFOBT screening and no screening for all 3 of these outcomes.<sup>68</sup> As mentioned, gFOBT was significantly less effective for colorectal neoplasia detection than FS.<sup>7</sup>

In a Cochrane SR&MA, no complications were reported after gFOBT itself, however, 0.03% of patients experienced major complications (bleeding, perforation, or death) within 30 days of screening, which were related to colonoscopy or surgical procedures after a positive screening test.<sup>67</sup>

### Fecal Immunochemical Test

No studies were found assessing FIT compared to no screening, but studies have shown FIT to have superior diagnostic accuracy compared to gFOBT. An SR&MA of 6 RCTs in average-risk populations found a superior colorectal neoplasia detection rate (RR, 2.15; 95% CI, 1.58–2.94) and a higher uptake rate (RR, 1.16; 95% CI, 1.05–1.28) with FIT vs gFOBT.<sup>7</sup>

FIT has been associated with lower rates of colorectal neoplasia detection compared to colonoscopy or FS, but higher rates of participation compared to colonoscopy in meta-analyses of studies in average-risk individuals.<sup>7</sup> There was only 1 RCT in individuals with an FH of CRC that compared FIT and colonoscopy, but as mentioned in the discussion regarding colonoscopy, its results are not reliable due to high risk of bias and serious imprecision.<sup>65</sup> A recent SR&MA, that was not available at the time of the consensus meeting, assessed the diagnostic accuracy of FIT in individuals with FH of CRC (vs colonoscopy as reference standard) and found high sensitivity (86%; 95% CI, 31%–99%) and specificity (91%; 95% CI, 89%–93%) for detection of CRC; for detection of advanced neoplasia (composite outcome of either CRC or advanced adenomas) specificity remained high (93%; 95% CI, 90%–95%), but sensitivity was disappointingly low (46%; 95% CI, 37%–56%).<sup>69</sup>

No data on all-cause or CRC mortality with FIT were found, however, long-term follow-up of ongoing RCTs in average-risk individuals will provide more information on these outcomes.<sup>70,71</sup> In the interim, the Consensus Group agreed that the reduction in CRC-related mortality with FIT would be expected to be greater than that seen with gFOBT. Data assessing gFOBT can be extrapolated to FIT because FIT is a more specific and sensitive test for FOB.<sup>51</sup> Compared to gFOBT, FIT has higher sensitivity for the detection of neoplasia and higher adherence rates.<sup>7</sup> SR&MA of studies conducted mainly in individual at average risk (excluding discontinued FITs) reported high sensitivity (0.82; 95% CI, 0.73–0.89) and specificity (0.94; 95% CI, 0.92–0.95).<sup>72</sup> The greater adherence to screening with FIT may be the result of fewer dietary restrictions, easier sample collection, and the requirement for fewer samples compared to gFOBT.<sup>18</sup> Higher sensitivity will result in more

positive tests requiring colonoscopy,<sup>18</sup> which could result in higher costs and more frequent complications than with gFOBT; however, FIT has been shown to be more cost-effective than gFOBT.<sup>73</sup>

### Patient Preferences

During the last 2 decades, guidelines recommending CRC screening for adults >50 years and the introduction of population-based screening programs have led to substantially increased uptake of CRC screening. Rates in the United States and Canada were about 25%–35% before 2003, but have increased to 55%–60% in 2012–2013 surveys.<sup>8,9</sup>

To help maximize uptake, patient acceptability (adherence) and satisfaction are important when making recommendations for a specific screening test. Overall, individuals with an FH of CRC have been shown to be more likely to adhere to CRC screening recommendations compared to those with no FH.<sup>3</sup> Among individuals with an FH of 1 or more FDRs with CRC, 71%–83% had ever undergone screening (FOBT, FS, or colonoscopy), but only 46% had undergone colonoscopy within 10 years, and 41% within 5 years.<sup>3,10–12</sup>

Studies assessing preferences for specific types of CRC screening tests were identified from an SR,<sup>74</sup> with no additional studies found by our updated literature search to January 2017. The 9 studies assessed all used a stated-preference method (eg, conjoint analysis or discrete-choice experiments) and compared 3 or more different CRC screening methods.<sup>75–83</sup> All 9 studies included individuals at average risk for CRC, and 7 also included individuals with an FH of CRC. The findings of the included studies were generally consistent and are summarized in Table 6.

Other studies in average-risk populations suggest there is some variation in preferences. While accuracy was typically considered the most important factor, some individuals may be more concerned with other factors, such as the potential inconvenience, pain, or discomfort related to testing.<sup>84–87</sup> Individuals have reported that bowel preparation was the most unpleasant aspect of colonoscopy, and that the procedure was less painful than anticipated.<sup>87</sup> This reinforces the need for proper counseling. In fact, an RCT found that a tailored intervention with FDRs of individuals

**Table 6.** Preferences for Colorectal Cancer Screening Tests Among Individuals With a Family History of Colorectal Cancer That May Affect Adherence<sup>74–83</sup>

Preferences
Greater likelihood of opting for CRC screening (vs no screening) among individuals with an FH of CRC
Greater preference for screening tests with high accuracy (or sensitivity) and improved outcomes of screening (eg, CRC incidence and mortality reduction) than for process-related features (such as preparation and pain)
Greater willingness to undergo more burdensome screening tests if this results in sufficient additional risk reduction of CRC-related mortality

diagnosed with colorectal neoplasia significantly improved the rate of uptake of colonoscopy screening compared to a control group (56.3% vs 35.4%,  $P = .0027$ ).<sup>88</sup>

### Cost-Effectiveness

Direct evidence supporting the cost-effectiveness of screening in those with a positive FH was not found. CRC screening has been shown to be cost-effective compared to no screening, but no single screening test has emerged as consistently more cost-effective in the average-risk population.<sup>73,89–92</sup> Because of the higher risk for CRC and the potential need for earlier and more frequent testing, data in average-risk individuals may not be applicable to individuals with an FH of CRC.

In the absence of data in individuals with an FH of CRC, an SR of analyses using simulation models to assess the cost-effectiveness of screening strategies in individuals with an FH of CRC was conducted for this guideline. Four cost-effectiveness modeling studies were identified (1 US study,<sup>93</sup> 1 Australian study,<sup>94</sup> and 2 European studies<sup>95,96</sup>) Three analyses were from the third-party payer perspective and considered direct costs only (ie, costs of screening, diagnostic tests, and treatment),<sup>94–96</sup> while 1 was from a societal cost perspective and included both direct and indirect costs (ie, those associated with attendance for screening, diagnostic, or surveillance procedures, or for treatment of cancer).<sup>93</sup> The screening strategies included various combinations of FIT every 2 or 5 years and colonoscopy every 5 or 10 years, generally beginning at age 40 or 50 years.

Overall, all 4 studies determined that colonoscopy performed every 5 years was cost-effective compared to no screening, FIT every 2 or 5 years, or colonoscopy every 10 years in individuals with an FH of 1 or more FDRs with CRC.<sup>93–96</sup> The incremental cost-effectiveness ratio of performing colonoscopy every 5 years was approximately US\$50,000/life-year gained in 2 studies,<sup>93,95</sup> AU\$12,405/life-year gained in a third study,<sup>94</sup> and €7250/life-year gained in the fourth study.<sup>96</sup> There were no direct comparisons of different starting ages for initiating screening.

Because all modeling studies made various assumptions, the most cost-effective strategy for screening individuals with an FH of CRC cannot be stated definitively. The available data suggested that the more intensive screening strategies for these high-risk populations using colonoscopy were cost-effective. The optimal interval of such screening may vary according to number and age at diagnosis of the affected FDRs.

No studies were found that assessed the effectiveness of various screening specifically in individuals with an FH of adenoma.

In summary, the Consensus Group agreed that the efficacy, patient preference, and cost-effectiveness data support the choice of colonoscopy as the preferred test for individuals at highest risk, but that FIT was an acceptable alternative depending on the individual's specific risk level, other patient factors, and the availability of resources.

Counseling and shared decision-making is critical to maximize uptake of CRC screening.

### **Q5. For an individual with an FH of CRC or adenoma, what are the recommended testing intervals?**

The interval for screening was extrapolated, in part, from data describing the natural history of adenomas in unselected individuals undergoing screening. The risks of advanced adenomas or CRC after a negative colonoscopy are low, particularly during the first 10 years of follow-up.<sup>97,98</sup> In addition, small adenomas are generally not malignant, and are unlikely to become invasive cancers within 5 years.<sup>43,44</sup> The malignant potential of adenomas increases with increasing size.<sup>43,44</sup> A study estimating the time to progression from normal, through adenoma, to invasive carcinoma, estimated 26 years for diminutive adenoma, 8 years for small adenoma, and 5 years for large adenoma.<sup>99</sup> Because of the high potential for malignant transformation of large adenomas, the efficacy of polypectomy decreases with increasing follow-up years.<sup>99</sup> The risk of developing CRC is also affected by the number and histology of the adenomas.<sup>44–46</sup> Therefore, based on the natural history of adenomas, guidelines recommend a 10-year interval for surveillance after a negative colonoscopy for individuals at average risk.<sup>17,18,47</sup>

There is currently little evidence to suggest that the natural progression of adenomas in individuals with an FH would differ from those without an FH. In one study, although individuals with a recurrence of adenomas (especially advanced adenomas) were more likely to have an FDR with CRC compared to those without recurrence, this was not statistically significant.<sup>100</sup> Evidence does suggest that the rate of progression from adenoma to CRC may be accelerated in individuals with some, but not other hereditary syndromes.<sup>101</sup> Currently, it is unknown whether an FH of nonhereditary CRC/adenomas would impact the natural history of adenomas in these individuals. If new evidence emerges confirming that the natural history remains the same, this would strengthen the current guideline. However, if emerging evidence shows that the pathophysiology of CRC is unique in individuals with an FH, this would weaken the confidence in the evidence, and would suggest the need to update the guidelines.

RCTs to determine the optimal interval for CRC screening are very limited. In an RCT in unselected, healthy individuals, both annual and biennial screening gFOBT resulted in significant reductions in the incidence of CRC (annual RR, 0.80; 95% CI, 0.70–0.90; biennial RR, 0.83; 95% CI, 0.73–0.94), as well as statistically lower CRC mortality (annual RR, 0.68; 95% CI, 0.56–0.82; biennial RR, 0.78; 95% CI, 0.65–0.93) compared with the control group.<sup>102,103</sup> The 2 approaches appeared to have similar efficacy, although, they were not compared statistically. Similarly, a population-based RCT evaluating FIT compared screening at 1-, 2-, or 3-year intervals, and found higher participation rates with biennial and triennial screening compared to annual screening, but there was no difference in detection of

advanced neoplasms or CRC.<sup>104</sup> Overall, the data assessing screening intervals for an FIT-type screening test are very-low quality and there remains substantial uncertainty as to whether 1-, 2-, or 3-year intervals would have the same efficacy or not.

In addition to the testing interval, the cutoff value for a positive FIT is also important. A diagnostic accuracy SR&MA of studies in average-risk individuals found that using a lower cut-off value (eg, <20 µg/g) significantly increased the sensitivity of FIT, but with a corresponding significant decrease in specificity.<sup>72</sup>

One study compared 2 different screening intervals for colonoscopy (1 follow-up colonoscopy at 6 years vs 2 follow-up colonoscopies, 1 at 3 years and the other at 6 years) in individuals with an FH of CRC,<sup>105</sup> but no definitive conclusions can be drawn from that study. Although it was described as an RCT, it was not truly randomized, was underpowered, and did not report cumulative incidence of advanced adenomas at the end of the study.<sup>105</sup>

Subgroup analyses of a large cohort study found that among individuals with an FH of CRC, a follow-up colonoscopy within 5 years significantly reduced the risk of CRC (HR, 0.44; 95% CI, 0.30–0.66 compared with no colonoscopy), but was not significant when follow-up colonoscopy took place beyond 5 years (HR, 0.91; 95% CI, 0.55–1.52, compared with no colonoscopy). In contrast, in individuals without an FH, the risk of CRC was significantly reduced (compared with no colonoscopy) in both subgroups, ie, follow up colonoscopy in <5 years and in ≥5 years. However, these were subgroup analyses and the sample size for those with an FH of CRC was small.<sup>106</sup>

No studies were found that assessed the effectiveness of various testing intervals specifically in individuals with an FH of adenoma. Overall, the Consensus Group agreed that the elevated risk warrants consideration of shorter intervals for repeat FIT and colonoscopy among some individuals with an FH of CRC or advanced adenoma compared to those at average risk. However, consideration should be given to the degree of elevated risk (eg, age and number of FDRs, and age of the individual) the quality of screening colonoscopy, and the findings at screening colonoscopy (eg, size, number, and histology of polyps) when considering the timing of subsequent testing.

## Clinical Recommendations

The individual recommendation statements are provided and include the strength of recommendation and quality of supporting evidence (according to the GRADE approach), and the voting result. This is followed by a discussion of the evidence considered for the specific statement. A summary of the recommendation statements is provided in [Tables 1](#) and [2](#).

**1. For an individual with 1 or more FDR with a history of CRC, we recommend screening over no screening.**  
GRADE: Strong recommendation, moderate-quality evidence.  
Vote: strongly agree, 100%

**Key evidence.** As discussed in Question 1, individuals with 1 or more FDRs are highly likely to have at least a 2-fold greater risk of CRC compared to those without an FH. Moderate-quality evidence has demonstrated the efficacy of screening programs in individuals at average risk (see Question 4), and this was extrapolated to individuals at elevated risk.

**Discussion.** The Consensus Group agreed that screening programs are effective in average-risk individuals, and that individuals at higher risk of CRC related to an FH of 1 or more FDRs with CRC would benefit at least as much, if not more, from screening programs over no screening.

### *Individuals With a Family History of 1 First-Degree Relative With Colorectal Cancer*

The scenario of an individual with an FH of 1 FDR diagnosed with CRC was used as the base case for initial discussions because the majority of data on the effects of FH are focused on this subgroup. Based on the evidence presented (see principal Question 4 and [Supplementary Tables 3](#) and [4](#)), the Consensus Group ranked the attributes of the 4 main testing strategies on a scale of 1 to 4 (with 1 being the preferred test for the given characteristic) ([Table 7](#)). When 2 or more tests were considered largely equivalent for a given characteristic, they were given the same rank. The results of this exercise are shown in [Table 7](#) for the scenario of an FH of 1 FDR with CRC. Based on the evidence for an increased risk of CRC for individuals in this subgroup, colonoscopy was identified as the preferred strategy, followed by FIT. This exercise allowed consideration of factors such as patient preferences, resource use, and feasibility, and was used to help guide decisions on the recommendation statements for this subgroup.

[Table 7](#) was created in the setting of North American subjects, with the Canadian and US gastroenterologists discussing whether differences in testing availability, cost, would impact the rankings. For the subgroup of individuals shown in [Table 7](#), the ranking remained the same for both Canada and the United States. It was suggested that these recommendations could be customized to other countries by using this approach and adjusting the relative rankings of the tests in different settings.

**2. For an individual with 1 FDR with a history of CRC, we suggest colonoscopy as the preferred screening test over no screening or all other screening modalities.**

GRADE: Conditional recommendation, very-low-quality evidence.

Vote: strongly agree, 88%; agree, 13%

**Key evidence.** See Question 4. Compared to no screening, the evidence for colonoscopy was determined to be of very-low quality (observational studies at high risk of bias). There was very sparse data comparing colonoscopy to other testing modalities in this population, making this evidence of very-low quality as well.

**Table 7.** Ranking of Attributes of Screening Tests for Colorectal Cancer in Individuals With a Family History of 1 First-Degree Relative With Colorectal Cancer

Characteristics	Colonoscopy	gFOBT	FS	FIT	Importance for decision
Desirable effects (efficacy)	1	4	2	2	High
Undesirable effects (complications)	4	1	3	2	High
Acceptability	1	4	3	2	High
Balance of effects	1	4	2	2	High
Resources required	4	1	3	2	Medium
Cost-effectiveness	1	2	2	2	Medium
Feasibility	1	1	1	1	Medium
Equity	3	1	3	1	Medium
<b>Overall ranking</b>	1	4	3	2	—

**Discussion.** Based on the ranking of attributes (Table 7), colonoscopy was determined to be the overall preferred screening test for individuals with 1 FDR with CRC. Colonoscopy offers the greatest efficacy, and while the RR of complications is highest with this test, the absolute risk of complications remains very low. In addition, although the resources required were ranked as high, the superior efficacy, which leads to better cost-effectiveness and patient acceptability, make colonoscopy the preferred option for individuals at elevated risk.

**3. For an individual with 1 FDR with a history of CRC, we suggest FIT as a second-line screening option.**  
 GRADE: Conditional recommendation, moderate-quality evidence.  
 Vote: strongly agree, 50%; agree, 38%; uncertain, 13%

**Key evidence.** See Question 4. No RCT data were found comparing FIT to no screening, so evidence was mainly extrapolated from studies comparing FIT with gFOBT, colonoscopy, and FS; however, these studies only accessed diagnostic accuracy and participation rates; no direct data are available on long-term clinical outcomes.

**Discussion.** Based on the ranking of attributes (Table 7), FIT was ranked second overall as a screening test for individuals with 1 FDR with CRC. While the Consensus Group agreed that colonoscopy is the preferred test for this subgroup, it was deemed necessary to offer an alternative test. With acceptable efficacy and adverse event profiles, FIT is a reasonable option in cases where an individual refuses colonoscopy, has higher than average risks of complications from colonoscopy, or if colonoscopy availability or wait times are an issue. In addition, equitable access can be an issue with colonoscopy and FS in geographic areas where these tests are not readily available.<sup>8,9,107</sup>

**4. For an individual with 1 FDR with a history of CRC undergoing screening colonoscopy, we suggest commencing CRC screening at age 40–50 years or 10 years younger than the age of diagnosis of the FDR, whichever is earlier.**  
 GRADE: Conditional recommendation, very-low-quality evidence.  
 Vote: strongly agree, 50%; agree, 50%

**5. For an individual with 1 FDR with a history of CRC undergoing screening with FIT, we suggest commencing CRC screening at age 40–50 years or 10 years younger than the age of diagnosis of FDR, whichever is earlier.**  
 GRADE: Conditional recommendation, very-low-quality evidence.  
 Vote: strongly agree, 25%; agree, 75%

**Key evidence.** See Question 3. There is evidence that risk of CRC increases with increasing age of the individual to be screened, and also with decreasing age at diagnosis of CRC in the FDR. However, risk falls on a continuum and a definitive cutoff age cannot be determined based on current evidence.

**Discussion.** The Consensus Group agreed that the clinical decision to initiate early screening should consider both the age of the individual and the age of the affected relative. For example, if the FDRs are much older at time of diagnosis (eg, 75–90 years), initiating colonoscopies at age 40 years may not be warranted. It is important to balance risk level against resource use. As the age to initiate screening decreases, the number of colonoscopies performed over the individual’s lifespan will increase. However, targeting the group of individuals (with FH of CRC) at age 40–50 years would be feasible, and the harms of missing a diagnosis of CRC are likely greater than in an older individual, in terms of potential life-years lost.

**6. For an individual with 1 FDR with a history of CRC undergoing screening with colonoscopy, we suggest 5–10 year screening intervals.**  
 GRADE: Conditional recommendation, very-low-quality evidence.  
 Vote: strongly agree, 25%; agree, 63%; uncertain, 13%

**7. For an individual with 1 FDR with a history of CRC undergoing screening with FIT, we suggest 1–2 year screening intervals.**  
 GRADE: Conditional recommendation, very low-quality evidence.  
 Vote: strongly agree, 38%; agree, 63%

**Key evidence.** See Question 5. Evidence for screening intervals was extrapolated, in part, from data describing the

natural history of adenomas in unselected individuals undergoing screening. While data suggest the rate of progression from adenoma to CRC in patients with some hereditary syndromes may be accelerated, it is unknown whether the rate of progression is affected by an FH of nonhereditary CRC. Data assessing different testing intervals for colonoscopy or FIT are very limited, especially in individuals with an FH.

**Discussion.** The Consensus Group agreed that the elevated risk associated with an FH of CRC in 1 FDR may warrant shorter intervals for repeat FIT and colonoscopy compared to those recommended for individuals at average risk. Again, clinical judgment is important when making decisions to shorten the screening interval, and should consider the degree of elevated risk (eg, age and number of FDRs, and age of the individual), the quality of screening colonoscopy, and the findings at screening colonoscopy (eg, size, number, and histology of polyps).

### *Two or More First-Degree Relatives With Colorectal Cancer*

As discussed in Question 1, an individual's CRC risk increases with an increasing number of affected FDRs. Individuals with 2 or more FDRs with CRC likely have a 4- to 6-fold greater risk than the general population. Although these individuals are at higher risk, the ranking of the attributes of the 4 main testing strategies remained unchanged compared to individuals with an FH of 1 FDR with CRC (Table 7), and colonoscopy continued to be the preferred strategy. As outlined in Statement 1, screening was strongly recommended over no screening in this subgroup of individuals.

**8. For an individual with 2 or more FDRs with a history of CRC, we recommend colonoscopy as the preferred screening test over no screening or all other screening modalities.**

GRADE: Strong recommendation, very-low-quality evidence.

Vote: strongly agree, 63%; agree, 38%

**Key evidence.** See Question 4 and Statement 2.

**Discussion.** Colonoscopy was recommended as the preferred screening test for all individuals in this subgroup because of the high efficacy rates and the very high risk of CRC associated with having 2 or more FDRs with CRC. This subgroup of individuals is much smaller than the subgroup with 1 FDR; therefore, it is likely feasible to screen all individuals in this group with colonoscopy. In unusual circumstances, such as when an individual refuses colonoscopy, another screening test should be performed, rather than no test, but all efforts should be made to perform colonoscopy.

Despite very-low QoE, the Consensus Group was given the option to vote on the strength of recommendation for colonoscopy because of the high-risk of life-threatening

negative consequences of missed lesions, and agreed that this should be a strong recommendation.

**9. For an individual with 2 or more FDRs with a history of CRC undergoing colonoscopy, we suggest commencing CRC screening at age 40 years or 10 years younger than the age of diagnosis of the earliest diagnosed FDR, whichever is earlier.**

GRADE: Conditional recommendation, very-low-quality evidence.

Vote: strongly agree, 63%; agree, 38%

**Key evidence.** See Question 3 and Statement 4.

**Discussion.** The Consensus Group agreed that in light of the very high risk associated with 2 or more FDRs, initiating screening at a young age is clearly warranted in this group of individuals. In addition, screening should begin 10 years younger than the age of diagnosis of the earliest diagnosed FDR. However, again clinical judgment is important; if the FDRs are much older at time of diagnosis, initiating colonoscopies at age 40 years may not be warranted, and genetic testing should be considered in those with a high CRC burden in a family.

**10. For an individual with 2 or more FDRs with a history of CRC undergoing screening with colonoscopy, we suggest 5-year screening intervals.**

GRADE: Conditional recommendation, very-low-quality evidence.

Vote: strongly agree, 38%; agree, 63%

**Key evidence.** See Question 5. Evidence for screening intervals was extrapolated, in part, from data describing the natural history of adenomas in unselected individuals and those with hereditary syndromes. Data suggest the rate of progression from adenoma to CRC in patients with Lynch syndrome is accelerated.<sup>101</sup> Observational studies have found cancers, even advanced-stage cancers, that have occurred within intervals of 3 years or fewer,<sup>108-110</sup> although it is not clear whether these cancers result from missed lesions at the first colonoscopy or a rapid rate of progression from adenoma to CRC. Currently, it is unknown whether the adenomas in individuals with an FH in multiple relatives lay on a continuum in terms of rate of progression compared to the adenomas found in individuals with hereditary syndromes or those at average risk.

**Discussion.** The Consensus Group agreed that the very high risk associated with multiple FDRs with CRC warrants a shorter interval for repeat colonoscopy compared to those recommended for individuals at average risk. It is important to investigate these individuals for an inherited syndrome (eg, Lynch syndrome, familial adenomatous polyposis), including a detailed personal and FH incorporating at least 3 generations and potentially genetic testing. Individuals found to have an FH of an inherited syndrome should undergo screening according to appropriate published guidelines.<sup>24</sup>



### One or More Second-Degree Relatives with Colorectal Cancer

As discussed in Question 1, an individual's CRC risk is associated with the degree of the relationship between the family member and the individual. Risk decreases with increasing distance from the affect relative. Among those with an affected SDR, reported elevations in CRC risk appears to be largely driven by the presence of a concomitant FDR. Although these individuals are likely at lower risk than those with 1 or more FDRs, the ranking of the attributes of the 4 main testing strategies remained unchanged compared to individuals with an FH of 1 FDR with CRC (Table 7). Although colonoscopy was still considered the overall best option, FIT continued to be ranked second overall.

**11. For an individual with 1 or more SDRs with a history of CRC, we recommend screening over no screening.**

GRADE: Strong recommendation, moderate-quality evidence.

Vote: strongly agree, 88%; agree, 13%

**Key evidence.** See Question 1 and Statement 1. Studies suggest that individuals with an affected SDR, without an affected FDR, may be at marginally increased risk for CRC, but these data do not appear to be statistically or clinically relevant. Risk appears to increase with increasing number of affected SDRs and decreases with the distance of the relative. Moderate-quality evidence has demonstrated the efficacy of screening programs in individuals at average risk (see Question 4), and this was extrapolated to individuals with SDRs with CRC, whose risk of CRC is at least that of average-risk individuals.

**Discussion.** The Consensus Group concluded that these individuals are likely at average risk. However, risk appears to fall on a biologic gradient, therefore, a thorough history should be taken. As per guidelines for screening individuals at average risk, screening is strongly recommended over no screening.<sup>14,15,17-20</sup>

**12. For an individual with 1 or more SDRs with a history of CRC, we suggest commencing CRC screening at age 50 years.**

GRADE: Conditional recommendation, low-quality evidence.

Vote: strongly agree, 50%; agree, 50%

**Key evidence.** See Questions 1 and 3. It has been clearly shown that the incidence and mortality of CRC increases with age, with a sharp increase at age 50 years.<sup>1,2,58</sup> For this reason, guidelines for individuals at average risk recommend screening for CRC starting at age 50 years.<sup>14,15,17-20</sup>

**Discussion.** Based on evidence suggesting individuals with an FH of CRC in 1 or more SDRs are at average or mildly elevated risk, the Consensus Group agreed with the

50-year age of initiation as per guidelines for individuals at average risk.<sup>14,15,17-20</sup>

**13. For an individual with 1 or more SDRs with a history of CRC, we suggest screening tests and intervals in accordance with average-risk guidelines.**

GRADE: Conditional recommendation, very-low-quality evidence.

Vote: strongly agree, 38%; agree, 63%

**Key evidence.** See Questions 1 and 3, and Statement 12.

**Discussion.** Based on the likelihood that these individuals are at average or minimally elevated risk for CRC, screening tests and the interval for screening should be chosen according to locally applicable average-risk guidelines.<sup>14,15,17-20</sup>

### One or More First-Degree Relatives With Advanced Adenoma

As discussed in Question 2, individuals may be unreliable in describing the histology of the polyp, adenoma, or advanced adenoma experienced by a relative; therefore, the Consensus Group defined this subgroup as individuals with an FH of "documented advanced adenoma." The Consensus Group emphasized the importance of the documentation in their recommendation; polyps without documentation should be considered "nonadvanced," see Statement 19. These individuals appear to be at increased risk of CRC and adenomas. When ranking the attributes of the 4 main testing strategies, the Consensus Group acknowledged that patient preferences, cost-effectiveness, and feasibility are different in this subgroup (Table 8) compared to individuals with an FH of 1 FDR with CRC (Table 7). The Consensus Group agreed that the advantages of colonoscopy over FIT in terms of cost-effectiveness and patient acceptability would be decreased in this subgroup. In addition, the high prevalence of adenomas would substantially impact the feasibility of performing colonoscopy or FS on all relatives of individuals with adenomas. Although the overall ranking continued to position colonoscopy first and FIT second overall, almost 40% of the Consensus Group advocated in favor of ranking these 2 options equally. Although colonoscopy would likely be a preferred strategy in the United States for this subgroup of individuals, the ranking remained the same for both Canada and the United States (Table 8).

**14. For an individual with 1 or more FDRs with a history of a documented advanced adenoma, we recommend screening over no screening.**

GRADE: Strong recommendation, moderate-quality evidence.

Vote: strongly agree, 63%; agree, 38%

**No recommendation.** For an individual with 1 or more FDRs with a history of a documented advanced adenoma, the Consensus Group was not able to make a recommendation (neither for nor against) on the use of colonoscopy as the preferred screening test over no screening or all other screening modalities.

**Table 8.** Ranking of Attributes of Screening Tests for Colorectal Cancer in Individuals With a Family History of 1 or More First-Degree Relatives With Advanced Adenoma

Characteristics	Colonoscopy	gFOBT	FS	FIT	Importance for decision
Desirable effects (efficacy)	1	4	2	2	High
Undesirable effects (complications)	4	1	3	2	High
Acceptability	1	4	3	1	High
Balance of effects	1	4	2	2	High
Resources required	4	1	3	2	Medium
Cost-effectiveness	1	1	1	1	Medium
Feasibility	3	1	3	1	Medium
Equity	3	1	3	1	Medium
<b>Overall ranking</b>	1	4	3	2 <sup>a</sup>	—

<sup>a</sup>Three of eight consensus participants had concerns regarding ranking FIT at a lower overall level compared with colonoscopy, in this subgroup of individuals.

**15. For an individual with 1 or more FDRs with a history of a documented advanced adenoma, we suggest colonoscopy or FIT over no screening or all other screening modalities.**  
 GRADE: Conditional recommendation, very-low-quality evidence.  
 Vote: strongly agree, 63%; agree, 38%

**Key evidence.** See Questions 2 and 4. While individuals with an FH of an advanced adenoma appear to be at marginally increased risk for CRC, data are sparse, and it is not clear whether the risk would meet the level of clinically relevant increased risk of 2-fold.

**Discussion.** The Consensus Group recommended some form of screening over no screening, based on the proven benefits of screening. However, the Consensus Group could not make a recommendation for or against the use of colonoscopy as a “preferred test.” Although the group agreed that colonoscopy is the most accurate test, some participants argued screening colonoscopy for all individuals with an FH of an FDR with an advanced adenoma (who may not be at elevated risk), would yield a high number of colonoscopies and likely would not be feasible in Canada. In contrast, the consensus participants from the United States argued that colonoscopy would be the preferred test for this subgroup in the United States.

FIT was considered to be a reasonable option, with acceptable sensitivity and specificity (see Question 4). In addition, while patient preference in individuals at elevated risk because of an FH of CRC is for the most accurate test (colonoscopy), this has not been shown in individuals with an FH of adenoma, and FIT is likely to be more acceptable.

**16. For an individual with 1 or more FDRs with a history of a documented advanced adenoma undergoing screening with colonoscopy or FIT, we suggest commencing CRC screening at age 40–50 years or 10 years younger than the age of diagnosis of the earliest diagnosed FDR, whichever is earlier.**  
 GRADE: Conditional recommendation, very-low-quality evidence.  
 Vote: strongly agree, 38%; agree, 38%; uncertain, 25%

**17. For an individual with 1 or more FDRs with a history of a documented advanced adenoma undergoing screening with colonoscopy, we suggest 5–10 year screening intervals.**  
 GRADE: Conditional recommendation, very-low-quality evidence.  
 Vote: strongly agree, 13%; agree, 75%; uncertain, 13%

**18. For an individual with 1 or more FDRs with a history of a documented advanced adenoma undergoing screening with FIT, we suggest 1–2 year screening intervals.**  
 GRADE: Conditional recommendation, very-low-quality evidence.  
 Vote: strongly agree, 38%; agree, 63%

**Key evidence.** See Questions 3 and 5. Individuals with an FH of an advanced adenoma appear to be at marginally increased risk of CRC.

**Discussion.** There was substantial discussion around whether the potential modest increase in CRC risk warranted either initiating testing at an earlier age or performing more frequent testing compared to average-risk individuals. Because of the uncertainty around the magnitude of increased risk, the Consensus Group agreed to provide ranges for the starting age and testing interval, with clinical judgment and other risk factors being considered in screening decisions. The group stressed that the interval for colonoscopy in most cases should not be fewer than 5 years, but as for average-risk individuals should not be more than 10 years. The US consensus participants argued that based on natural history data suggesting high-grade dysplasia has a high risk of developing into CRC, the preferred screening for these individuals in the United States would be colonoscopy every 5 years.

*One or More First-Degree Relatives With Any Adenoma*

**19. For an individual with 1 or more FDRs with a history of a nonadvanced adenoma or polyp of unknown histology, we suggest screening in accordance with average-risk guidelines.**  
 GRADE: Conditional recommendation, low-quality evidence.  
 Vote: strongly agree, 63%; agree, 38%

**Key evidence.** See Questions 2 and 5. There was no evidence that individuals with an FH of nonadvanced adenomas are at increased risk of CRC.

**Discussion.** The Consensus Group agreed that this subgroup (usually defined as those with  $\leq 2$  non-advanced adenomas that are  $< 10$  mm in size and those without neoplasia), should be screened according to guidelines for average-risk individuals.<sup>14,15,17-20</sup> Persons whose polyp is of unknown histology should be screened according to guidelines for average-risk individuals (please also refer to the discussion for Statements 11-13).

## Future Directions

There is a need for well-designed, large, prospective, and retrospective observational studies that will accurately quantify how an FH of CRC or adenoma affects the risk of CRC. Specifically, prospective studies that assess the optimal time to initiate screening and appropriate intervals between screening should be a priority. These studies should strive to avoid the limitations of the existing studies.

There is also a need for well-designed RCTs assessing the effects of FIT compared to gFOBT or colonoscopy on critical clinical outcomes (long-term CRC incidence and mortality) in this patient population. Similarly, the results of ongoing follow-up of RCTs in average-risk individuals, assessing critical long-term outcomes (eg, CRC mortality and incidence) with colonoscopy compared to no screening or FIT should help inform future guidelines.<sup>70,71,111</sup>

Finally, while there are some studies suggesting that patient preferences and values, as well as barriers and facilitators to CRC screening, may differ in average-risk vs high-risk populations, this needs to be more clearly defined in both populations.

## Canadian Association of Gastroenterology Statement

This CPG on screening for CRC in individuals with a family history of nonhereditary CRC or adenoma was developed under the direction of Drs Desmond Leddin and David A. Lieberman, in accordance with the policies and procedures of the CAG and under the direction of CAG Clinical Affairs. It has been reviewed by the CAG Practice Affairs and Clinical Affairs Committees and the CAG Board of Directors. The CPG was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian and International panel composed of experts on this topic. The CPG aims to provide a reasonable and practical approach to care for specialists and allied health professionals charged with the duty of providing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The CPG is not intended to be a substitute for physicians using their individual judgment in managing clinical care in consultation with the patient, with appropriate regard to all the

individual circumstances of the patient, diagnostic and treatment options available, and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at [www.gastrojournal.org](http://www.gastrojournal.org), and at <https://doi.org/10.1053/j.gastro.2018.08.017>.

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#### Acknowledgments

The Canadian Association of Gastroenterology (CAG) would like to thank the Canadian Partnership Against Cancer (CPAC) for their generous support of the guideline process. The Consensus Group would like to thank the following people for their contributions: Paul Sinclair and Lesley Marshall

(CAG representatives: administrative and technical support, and logistical assistance), Pauline Lavigne and Steven Portelance (unaffiliated, provided medical writing services on their behalf and supported by funds from the Canadian Association of Gastroenterology). Finally, the authors would like to thank their patient advocate, Betty Ball, for valuable insight.

Author contributions: The Clinical Practice Guideline Committee (DL, DAL, ANB, NJS, HS, JJT, JT, ANW), GIL, and FT reviewed the literature and drafted the statements. GIL, FT, and AMA-S assessed the evidence and provided GRADE (Grading of Recommendation Assessment, Development and Evaluation) evaluations. All members of the Consensus Group voted on the recommendations. The manuscript was initially drafted by the co-chairs (DL, DAL) and GIL, after which it was revised based on input from all members of the Consensus Group and the moderator (JKM). As per CAG policy for all clinical practice guidelines, the manuscript was made available to all CAG members for commenting before submission for publication. Members were notified that the manuscript was available on the members-only section of the CAG website and open for comment for a 2-week period.

#### Conflicts of interest

These authors disclose the following: Advisory Board: Abbvie (JKM), Allergan (JKM), AstraZeneca (JKM), Boehringer Ingelheim (JKM), Celgene (JKM), Celltrion (JKM), EXACT Sciences (DAL), Ferring (JKM, HS), Given Imaging (DAL), Hospira (JKM), Janssen Canada (JKM), Merck (JKM), Pendopharm (HS), Pfizer (JKM), PharmaScience (JKM), Proctor and Gamble (JKM), Shire Canada (JKM), Takeda (JKM). Consulting: Abbvie (JKM), Allergan (JKM), AstraZeneca (JKM), Boehringer Ingelheim (JKM), Celgene (JKM), Celltrion (JKM), Ferring (JKM), Hospira (JKM), Janssen Canada (JKM), Merck (JKM), Pfizer (JKM), PharmaScience (JKM), Proctor and Gamble (JKM), Shire Canada (JKM), Takeda (JKM). Speaker's Bureau: Abbvie (JKM), Allergan (JKM), Cook Medical Inc. (NJS), Ferring (JKM), Janssen Canada (JKM), Proctor and Gamble (JKM), Shire Canada (JKM), Takeda (JKM). Funding: Merck (HS). The remaining authors disclose no conflicts.

#### Funding

This guideline was supported through an unrestricted grant to the Canadian Association of Gastroenterology (CAG) by the Canadian Partnership Against Cancer.

## Supplementary Table 1. Systematic Reviews Performed

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### Search for CPGs

Database: PubMed

Language: English

Species: Humans

Publication dates: From January 1, 2000 to January 31, 2017

Search string: ("colorectal neoplasms"[MeSH Terms] OR ("colorectal"[All Fields] AND "neoplasms"[All Fields]) OR "colorectal neoplasms"[All Fields] OR ("colorectal"[All Fields] AND "cancer"[All Fields]) OR "colorectal cancer"[All Fields] OR "colon cancer"[All Fields] OR "rectal cancer"[All Fields]) AND (screen OR screening OR surveillance OR "mass screening"[MeSH Terms]) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR "Task Force"[Title

Results: 261 articles

Reference lists of identified articles were also searched

### Search for relevant randomized controlled trials (RCTs)

Database: PubMed

Language: English

Species: Humans

Publication dates: From January 1, 2011 (rationale: the literature search by the German Institute for Quality and Efficiency in Health Care was conducted in 2011), to January 31, 2017

Search string: Family[All Fields] AND (("colorectal neoplasms"[MeSH Terms] OR ("colorectal"[All Fields] AND "neoplasms"[All Fields]) OR "colorectal neoplasms"[All Fields] OR ("colorectal"[All Fields] AND "cancer"[All Fields]) OR "colorectal cancer"[All Fields] OR "colon cancer"[All Fields] OR "rectal cancer"[All Fields]) AND (screen OR screening OR surveillance OR "mass screening"[MeSH Terms])) AND Randomized Controlled Trial[ptyp]

Results: 97 articles

### Broad search for relevant systematic reviews

Database: PubMed

Language: English

Species: Humans

Publication dates: From January 1, 2015 to January 31, 2017

Search string: ("colorectal neoplasms"[MeSH Terms] OR ("colorectal"[All Fields] AND "neoplasms"[All Fields]) OR "colorectal neoplasms"[All Fields] OR ("colorectal"[All Fields] AND "cancer"[All Fields]) OR "colorectal cancer"[All Fields] OR "colon cancer"[All Fields] OR "rectal cancer"[All Fields]) AND (screen OR screening OR surveillance OR "mass screening"[MeSH Terms])

Search field filter: Title and abstract

PubMed article type filter: systematic reviews OR meta-analysis

Results: 129 articles

### Focused search for relevant systematic reviews

Database: PubMed

Language: English

Species: Humans

Publication dates: From January 1, 2011 (rationale: the literature search by the German Institute for Quality and Efficiency in Health Care was conducted in 2011), to January 31, 2017

Search string: Family[All Fields] AND (("colorectal neoplasms"[MeSH Terms] OR ("colorectal"[All Fields] AND "neoplasms"[All Fields]) OR "colorectal neoplasms"[All Fields] OR ("colorectal"[All Fields] AND "cancer"[All Fields]) OR "colorectal cancer"[All Fields] OR "colon cancer"[All Fields] OR "rectal cancer"[All Fields]) AND (screen OR screening OR surveillance OR "mass screening"[MeSH Terms])

PubMed article type filter: systematic reviews OR meta-analysis

Results: 93 articles

### Search for any type of publication focused on screening or surveillance for familial CRC

Database: PubMed

Language: English

Species: Humans

Publication dates: From January 1, 2011 (rationale: the literature search by the German Institute for Quality and Efficiency in Health Care was conducted in 2011), to January 31, 2017

Search string: (family OR familial) AND "colorectal cancer" AND (screen OR screening OR surveillance)

Search field: Title and abstract

Results: 609 articles



Focused search for relevant RCTs

Database: PubMed

Language: English

Species: Humans

Publication Dates: August 1, 2014 (rationale: the systematic review by CCO (Cancer Care Ontario) searched the literature in Sept 2014) to January 31, 2017

Field: title and abstract

Search string: ((colorectal AND neoplasms OR neoplasms OR cancer OR cancers) OR "colorectal cancer\*" OR "colon cancer\*" OR "rectal cancer\*") AND (fecal OR faecal OR FOBT OR gFOBT OR FIT OR sigmoidoscopy OR colonoscopy OR CT) AND (screened OR screening OR surveillance OR "mass screening"[MeSH Terms]) AND (randomized OR randomised OR random OR randomly)

Results: 356

Focused search for systematic reviews of studies on patients' values and preferences

Database: PubMed

Language: English

Species: Humans

Publication dates: Oct 01, 2013 (rationale: CTFPHC searched the literature in Nov 2013) to January 31, 2017

Field: title and abstract

Search string: ((colorectal AND neoplasms OR neoplasms OR cancer OR cancers) OR "colorectal cancer\*" OR "colon cancer\*" OR "rectal cancer\*") AND (fecal OR faecal OR FOBT OR gFOBT OR FIT OR sigmoidoscopy OR colonoscopy OR CT) AND (screened OR screening OR surveillance) AND (acceptance OR preference OR preferences OR satisfaction OR experience OR value OR values)

PubMed article type filter: systematic reviews

Results: 36

Focused search for cost-effectiveness studies

Database: PubMed

Language: English

Species: Humans

Publication dates: January 31, 2010 to January 31, 2017

Field: title and abstract

Search string: ("colorectal cancer\*" OR "colon cancer\*" OR "rectal cancer\*") AND (fecal OR faecal OR FOBT OR gFOBT OR FIT OR sigmoidoscopy OR colonoscopy) AND (screened OR screening OR surveillance) AND ("cost-effectiveness" OR "cost effectiveness" OR "quality of life" OR "quality-of-life" OR "QALY" OR "Quality Adjusted Life Year\*" OR "Cost Utility Analysis" OR "Cost Benefit Analysis" OR "Cost Efficiency Analysis" OR "Cost-Utility Analysis" OR "Cost-Benefit Analysis" OR "Cost-Efficiency Analysis")

Results: 188

Highly focused search for cost-effectiveness studies in people with FH of CRC

Database: PubMed

Language: English

Species: Humans

Publication dates: January 31, 2010 to January 31, 2017

Field: title and abstract

Search string: ("colorectal cancer\*" OR "colon cancer\*" OR "rectal cancer\*") AND (fecal OR faecal OR FOBT OR gFOBT OR FIT OR sigmoidoscopy OR colonoscopy) AND (screened OR screening OR surveillance) AND ("cost-effectiveness" OR "cost effectiveness" OR "quality of life" OR "quality-of-life" OR "QALY" OR "Quality Adjusted Life Year\*" OR "Cost Utility Analysis" OR "Cost Benefit Analysis" OR "Cost Efficiency Analysis" OR "Cost-Utility Analysis" OR "Cost-Benefit Analysis" OR "Cost-Efficiency Analysis") AND family

Results: 19

Search for prospective studies on the risk of CRC of asymptomatic individuals with an FH of CRC/adenoma vs those without an FH

Database: MEDLINE, EMBASE, EBM Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Cochrane Database of Systematic Reviews

Language: English

Publication dates: 1 January 1996 to Oct 8, 2016

## Supplementary Table 1. Continued

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Search string:

1. exp colorectal neoplasms/ or exp colon cancer/ or exp rectum cancer/
2. ((colon\* or colorectal or rectal or rectum) adj3 (cancer\* or carcinoma\* or malignan\* or tumor\* or tumour\* or neoplas\* or adenocarcinoma\*)).tw,kw.
3. exp Colonic Polyps/ or exp colon polyp/ or exp colorectal polyp/ or exp rectum polyp/
4. ((colon\* or colorectal or rectal or rectum) adj3 (adenoma\* or polyp\*)).tw,kw.
5. 1 or 2 or 3 or 4
6. exp Colonoscopy/ or exp sigmoidoscopy/
7. (colonoscop\* or sigmoidoscop\*).tw,kw.
8. 6 or 7
9. (screening or screened or surveillance).tw,kw.
10. (family history or familial or sibling\* or paternal or maternal or parent or parents or mother or father or brother or brothers or sister or sisters or “degree relative\*” or relatives or family member\*).tw,kw.
11. (risks or risk factors or risk assessment\* or risk prediction\*).ti.
12. or/8-11
13. 5 and 12
14. ((exp animals/ or exp nonhuman/ or exp animal experiment/) not (humans/ or human/)) or ((rats or mice or mouse or cats or dogs or animal\* or cell lines or rat or cat or in vivo or in vitro) not (human\* or men or women)).ti.
15. case report/ or case reports/ or case report.ti.
16. note/ or editorial/ or letter/ or Comment/ or news/
17. conference abstract.pt. or Congresses as Topic/
18. or/14-17
19. 13 not 18
20. limit 19 to English language [Limit not valid in CDSR; records were retained]
21. limit 20 to yr=“1996 -Current”

Results: 58,131 (after removing duplicates: 35,105)

Full-text screening: 2094 publications

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CDSR, Cochrane Database of Systematic Reviews; CTFPHC, Canadian Task Force on Preventive Health Care; MeSH, medical subject headings; QALY, quality-adjusted life year.