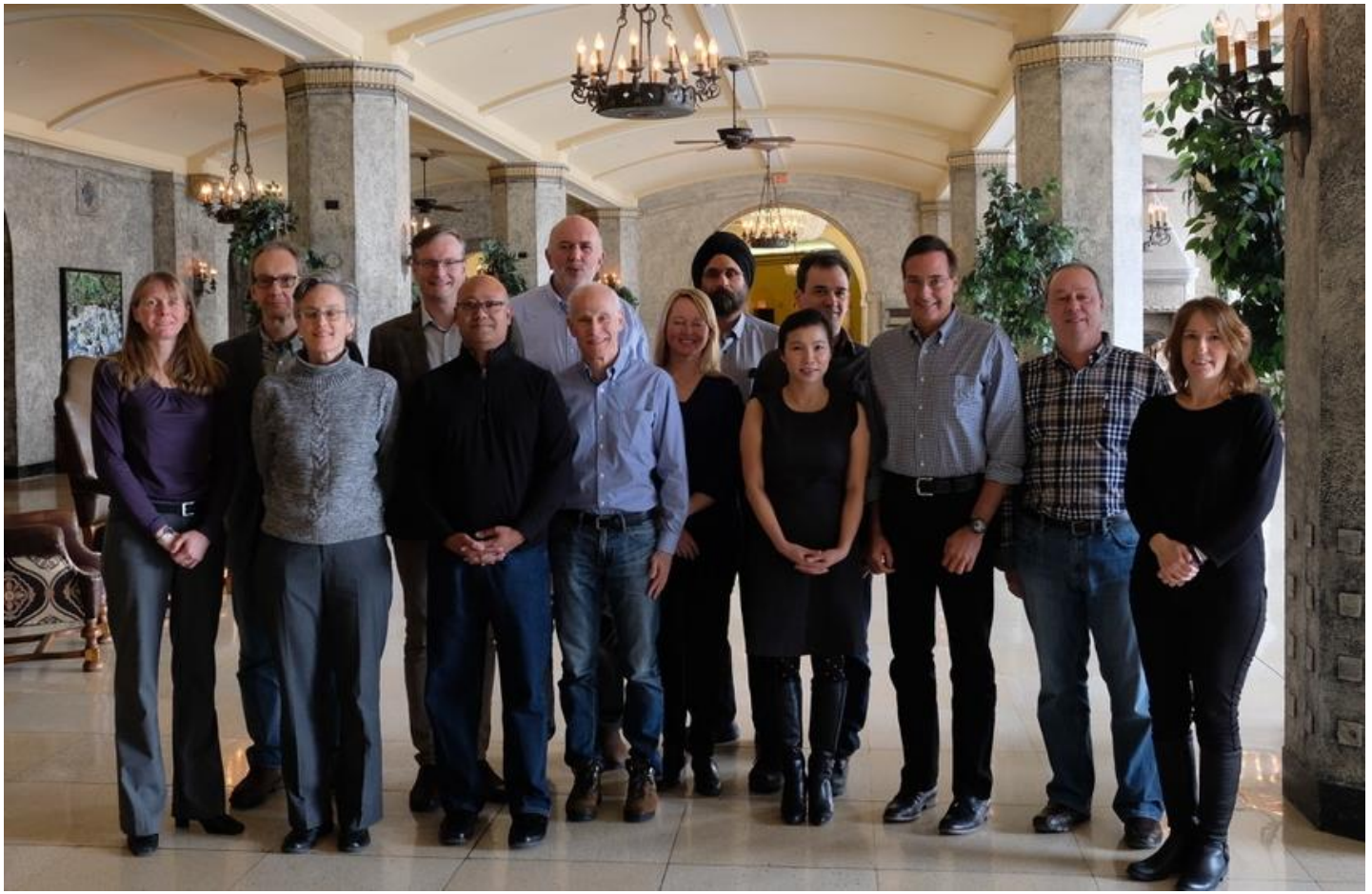
Clinical Practice Guideline on Screening for Colorectal Cancer in Individuals with a family history of Non Hereditary Colorectal Cancer or Adenoma

D Leddin,
D Lieberman,
G Leontiadis,
F Tse,
AN Barkun,
J Marshall,
N Samadder,
H Singh,
JJ Telford,
J Tinmouth,
A Abou-Setta,
AN Wilkinson



CAG GI BANFF CONSENSUS MEMBERS

CANADIAN PARTNERSHIP AGAINST CANCER | PARTENARIAT CANADIEN CONTRE LE CANCER

Canadian Association of Gastroenterology | L'Association Canadienne de Gastroentérologie

American Gastroenterological Association

Name: Dr. Alan Barkun

Conflict of Interest Disclosure

(over the past 24 months)

Commercial or Non-Profit Interest	Relationship
Cook Medical Inc.	advisory board, consultant
Olympus Inc.	advisory board, consultant
Pendopharm Inc.	advisory board, consultant, research support
ATGEN Inc.	advisory board, research support

Gastroenterology 2018;155:1325–1347

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

Desmond Leddin,[1,2,*] **David A. Lieberman**,[3,*] Frances Tse,[4] Alan N. Barkun,[5] Ahmed M. Abou-Setta,[6] John K. Marshall,[4] N. Jewel Samadder,[7] Harminder Singh,[6,8] Jennifer J. Telford,[9] Jill Tinmouth,[10] Anna N. Wilkinson,[11] and Grigorios I. Leontiadis[4]

Background

- CRC second leading cause of deaths in US and Canada
- Prevalence of an individual having
  - ≥1 or more FDR with CRC: 3-10%
  - ≥ 2 FDR: 0.3%
- Individuals with a positive family history are at increased risk of developing CRC
- Few guidelines on detailed recommendations for those with FH history of CRC or adenoma
  - Have not systematically reviewed the literature
  - No recent CAG guideline on the topic

http://www.cancer.ca/w/media/cancer.ca/CW/publications/Canadian%20Cancer%20Statistics/Canadian-Cancer-Statistics-2017-EN.pdf; https://seer.cancer.gov/csr/1975_2014/; Henrikson, Genet Med, 2015

Background 2

- Individuals with a FHx of CRC are more likely to adhere to CRC screening recommendations compared to those without
- But even among this higher-risk population, participation rates remain less than optimal

Henrikson, Genet Med, 2015

Objectives

- The purpose of this guideline was to systematically and critically review the literature and provide specific recommendations for CRC screening of individuals with a FH of nonhereditary CRC or adenoma
- This is a CAG guideline, that was endorsed post hoc by the AGA

Targeted patient population

- This guideline specifically excludes individuals with hereditary syndromes (~5% of all CRC), 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

Methods

- The review process focused on 5 principal questions:
  - For an individual, how does the FH of CRC (including the number and family connection of affected relatives) or the FH of adenoma (including the stage of adenoma) affect his/her own risk of CRC?
  - For an individual with a FH of CRC or adenoma, at what age should screening begin?
  - For an individual with a FH of CRC or adenoma, what is/are the optimal screening test(s)?
  - For an individual with a FH of CRC or adenoma, what are the optimal testing intervals?

Overview of methodology

- **Evidence for guidelines:**
  - **Multiple parallel systematic reviews**
  - **10 literature searches (>35,000 titles)**
  - **> 2000 full texts reviewed**
- **GRADE methodology and Evidence to Decision framework (where relevant) applied**
- **Anonymous voting**

Slide courtesy of Dr. J Tinmouth, CDDW 2019

Recommendations

- 19 recommendation statements developed and voted on
  - Accepted if ≥75% of participants voted agree or strongly agree
- Strength of recommendations
  - QoE**, benefit/harm balance, patients' values/preferences, and resource requirements
  - Strong = "we recommend"
  - Conditional = "we suggest"

Slide courtesy of Dr. J Tinmouth, CDDW 2019

Because of the nature of the evidence, concept of “spectrum of risk” is important

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[a]

	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 FIT	No recommendation for a preferred test. Colonoscopy or FIT are both options	According to average-risk guidelines	
Age	40 y or 10 y younger than age of diagnosis of earliest diagnosed FDR, whichever is earlier[a]	40–50 y or 10 y younger than age of diagnosis of FDR, whichever is earlier[a]	40–50 y or 10 y younger than age of diagnosis of earliest diagnosed FDR, whichever is earlier[a]	50 y	
Interval	Colonoscopy: 5 y	Colonoscopy: 5–10 y FIT: 1–2 y	Colonoscopy: 5–10 y FIT: 1–2 y	According to average-risk guidelines	

[a] The age of the affected relative should be considered when making clinical decisions regarding screening.

Principal Question: #1 - a

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?

- **Taking the data altogether, an RR of 2 or more was a reasonable cutoff point to define a clinically significant increased risk of CRC**
- **An individual with an FH of 1 FDR with CRC is likely at a 2-fold higher risk of CRC compared to those without**
- **An individual's CRC risk increases with an increasing number of affected FDRs (as eg: 3-6x increase if >2 FDR w CRC)**

Principal Question: #1 - b

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?

- **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 (RR ~1.2)**
- **Individuals whose FHx includes only SDRs with CRC can be regarded as average-risk individuals**
- **CAUTION:**
  - **Take a careful FHx**
  - **Germline genetic testing should be considered in those with a high burden of CRC among relatives**

Principal Question: #2 - a

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?

- The malignant potential of an adenoma increases with size, histology, and number
- Prevalence of adenomas: 20-30%, advanced adenomas 6-7%
- Evidence for an **increased risk of CRC** in individuals with a FHx of adenomas is very limited and appears low (OR as low as 0.86), but with a **greater risk** (RR~1.68) amongst patients with a FHx of **advanced adenomas**

Principal Question: #2 - b

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?

- **Siblings of individuals with ≥1 advanced adenoma had**
  - **6-fold increased odds of advanced adenoma and**
  - **3-fold increased odds of any adenoma**
- **Elevated risks when FDR with advanced adenoma <60 yrs; still elevated when >60 yrs**
- **So mainly increased risk for FHx of ADVANCED adenoma (even if most patients unaware); guidelines thus focus on these but only if documented as such (if not assume not)**

Principal Question: #3 - a

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)?

- In 3 recent studies the RR was **2.35** (1.92–2.86) when FDR **<60 yrs and 1.79** (1.58–2.03) **if > 60 yrs** - P=.02, thought clinically important
- The (HR) **risk decreases as age of FDR increases, but remains elevated for any age cut-off** (HR from 2.53 to 1.69 per 10 yrs ranges <40 and ≥80)
- There is thus a **continuum for increased risk** based on the age of FDR CRC diagnosis, but a cutoff of age at 50 or 60 years is rather arbitrary
- The FDR age should be considered when making clinical decisions regarding screening

Principal Question: #3 - b

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)?

- Data assessing the age of the individual to be screened for CRC have shown that the risk of CRC increases with age in both average- and high-risk populations
- The evidence supports an elevated risk of CRC for all individuals with a FHx, and screening programs are likely effective in all age subgroups
- No age-specific risk of CRC data for FHx of adenomas
- The clinical decision to initiate early screening should consider both the ages of the individual and affected relative; age-specific risk of CRC is a continuum and is elevated at all ages compared to those with no FH

Principal Question: #4 - a

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

- The 4 main testing strategies considered were colonoscopy, FS, gFOBT, and FIT
- Evidence extrapolated from average-risk populations
- Only 1 RCT in individuals with FHx CRC comparing FIT and colonoscopy, but results not reliable due to high risk of bias and serious imprecision
- Individuals with FHx of CRC are more likely to adhere to CRC screening recommendations
- Patient preference and cost-effectiveness are also considerations

Principal Question: #4 - b

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

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

Principal Question: #5

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

- **Screening interval extrapolated from the natural history of adenomas in unselected screened individuals**
- **There is little evidence to suggest the natural progression of adenomas in individuals with a FHx would differ from those without a FHx**
- **No good data to confidently inform screening intervals for a FHx of CRC or adenomas**

AND NOW (FINALLY) THE RECOMMENDATIONS

Screen vs No screen

- For an individual with ≥1 FDR with CRC, we recommend screening over no screening
- For an individual with ≥1 SDR with CRC, we recommend screening over no screening
- For an individual with ≥1 FDR with documented AA, we recommend screening over no screening

Strong Evidence
SA 100%

Mod Evidence
SA 88%
A 13%

Mod Evidence
SA 63%
A 38%

1 FDR with CRC

- We suggest **colonoscopy** as the preferred screening test over no screening or all other screening modalities

V Low Evid
SA 88%
A 13%

- We suggest **starting colonoscopy at age 40-50 y or 10 y younger** than the age of diagnosis of the FDR, whichever is earlier

V Low Evid
SA 50%
A 50%

- We suggest screening with colonoscopy at **5-10 y intervals**

V Low Evid
SA 25%
A 63%
Unc 13%

1 FDR with CRC

- We suggest FIT as a 2nd-line screening option

Mod Evid
SA 50%
A 38%
Unc 13%

- We suggest starting FIT at age 40-50 y or 10 y younger than the age of diagnosis of the FDR, whichever is earlier

V Low Evid
SA 25%
A 75%

- We suggest screening with FIT at 1-2 y intervals

V Low Evid
SA 38%
A 63%

≥2 FDR with CRC (*consider inherited syndromes)

- We recommend **colonoscopy** as the preferred screening test vs no screening or all other screening tests

V Low Evid
SA 63%
A 38%

- We suggest **starting colonoscopy at age 40 y or 10 y younger than** the age of diagnosis of the FDR, whichever is earlier

V Low Evid
SA 63%
A 38%

- We suggest screening with colonoscopy at **5 y intervals**

V Low Evid
SA 38%
A 63%

≥1 SDR with CRC

- We suggest starting screening at age 50 y

- We suggest screening tests and intervals in accordance with average risk guidelines

Low Evidence
SA 50%
A 50%

V Low Evid
SA 38%
A 63%

≥1 FDR with documented Advanced Adenoma

- No recommendation for the preferred screening test

- We suggest colonoscopy or FIT vs no screening or all other screening modalities

V Low Evid
SA 63%
A 38%

≥1 FDR with documented Advanced Adenoma

- We suggest starting colonoscopy or FIT at age 40-50 y or 10 y younger than the age of diagnosis of the FDR, whichever is earlier

V Low Evid
SA 38%
A 38%
Unc 26%

- We suggest screening with colonoscopy at 5-10 y intervals

V Low Evid
SA 13%
A 75%
Unc 13%

- We suggest screening with FIT at 1-2 y intervals

V Low Evid
SA 38%
A 63%

≥1 FDR with non-advanced adenoma or polyp of unknown histology

- We suggest screening in accordance with average risk guidelines

Low Evidence
SA 63%
A 38%

	→FH according to decreasing level of elevated risk of CRC→ Highest risk → → → → → → → → → → → → Lowest risk				
	2 or more FDR 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	No recommendation for a preferred test. Colonoscopy or FIT are both options	According to average risk guidelines	
2nd-line option		FIT			
Age	40 y or 10 y younger than age of diagnosis of earliest diagnosed FDR, whichever is earlier*	40-50 y or 10 y younger than age of diagnosis of FDR, whichever is earlier*	40-50 y or 10 y younger than age of diagnosis of earliest diagnosed FDR, whichever is earlier*	50 y	
Interval	Colonoscopy: 5 y	Colonoscopy: 5-10 y FIT: 1-2 y	Colonoscopy: 5-10 y FIT: 1-2 y	According to average risk guidelines	

CRC = colorectal cancer; FDR = first-degree relative; FH = family history; FIT = fecal immunochemical test; SDR = second-degree relative

*The age of the affected relative should be considered when making clinical decisions regarding screening.

Acknowledgments

- CAG: Paul Sinclair, Lesley Marshall
- CPAC: David Armstrong
- GRADE Methodologists: Grigorios Leontiadis, Frances Tse, Ahmed Abu-Setta
- Consensus group members: Des Leddin, David Lieberman, Alan Barkun, Jewel Samadder, Harminder Singh, Jennifer Telford, Jill Tinmouth, Anna Wilkinson
- Moderator: John Marshall
- Medical writer: Pauline Lavigne