Evidenced-Based Screening Strategies for a Positive Family History

Jennifer M. Kolb, MD[a,*], Dennis J. Ahnen, MD[a], N. Jewel Samadder, MD, MSc[b,c]

KEYWORDS

• Advanced adenoma • First-degree relative • Second-degree relative
• Colorectal cancer • Colon cancer screening

KEY POINTS

- Common familial colorectal cancer refers to the associated risk to family members from a sporadic colorectal cancer in probands.
- Individuals with a first-degree relative with colorectal cancer are at a 2-fold or higher risk of colorectal cancer and advanced neoplasia.
- Individuals with a first-degree relative with advanced adenoma have an increased risk of colorectal cancer and advanced neoplasia.
- Professional gastroenterology and oncology society guidelines recommend starting colorectal cancer screening by age 40 in high-risk groups with a positive family history.

INTRODUCTION

Successful implementation and uptake of colorectal cancer (CRC) screening in the United States have had a meaningful impact toward decreasing the incidence and mortality of CRC.[1] However, CRC remains the fourth most common cause of cancer in the United States and the second leading cause of cancer death with 51,020 deaths estimated to occur in 2019.[2] Because colon cancer is preventable, identifying those who might benefit most from screening has the greatest potential to decrease disease burden.

Funding Support: J.M. Kolb is supported in part by the NIH Gastrointestinal Diseases Training Grant (T32-DK007038).
[a] Division of Gastroenterology & Hepatology, University of Colorado Hospital, Anschutz Medical Campus, Aurora, CO, USA; [b] Division of Gastroenterology & Hepatology, Mayo Clinic, 5881 East Mayo Boulevard, Phoenix, AZ 85054, USA; [c] Department of Clinical Genomics, Mayo Clinic, Phoenix, AZ, USA
* Corresponding author. Division of Gastroenterology & Hepatology, University of Colorado Hospital, Anschutz Medical Campus, 1635 Aurora Court, F735, Aurora, CO 80045.
E-mail address: jennifer.m.kolb@cuanschutz.edu

Gastrointest Endoscopy Clin N Am 30 (2020) 597–609
https://doi.org/10.1016/j.giec.2020.02.015
giendo.theclinics.com

The most commonly recognized high-risk group for CRC is individuals with a positive family history. It is generally recognized that those with a first-degree relative (FDR) with CRC are at a 2-fold or higher risk of CRC or advanced neoplasia. FDRs of patients with advanced adenomas (AAs) have a similarly increased risk. Accordingly, all major US guidelines recommend starting CRC screening by age 40 in these groups.[3–5] Recommendations on screening interval and type of examination are more nuanced and vary between guidelines.

The aims of this paper are to (1) define high-risk populations with a positive family history, (2) describe the risk in those with a positive family history, (3) review the current guidelines for screening and the strength of the recommendations, (4) review the evidence for earlier screening, and (5) discuss challenges and strategies to screening this group.

IDENTIFYING HIGH-RISK PATIENTS WITH A POSITIVE FAMILY HISTORY

In any patient with CRC, it is important to assess family history to see if the individual meets clinical criteria for genetic testing. The National Comprehensive Cancer Network (NCCN) recommends genetics evaluation in anyone with CRC under the age of 50 or with an FDR (parent, sibling, or child) with CRC under the age of 50.[6] In the most extreme situations, such as heritable, monogenic syndromes, such as Lynch syndrome or polyposis syndromes, the risk of CRC can approach 80% to 100%. These patients undergo specialized screening protocols that are beyond the scope of this article and are summarized elsewhere.[6,7]

In the present review, the authors focus on sporadic CRC in probands and the associated risk to family members often referred to as *common familial* CRC. In addition, the authors focus on a family history of AA as a risk factor. AAs are traditionally defined as large ($\geq$1 cm) tubular adenomas or any adenoma with high-grade dysplasia or villous histology. AAs are high-risk polyps that confer an increased risk of future colorectal neoplasia to the affected individual[8–11] and are considered the immediate precursors to CRC and the target of CRC screening.[12,13] Family history in the setting of advanced serrated polyps (ASPs), the analogous, potentially high-risk lesions in the serrated pathway, are also discussed.

RISK IN INDIVIDUALS WITH A POSITIVE FAMILY HISTORY OF COLORECTAL CANCER

The lifetime risk of CRC in average risk individuals is approximately 4.5% and approximately double in individuals with a positive family history.[14] Familial CRC may have some component that is genetic in origin or may be an effect of shared environmental exposures. It is estimated that approximately 10% of the general population aged 30 to 70 years old have an FDR affected by CRC,[15] and up to 30% will have an FDR or second-degree relative (SDR) with CRC.[16]

Numerous studies dating back to the 1980s and incorporated into screening guidelines provided data supporting an increased risk of CRC in patients with FDRs with CRC.[17] One of the first prospective studies by Fuchs and colleagues[18] with greater than 100,000 people using self-reported family history questionnaires demonstrated increased risk among those with affected FDRs compared with no family history (relative risk [RR] 1.72, 95% confidence interval [CI] 1.34–2.19) and even higher risk in younger patients less than 45 years (RR 5.37, 95% CI 1.98–14.6). Most other original studies were retrospective case control or cohort studies with inherent study limitations (did not control for confounders and were limited by self-reported family history); however, they still provided meaningful data on the increased familial risk outside of genetic syndromes.[19–21] These data have been summarized in meta-analyses that

indicate a more than 2-fold higher risk of CRC (RR 2.24–2.81) in those with an FDR with CRC (Table 1).[22–24] In 2013, Johnson and colleagues[25] evaluated 12 different risk factors for CRC and identified an FDR with CRC as a significant factor associated with increased risk (RR 1.80, 95% CI 1.61–2.02). More recent studies from the authors' group in Utah using the specialized resources of the Utah Population Database, which houses genealogic data in association with linked cancer records, provides robust estimates of familial CRC risk without the family history recall bias of past studies. These data reported a 1.8-fold (95% CI 1.59–2.03) risk of CRC in those with an FDR with CRC and importantly demonstrated that the risk of CRC remains elevated no matter the age of the affected relative.[26,27]

ADDITIONAL FACTORS THAT INFLUENCE RISK IN INDIVIDUALS WITH A POSITIVE FAMILY HISTORY OF COLORECTAL CANCER

Several additional factors related to family history also influence the risk of CRC, including (1) proband age, (2) number of affected family members, (3) type of relative, and (4) site of cancer.

All relatives of individuals with CRC are at increased risk regardless of the age of the affected patient, but in general, the risk appears to be higher the younger the proband. A 2015 systematic review and meta-analysis reported the highest risk in those with an FDR who had CRC at age less than 50 (pooled risk 3.55, 95% CI 1.84–6.83).[28] Since that publication, data from the Utah Population Database and linked cancer registry showed highest risk when index CRC patients were diagnosed at age less than 40 years (hazard ratio 2.53, 95% CI 1.7–3.79).[27] This study and 2 others were included in a meta-analysis for the Banff consensus statement that reported a pooled RR of 2.35 (95% CI 1.92–2.86) for individuals with an FDR with CRC diagnosed at less than 60 years compared with no family history, and for FDR with CRC at $\geq$60 years, the RR was 1.79 (95% CI 1.58–2.03) (P = .02).[4] A more recent analysis similarly showed significantly elevated risk if the FDR had CRC at age less than 50 (RR 3.57,

Table 1
Risk estimates for family history of colorectal cancer in meta-analyses

Metaanalysis	RR for FDR (95% CI)	RR for FDR According to Proband Age (95% CI)
Johns et al,[22] 2001	2.25 (2.00–2.53)	<45: 3.87 (2.40–6.22) 45–59: 2.25 (1.85–2.72) >60: 1.82 (1.47–2.25)
Baglietto et al,[23] 2006	2.26 (1.86–2.73)	
Butterworth et al,[24] 2006	2.24 (2.06–2.43)	<50: 3.55 (1.84–6.83) >50: 2.18 (1.56–3.04)
Johnson et al,[25] 2013	1.80 (1.61–2.02)	—
Wong et al,[70] 2018	1.76 (1.57–1.97)	<50: 2.81 (1.94–4.07) >50: 1.47 (1.28–1.69)
Leddin et al,[4] 2018	1.31 (1.11–1.55)	<60: 2.35 (1.92–2.86) >60: 1.79 (1.58–2.03)
Mehraban Far et al,[71] 2019	1.87 (1.68–2.09)	
Roos et al,[29] 2019	1.92 (1.53–2.41)[a] 1.37 (0.76–2.46)[b]	<50: 3.57 (1.07–11.85)[a] >50: 3.25 (2.82–3.77)[b]

[a] For case-control studies (n = 42).
[b] For cohort studies (n = 20).

95% CI 1.73–4.55 for case control studies and RR 3.26, 95% CI 2.82–3.77 for cohort studies).[29]

The number of affected family members also impacts the risk of CRC. In a constellation approach using the Utah statewide cancer records linked to genealogy whereby the RR of CRC with ≥1 affected FDR with CRC was consistent with published estimates (2.05, 95% CI 1.96–2.14), the RR was modestly increased for 1 affected FDR, 1 affected SDR, and 0 affected third-degree relatives (TDR) (RR 1.88, 95% CI 1.59–2.20).[30] Risk significantly increased with the addition of affected relatives (RR 3.28, 95% CI 2.44–4.31 for 1 FDR, 1 SDR, and ≥3 TDRs affected). In the absence of an affected FDR, risk remained elevated compared with no family history when 1 SDR and 2 TDRs were affected (RR 1.33, 95% CI 1.13–1.55). More recent pooled risk estimates suggest a nearly 4-fold increase in risk for 2+ affected FDRs compared with no family history (RR 3.97, 95% CI 2.60–6.06).[28] The risk of CRC in more distant relatives is modestly increased,[14,28] but likely does not meet the need for clinical screening.[31]

There also appears to be a differential risk according to the type of FDR, whereby multiple studies demonstrate higher CRC risk in siblings versus parents,[32–34] although this finding may be limited to individuals greater than 50 years old.[31] Finally, the site of cancer (colon vs rectum) may also impact familial risk. Earlier studies suggest higher risk with colon versus rectal cancer,[35] but a large population-based study in Utah reported no difference according to the subsite of primary cancer.[36]

RISK IN INDIVIDUALS WITH A POSITIVE FAMILY HISTORY OF ADVANCED ADENOMAS

There is evidence of an increased CRC risk in those with an FDR with an AA, although the risk estimates may be less than having a relative with CRC (**Table 2**). Of note, although earlier studies suggested higher risk with family history of non-AA,[22,37] more recent analyses have shown that the presence of a non-AA does not significantly impact risk for AA or CRC.[38]

Many of the studies evaluating familial risk with AA focus only on a subtype of AA (advanced by size vs by polyp histology) and also are designed to report varying outcomes (advanced neoplasia, CRC). A large cross-sectional study from Hong Kong reported that siblings with AA had a 6-fold higher risk of having an AA than siblings of those with a normal colonoscopy (odds ratio [OR] 6.05, 95% CI 2.74–13.36) and even higher for adenoma with high-grade dysplasia (OR 19.98,

Table 2
Level of risk for family member of patients with advanced colorectal polyps

	Risk in FDR, OR/RR (95% CI)	
Pathology in Proband	**AA**	**CRC**
Advanced Adenoma	6.05 (2.74–13.36)[39,a]	—
Tubular adenoma ≥10 mm	8.59 (3.4–21.45)[39]	3.9 (0.89–17.01)[40]
Adenoma with villous histology	2.27 (1.01–5.09)[40,b] 1.65 (1.28–2.14)[37,c] 6.28 (2.02–19.53)[39]	1.68 (1.29–2.18)[37]
Adenoma with high-grade dysplasia	19.98 (2.03–1.97)[39]	—

[a] In siblings.
[b] For composite endpoint of large adenoma and/or CRC.
[c] For adenoma with villous histology only (not advanced by size or high-grade dysplasia).

95% CI 2.03–19.7).[39] A French case control study showed that FDRs of those with large adenomas were at least 2 times more likely to develop a composite endpoint of CRC and large adenomas (OR 2.27, 95% CI 1.01–5.09).[40] A nested case control study from Utah showed 1.7 times higher risk of CRC in those with an FDR with a villous adenoma (RR 1.65, 95% CI 1.28-2.18).[37]

Recognition of the serrated pathway contributing to up to 30% of CRC has prompted consideration for analogous lesions referred to as ASPs.[41,42] Similar to conventional AA, these are defined as sessile serrated polyp (SSP) $\geq$1 cm, SSP with any degree of cytologic dysplasia, or traditional serrated adenoma (TSA). TSAs of any size are considered advanced as related to surveillance (3-year interval recommended)[43] but only TSA $\geq$1 cm are considered advanced as related to the recommendation for earlier screening for FDRs.[3] There are no studies on familial risk with ASP, and therefore, the magnitude of risk is unknown, although presumed to be elevated.

CURRENT SCREENING GUIDELINES FOR POSITIVE FAMILY HISTORY

US guidelines recommending earlier screening for those with an FDR with CRC have been in place for nearly 30 years, with slight modifications over time. The US Multi-Society Task Force (US-MSTF), made up by the 3 major gastrointestinal societies, including the American Gastroenterological Association (AGA), the American Society for Gastrointestinal Endoscopy, and the American College of Gastroenterology, last released CRC screening guidelines in 2017.[3] The NCCN updates their CRC screening guidelines annually, although the 2019 recommendations are largely the same as previous years.[5] In 2018, the Canadian Association for Gastroenterology (CAG) in conjunction with the AGA released the Banff consensus statement for CRC screening in those with nonhereditary family history of CRC.[4] The US-MSTF, NCCN, and Banff statement all provide recommendations for screening individuals with a family history of CRC (**Table 3**) and a family history of AA (**Table 4**).

The US-MSTF recommends that individuals who have a single FDR with CRC at less than 60 years old (or in 2 FDRs of any age) start screening at age 40, or 10 years before the age of the youngest affected relative (whichever is earlier). Colonoscopy is the preferred screening test (with a 5-year interval), and if declined, fecal immunochemical test (FIT) should be offered. If the affected relative was $\geq$60 years old, screening should commence at age 40 with the same tests and intervals as average-risk individuals. The US-MSTF recommends the exact same approach whether the relative had CRC or AA. In addition, the US-MSTF suggests that individuals with FDR with ASPs can be treated similarly to those with conventional AA. All of these statements for family history of CRC/AA are noted to be weak recommendations based on low- or very-low-quality evidence.

The NCCN is largely similar to the US-MSTF with the 1 major difference being that age of the proband affected by CRC or AA/ASP is not taken into account in screening recommendations for FDRs. The other nuance is that the NCCN recommends commencing screening at age 40, or at the age of diagnosis of AA in the FDR. That means if the AA was diagnosed at age 45, the time to start screening would differ between the US-MSTF (age 35) and NCCN (age 40). The Banff consensus statement used robust methodology (systematic review and meta-analysis with the GRADE system) to evaluate the quality of the evidence and strength of the recommendation. Like the NCCN, there is no distinction according to age of the affected relative. Normal average risk approach is recommended for those with a family history of non-AAs or only SDRs with CRC. Most of these statements are conditional recommendations based on low- or very-low-quality evidence. Of note, the American Cancer Society

Table 3
Colorectal cancer screening guidelines and strength of recommendation for individuals with a family history of colorectal cancer

	Family History	Age to Initiate Screening	Preferred Test, Interval
Banff Consensus Statement (CAG/AGA)[4]	CRC in 1 FDR[a]	Age 40–50, or 10 y younger than age of diagnosis of FDR[b]	Colonoscopy preferred every 5–10 y or FIT[c] every 1–2 y
		GRADE: conditional recommendation, very-low-quality evidence	
	CRC in ≥2 FDR	Age 40, or 10 y younger than age of diagnosis of FDR[b]	Colonoscopy[d] every 5 y
		GRADE: conditional recommendation, very-low-quality evidence	
US-MSTF[3]	CRC in 1 FDR <60 y or in 2 FDRs with CRC (any age)	Age 40, or 10 y younger than age of diagnosis of FDR[b]	Colonoscopy[e] every 5 y
		Weak recommendation, low-quality evidence	
	CRC in 1 FDR ≥60 y	Age 40	Same as for average-risk persons (colonoscopy every 10 y or FIT annually)
		Weak recommendation, very-low-quality evidence	
NCCN[5]	≥1 FDR with CRC at any age	Age 40, or 10 y younger than age of diagnosis of FDR	Colonoscopy every 5 y
		Category 2A recommendation	

[a] Recommend screening over no screening (*GRADE: strong recommendation, moderate-quality evidence*).
[b] Whichever is earlier.
[c] FIT as second-line screening option *(GRADE: conditional recommendation, moderate-quality evidence)*.
[d] Colonoscopy as the preferred screening test over no screening or all other modalities *(GRADE: strong recommendation, very-low-quality evidence)*.
[e] Persons should be offered annual FIT if they decline colonoscopy *(GRADE: strong recommendation, moderate-quality evidence)*.

and US Preventive Services Task Force only provide recommendations on CRC screening for average-risk individuals.[44]

EVIDENCE THAT EARLIER SCREENING IS EFFECTIVE IN THOSE WITH A FAMILY HISTORY

The increased RR of CRC in individuals with an FDR with CRC (or AA) has been shown in many studies, but it is more difficult to study the benefit that has been appreciated from earlier screening in this group. The main reason to start screening earlier is that individuals with a positive family history of CRC have an earlier median age of CRC compared with those without a family history. Although there are no randomized controlled trials to guide the optimal interval for CRC screening in this group, the effectiveness of screening and the shorter screening interval were demonstrated in a large cohort study examining the incidence of CRC after a negative colonoscopy.[45] In the first 5 years after a negative colonoscopy, the incidence of

Table 4
Colorectal cancer screening guidelines and strength of recommendation for individuals with a family history of advanced colorectal polyp

	Family History	Age to Initiate Screening	Preferred Test, Interval
Banff Consensus Statement (CAG/AGA)[4]	*Documented* AA in >1 FDR (any age)[a]	Age 40–50, or 10 y younger than age of diagnosis of FDR[b]	Colonoscopy every 5–10 y or FIT every 1–2 y
		GRADE: conditional recommendation, very-low-quality evidence[c]	
US-MSTF[3]	Documented AA in 1 FDR <60 y or in 2 FDRs with AA (any age)	Age 40, or 10 y younger than age of diagnosis of FDR[b]	Colonoscopy[d] every 5 y
		Weak recommendation, low-quality evidence	
	AA in 1 FDR ≥60 y	Age 40	Same as for average-risk persons (colonoscopy every 10 y or FIT annually)
		Weak recommendation, very-low-quality evidence	
	Documented ASL in >1 FDR	According to recommendations for family history of documented AA	
		Weak recommendation, very-low-quality evidence	
NCCN[5]	*Confirmed* AA or ASL in 1 FDR (any age)	Age 40, or at age of diagnosis of AA in FDR[b]	Colonoscopy every 5–10 y
		Category 2A recommendation	

Abbreviation: ASL, advanced serrated lesions.
[a] Recommend screening over no screening (*GRADE: strong recommendation, moderate-quality evidence*).
[b] Whichever is earlier.
[c] Consensus group was not able to make a recommendation (neither for or against) the use of colonoscopy as the preferred screening test over no screening or all other screening modalities.
[d] Persons should be offered annual FIT if they decline colonoscopy *(GRADE: strong recommendation, moderate-quality evidence)*.

CRC was significantly lower in those with an FDR with CRC (standardized incidence ratio [SIR] 0.39, 95% CI 0.13–0.64), but not when the interval was greater than 5 years (SIR 0.74, 95% CI 0.32–1.16). Thus, a negative colonoscopy in individuals with an FDR with CRC confers a 45% lower reduction in CRC risk compared with those without family history, supporting a shorter interval in this high-risk group.

INTERNATIONAL APPROACHES TO FAMILY-BASED COLORECTAL CANCER SCREENING

Outside of the United States, many countries have tried to implement updates to their CRC screening programs that incorporate family history. In 2008 in Canada, a population-based screening program for individuals with a family history was introduced, and a microsimulation modeling study examined the potential impact of this new strategy over the following 30 years.[46] Compared with a regular guaiac fecal occult blood program, a family history–based program was projected to prevent 40% additional deaths while requiring 93% additional colonoscopies. In the Netherlands, where they have population-based FIT screening, they evaluated the

impact of offering colonoscopy to a target group who were both FIT positive and had an FDR with CRC.[47] This strategy would increase the yield of advanced neoplasia from 3.2% to 4.8%, with a number needed to scope to detect 1 subject with advanced neoplasia of 5.0 compared with 2.8.

In Ireland, they implemented a special CRC screening service where they used family history questionnaires to stratify patients into risk categories (low risk, moderate risk, Lynch syndrome suspected or diagnosed).[48] Moderate risk was defined as 1 FDR with CRC diagnosed less than 60 years, or 2 FDR with CRC or 2 SDR with CRC diagnosed less than 60 years. At index colonoscopy in this group, they detected adenomas in 16.4% and AA in 4.4%. Interestingly, they did not find any difference in adenoma or AA yield according to risk category, although overall, they had low adenoma detection rate (18%). A US study evaluating screening computed tomographic colonography found no significant difference in rates of AA, non-AA, or cancer in patients with an FDR with CRC versus no family history.[49]

COST-EFFECTIVENESS OF SCREENING IN THOSE WITH FAMILY HISTORY

The cost-effectiveness of screening individuals with positive family history earlier and more frequently has been evaluated and appears to vary according to the number of affected FDRs.[50] Naber and colleagues[51] used the Microsimulation Screening Analysis model to determine the impact of various screening intervals for this high-risk group using a cost-effectiveness ratio less than $100,000 per quality-adjusted life-year as a threshold. Their results showed that the most cost-effective strategy for individuals with 1 affected FDR was to begin screening at age 40 and continue every 3 years, then to gradually extend the interval to 5 years (at age 45) and then 7 years (at age 55) if no adenomas are found. These results lend credence to current guidelines recommending initiation of screening at an earlier age from the perspective of societal cost. The finding that it is cost-effective to gradually increase the screening interval after a negative colonoscopy is important; however, cost is not currently factored into screening guidelines in the United States.

BARRIERS TO USE OF FAMILY CANCER HISTORY IN PRACTICE

The challenges to CRC screening for individuals with a positive family history are multifactorial and include patient level factors, provider limitations in collecting family history, and insufficient application of guidelines resulting in inadequate screening practices.

In general, patients have poor knowledge of their family history of cancer and know even less about their family history of colon polyps. When surveyed, almost a quarter of patients did not know which family members had polyps, and a large proportion of patients did not know the age at diagnosis (43%), polyp type (71%), number of polyps found (91%), or polyp size (97%).[52] With limited knowledge of polyps in relatives, it is nearly impossible to identify those with AA and incorporate this information into practice. On the provider side, physicians may not take comprehensive family histories[53] and may lack the knowledge to assess risk.[54] Multiple different online family history questionnaires have been developed to overcome these barriers, although most of them have failed to facilitate enrolling additional relatives in screening or surveillance programs for CRC.[55] In conjunction with the National Colorectal Cancer Roundtable, the authors' group has provided a guide for endoscopists to appreciate guideline recommendations for CRC screening in individuals with a family history of AA and tools to implement these recommendations in routine clinical practice.[56]

Adherence to screening in individuals with family history of CRC is suboptimal, although may be higher than the general population.[57,58] One study using National Health Interview Survey data revealed that FDRs were nearly twice as likely as those without family history to get a colonoscopy (adjusted odds ratio 1.7, 95% CI 1.5–1.9), but still only 46% of this at-risk group completed a colonoscopy.[59–61] Multiple interventions have been tried to improve colonoscopy utilization in this high-risk group. A tailored telephone counseling intervention for individuals with a positive family history who were due for colonoscopy within 24 months achieved a 32% increase in screening adherence compared with a mailed packet with general information about screening.[62]

Recent literature shows the success and cost-effectiveness of state-wide patient navigation (PN) programs to target priority patients for CRC screening.[63,64] PN has also been studied in high-risk patients with a positive family history. Paskett and colleagues[65] assessed adherence to screening recommendation in a randomized clinical trial comparing a Web site intervention (survey and personal CRC screening recommendation) versus the Web site plus the addition of a PN intervention via telephone in patients with an FDR with CRC. Overall adherence was 79% (similar in both groups), and PN was only useful in cases whereby screening was needed immediately. Even in high-risk groups with targeted interventions, adherence to screening recommendations still falls short.

IMPACT OF FAMILY HISTORY ON THE INCREASE OF EARLY-ONSET COLORECTAL CANCER

There has been an unprecedented increase in the incidence of early onset (EO) CRC in young adults less than 50 years old worldwide with ongoing studies to identify the drivers of increasing disease. Although reports in the literature identify the majority of this young cohort as not having a positive family history, still an FDR with CRC has been shown to be associated with EO-CRC (OR 8.61, 95% CI 4.83–15.75) outside of hereditary cancers.[66,67] As we search for markers to indicate which young adults may be at increased risk, at a minimum, those with FDR with CRC or AA should be targeted for earlier screening.

FUTURE DIRECTIONS

Risk stratification for CRC is primarily driven by family history. More, and better, data are needed to more clearly understand the risk to family members and to help guide screening practices. Efforts should focus on improving acquisition of family history and better adherence to guidelines. New approaches for familial risk assessment include prediction algorithms through computation analyses and artificial neural networks to accurately stratify risk.[68,69] Perhaps genomic analysis may add to or replace family history information. However, most of these technologies still rely on self-reported family history, which requires individuals to be knowledgeable about their family members' colonoscopy findings (polyp and CRC). Providers should make a conscious effort to ascertain family history of cancer or polyps in all of their patients, inform their patients of colonoscopy findings and to share these with their relatives, and follow guidelines for earlier screening for those with a positive family history.

DISCLOSURE

None.

REFERENCES

1. Ansa BE, Coughlin SS, Alema-Mensah E, et al. Evaluation of colorectal cancer incidence trends in the United States (2000-2014). J Clin Med 2018;7(2) [pii:E22].
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019; 69(1):7–34.
3. Rex DK, Boland CR, Dominitz JA, et al. Colorectal cancer screening: recommendations for physicians and patients from the U.S. Multi-Society Task Force on colorectal cancer. Gastroenterology 2017;153(1):307–23.
4. Leddin D, Lieberman DA, Tse F, et al. 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. Gastroenterology 2018;155(5):1325–47.e3.
5. National Comprehensive Cancer Network. Colon Cancer. Version 2, 2019. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed November 1, 2019.
6. National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal. Version 3, 2019. https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf. Accessed November 1, 2019.
7. Kastrinos F, Samadder NJ, Burt RW. Use of family history and genetic testing to determine risk of colorectal cancer. Gastroenterology 2020;158(2):389–403.
8. Click B, Pinsky PF, Hickey T, et al. Association of colonoscopy adenoma findings with long-term colorectal cancer incidence. JAMA 2018;319(19):2021–31.
9. Cottet V, Jooste V, Fournel I, et al. Long-term risk of colorectal cancer after adenoma removal: a population-based cohort study. Gut 2012;61(8):1180–6.
10. Leung K, Pinsky P, Laiyemo AO, et al. Ongoing colorectal cancer risk despite surveillance colonoscopy: the Polyp Prevention Trial Continued Follow-up Study. Gastrointest Endosc 2010;71(1):111–7.
11. Lieberman DA, Weiss DG, Harford WV, et al. Five-year colon surveillance after screening colonoscopy. Gastroenterology 2007;133(4):1077–85.
12. Toll AD, Fabius D, Hyslop T, et al. Prognostic significance of high-grade dysplasia in colorectal adenomas. Colorectal Dis 2011;13(4):370–3.
13. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell 1990; 61(5):759–67.
14. Tian Y, Kharazmi E, Sundquist K, et al. Familial colorectal cancer risk in half siblings and siblings: nationwide cohort study. BMJ 2019;364:l803.
15. Weigl K, Tikk K, Hoffmeister M, et al. Prevalence of a first-degree relative with colorectal cancer and uptake of screening among persons 40 to 54 years old. Clin Gastroenterol Hepatol 2019. [Epub ahead of print].
16. Mitchell RJ, Campbell H, Farrington SM, et al. Prevalence of family history of colorectal cancer in the general population. Br J Surg 2005;92(9):1161–4.
17. Levin B, Murphy GP. Revision in American Cancer Society recommendations for the early detection of colorectal cancer. CA Cancer J Clin 1992;42(5):296–9.
18. Fuchs CS, Giovannucci EL, Colditz GA, et al. A prospective study of family history and the risk of colorectal cancer. N Engl J Med 1994;331(25):1669–74.
19. Ponz de Leon M, Antonioli A, Ascari A, et al. Incidence and familial occurrence of colorectal cancer and polyps in a health-care district of northern Italy. Cancer 1987;60(11):2848–59.
20. Lovett E. Family studies in cancer of the colon and rectum. Br J Surg 1976; 63(1):13–8.

21. St John DJ, McDermott FT, Hopper JL, et al. Cancer risk in relatives of patients with common colorectal cancer. Ann Intern Med 1993;118(10):785–90.
22. Johns LE, Houlston RS. A systematic review and meta-analysis of familial colorectal cancer risk. Am J Gastroenterol 2001;96(10):2992–3003.
23. Baglietto L, Jenkins MA, Severi G, et al. Measures of familial aggregation depend on definition of family history: meta-analysis for colorectal cancer. J Clin Epidemiol 2006;59(2):114–24.
24. Butterworth AS, Higgins JP, Pharoah P. Relative and absolute risk of colorectal cancer for individuals with a family history: a meta-analysis. Eur J Cancer 2006;42(2):216–27.
25. Johnson CM, Wei C, Ensor JE, et al. Meta-analyses of colorectal cancer risk factors. Cancer Causes Control 2013;24(6):1207–22.
26. Samadder NJ, Curtin K, Tuohy TM, et al. Increased risk of colorectal neoplasia among family members of patients with colorectal cancer: a population-based study in Utah. Gastroenterology 2014;147(4):814–21.e5 [quiz: e815-816].
27. Samadder NJ, Smith KR, Hanson H, et al. Increased risk of colorectal cancer among family members of all ages, regardless of age of index case at diagnosis. Clin Gastroenterol Hepatol 2015;13(13):2305–11.e1-2.
28. Lowery JT, Ahnen DJ, Schroy PC, et al. Understanding the contribution of family history to colorectal cancer risk and its clinical implications: a state-of-the-science review. Cancer 2016;122(17):2633–45.
29. Roos VH, Mangas-Sanjuan C, Rodriguez-Girondo M, et al. Effects of family history on relative and absolute risks for colorectal cancer: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2019;17(13):2657–67.e9.
30. Taylor DP, Burt RW, Williams MS, et al. Population-based family history-specific risks for colorectal cancer: a constellation approach. Gastroenterology 2010;138(3):877–85.
31. Kim NH, Yang HJ, Park SK, et al. The risk of colorectal neoplasia can be different according to the types of family members affected by colorectal cancer. J Gastroenterol Hepatol 2018;33(2):397–403.
32. Hemminki K, Chen B. Familial risks for colorectal cancer show evidence on recessive inheritance. Int J Cancer 2005;115(5):835–8.
33. Boardman LA, Morlan BW, Rabe KG, et al. Colorectal cancer risks in relatives of young-onset cases: is risk the same across all first-degree relatives? Clin Gastroenterol Hepatol 2007;5(10):1195–8.
34. Carstensen B, Soll-Johanning H, Villadsen E, et al. Familial aggregation of colorectal cancer in the general population. Int J Cancer 1996;68(4):428–35.
35. Yu H, Hemminki A, Sundquist K, et al. Familial associations of colon and rectal cancers with other cancers. Dis Colon Rectum 2019;62(2):189–95.
36. Samadder NJ, Smith KR, Mineau GP, et al. Familial colorectal cancer risk by subsite of primary cancer: a population-based study in Utah. Aliment Pharmacol Ther 2015;41(6):573–80.
37. Tuohy TM, Rowe KG, Mineau GP, et al. Risk of colorectal cancer and adenomas in the families of patients with adenomas: a population-based study in Utah. Cancer 2014;120(1):35–42.
38. Ng SC, Kyaw MH, Suen BY, et al. Prospective colonoscopic study to investigate risk of colorectal neoplasms in first-degree relatives of patients with non-advanced adenomas. Gut 2019;69(2):304–10.
39. Ng SC, Lau JY, Chan FK, et al. Risk of advanced adenomas in siblings of individuals with advanced adenomas: a cross-sectional study. Gastroenterology 2016;150(3):608–16 [quiz: e616–7].

40. Cottet V, Pariente A, Nalet B, et al. Colonoscopic screening of first-degree relatives of patients with large adenomas: increased risk of colorectal tumors. Gastroenterology 2007;133(4):1086–92.
41. Kolb JM, Soetikno RM, Rao AK, et al. Detection, diagnosis, and resection of sessile serrated adenomas and polyps. Gastroenterology 2017;153(3):646–8.
42. Noffsinger AE. Serrated polyps and colorectal cancer: new pathway to malignancy. Annu Rev Pathol 2009;4:343–64.
43. Lieberman DA, Rex DK, Winawer SJ, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2012;143(3):844–57.
44. Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin 2018;68(4):250–81.
45. Samadder NJ, Pappas L, Boucherr KM, et al. Long-term colorectal cancer incidence after negative colonoscopy in the state of Utah: the effect of family history. Am J Gastroenterol 2017;112(9):1439–47.
46. Goede SL, Rabeneck L, Lansdorp-Vogelaar I, et al. The impact of stratifying by family history in colorectal cancer screening programs. Int J Cancer 2015; 137(5):1119–27.
47. Kallenberg FGJ, Vleugels JLA, de Wijkerslooth TR, et al. Adding family history to faecal immunochemical testing increases the detection of advanced neoplasia in a colorectal cancer screening programme. Aliment Pharmacol Ther 2016;44(1): 88–96.
48. Walshe M, Moran R, Boyle M, et al. High-risk family colorectal cancer screening service in Ireland: critical review of clinical outcomes. Cancer Epidemiol 2017; 50(Pt A):30–8.
49. Pickhardt PJ, Mbah I, Pooler BD, et al. CT colonographic screening of patients with a family history of colorectal cancer: comparison with adults at average risk and implications for guidelines. AJR Am J Roentgenol 2017;208(4):794–800.
50. Wilschut JA, Steyerberg EW, van Leerdam ME, et al. How much colonoscopy screening should be recommended to individuals with various degrees of family history of colorectal cancer? Cancer 2011;117(18):4166–74.
51. Naber SK, Kuntz KM, Henrikson NB, et al. Cost effectiveness of age-specific screening intervals for people with family histories of colorectal cancer. Gastroenterology 2018;154(1):105–16.e120.
52. Elias PS, Romagnuolo J, Hoffman B. Poor patient knowledge regarding family history of colon polyps: implications for the feasibility of stratified screening recommendations. Gastrointest Endosc 2012;75(3):598–603.
53. Solomon BL, Whitman T, Wood ME. Contribution of extended family history in assessment of risk for breast and colon cancer. BMC Fam Pract 2016;17(1):126.
54. Schroy PC 3rd, Barrison AF, Ling BS, et al. Family history and colorectal cancer screening: a survey of physician knowledge and practice patterns. Am J Gastroenterol 2002;97(4):1031–6.
55. Kallenberg FGJ, Aalfs CM, The FO, et al. Evaluation of an online family history tool for identifying hereditary and familial colorectal cancer. Fam Cancer 2018;17(3): 371–80.
56. Molmenti CL, Kolb JM, Karlitz JJ. Advanced colorectal polyps on colonoscopy: a trigger for earlier screening of family members. The Am J Gastroenterol 2020; 115(3):311–4.

57. Dillon M, Flander L, Buchanan DD, et al. Family history-based colorectal cancer screening in Australia: a modelling study of the costs, benefits, and harms of different participation scenarios. PLoS Med 2018;15(8):e1002630.
58. Henrikson NB, Webber EM, Goddard KA, et al. Family history and the natural history of colorectal cancer: systematic review. Genet Med 2015;17(9):702–12.
59. Tsai MH, Xirasagar S, Li YJ, et al. Colonoscopy screening among US adults aged 40 or older with a family history of colorectal cancer. Prev Chronic Dis 2015; 12:E80.
60. Bronner K, Mesters I, Weiss-Meilnik A, et al. Do individuals with a family history of colorectal cancer adhere to medical recommendations for the prevention of colorectal cancer? Fam Cancer 2013;12(4):629–37.
61. Taylor DP, Cannon-Albright LA, Sweeney C, et al. Comparison of compliance for colorectal cancer screening and surveillance by colonoscopy based on risk. Genet Med 2011;13(8):737–43.
62. Lowery JT, Horick N, Kinney AY, et al. A randomized trial to increase colonoscopy screening in members of high-risk families in the colorectal cancer family registry and cancer genetics network. Cancer Epidemiol Biomarkers Prev 2014;23(4): 601–10.
63. Rice K, Sharma K, Li C, et al. Cost-effectiveness of a patient navigation intervention to increase colonoscopy screening among low-income adults in New Hampshire. Cancer 2019;125(4):601–9.
64. DeGroff A, Gressard L, Glover-Kudon R, et al. Assessing the implementation of a patient navigation intervention for colonoscopy screening. BMC Health Serv Res 2019;19(1):803.
65. Paskett ED, Bernardo BM, Young GS, et al. Comparative effectiveness of two interventions to increase colorectal cancer screening for those at increased risk based on family history: results of a randomized trial. Cancer Epidemiol Biomarkers Prev 2019;29(1):3–9.
66. Stoffel EM, Murphy CC. Epidemiology and mechanisms of the increasing incidence of colon and rectal cancers in young adults. Gastroenterology 2019; 158(2):341–53.
67. Gausman V, Dornblaser D, Anand S, et al. Risk factors associated with early-onset colorectal cancer. Clin Gastroenterol Hepatol 2019. [Epub ahead of print].
68. Rieger AK, Mansmann UR. A Bayesian scoring rule on clustered event data for familial risk assessment–an example from colorectal cancer screening. Biom J 2018;60(1):115–27.
69. Nartowt BJ, Hart GR, Roffman DA, et al. Scoring colorectal cancer risk with an artificial neural network based on self-reportable personal health data. PLoS One 2019;14(8):e0221421.
70. Wong MCS, Chan CH, Lin J, et al. Lower relative contribution of positive family history to colorectal cancer risk with increasing age: a systematic review and meta-analysis of 9.28 million individuals. Am J Gastroenterol 2018;113(12): 1819–27.
71. Mehraban Far P, Alshahrani A, Yaghoobi M. Quantitative risk of positive family history in developing colorectal cancer: a meta-analysis. World J Gastroenterol 2019;25(30):4278–91.