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Understanding the Contribution of Family History to Colorectal Cancer Risk and Its Clinical Implications: A State-of-the-Science Review

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Abstract

Background—Persons with a family history (FH) of colorectal cancer (CRC) or adenomas that are not due to known hereditary syndromes have increased risk for CRC. Understanding these risks, screening recommendations and screening behaviors can inform strategies to reduce CRC burden in these families.

Methods—A comprehensive review of literature published within the past 10 years was conducted to assess what is known about cancer risk, screening guidelines, adherence and barriers to screening and effective interventions in persons with FH of CRC, and to identify FH tools used to identify these individuals and inform care.

Results—Existing data show that having one affected first-degree relative (FDR) increases CRC risk by 2-fold, and risk increases with multiple affected FDRs and younger age at diagnosis. There was variability in screening recommendations across consensus guidelines. Screening adherence was <50% and lower in persons under age 50. Having a provider's recommendation, multiple affected relatives and family encouragement facilitated screening; insufficient collection of FH, low knowledge of guidelines, and poor family communication were important barriers. Effective interventions incorporated strategies for overcoming barriers but these have not been tested broadly in clinical settings.

Conclusions—Four strategies for reducing CRC in persons with familial risk are suggested: 1) improve how we collect and utilize cancer FH, 2) establish consensus for screening guidelines by FH, 3) enhance provider-patient knowledge of guidelines and communication about CRC risk, 4)

encourage survivors to promote screening within their families, and partner with existing screening programs to expand reach to high-risk groups.

Keywords

Family history; colorectal cancer; risk; screening adherence; interventions

Introduction/Background

Colorectal cancer (CRC) remains a common yet preventable disease; it is the fourth most frequently diagnosed cancer in the U.S., and the second most common cause of cancer death. [1] More than 130,000 Americans will be diagnosed and 50,000 will die from CRC in 2015.[1] The lifetime risk for developing CRC in the general population is about 6%, but this risk is believed to be much higher for persons with a family history (FH) of CRC. It is estimated that up to 10 percent of U.S. adults have a first-degree relative (FDR) that has been diagnosed with CRC and about 30% have an affected first or second-degree relative. [2–6]

CRC can be detected early through screening and prevented by removal of polyps, yet adherence to screening remains suboptimal. Overall, adherence to CRC screening has steadily increased in the US; in 2014 approximately 65% of the general population reported having had some form of CRC screening.[7] Although guidelines vary somewhat, individuals with a FH of CRC or a documented FH of a large (>1cm) or histologically advanced (villous architecture or high grade dysplasia) adenoma are typically advised to utilize colonoscopy as the preferred screening test, to start screening earlier than age 50 and repeat screening at more frequent intervals than average risk groups. The few studies of screening rates among individuals with a FH of CRC suggest that less than half of these individuals may be adherent with risk-based guidelines.[8–10] Because of their heightened risk, assuring that these families are properly screened is critical for reducing morbidity and mortality in these families.

The FH Task Group of the National Colon Cancer Roundtable (NCCRT) conducted this review to better understand the current state of knowledge regarding FH and CRC in terms of disease risk, screening adherence, barriers to screening, and effective interventions in order to inform future strategies to improve screening rates in persons with familial risk. The focus of this review is persons with a FH of CRC and/or colonic adenomas excluding those from families with known hereditary CRC syndromes such as Lynch Syndrome or Familial Adenomatous Polyposis (FAP). The hereditary syndromes represent very high-risk populations (40–100% life-time CRC risk) that together account for about 5% of all CRCs. These syndromes and have well established guidelines for risk assessment and medical management and have been reviewed in detail. [11–15] Also excluded (when possible) are persons in families that met clinical criteria for Hereditary Non-polyposis Colorectal Cancer Syndrome without known mutations such as Familial Colon Cancer Type X that are known to have higher CRC risk and require more intense screening.[16] The primary focus of this review is the larger at- risk population; persons with first-degree and second-degree relative history of CRC or adenomatous polyps.

Methods

A standardized protocol was followed for developing the search strategy, establishing inclusion criteria, abstracting data and synthesizing results. The search strategy was developed with the help of a reference librarian to identify articles that addressed each of six key questions identified by the Task Group that are listed below:

Key Questions

1. What are the risks for CRC associated with FH of CRC or adenomatous polyps (adenomas)?
2. What are the existing screening recommendations for persons with a FH of CRC and/or adenomas in the U.S.?
3. What are the rates of adherence to screening recommendations among persons with a FH of CRC and/or adenomas?
4. What are the predictors and barriers to CRC screening in these high-risk populations?
5. What interventions have proven effective for improving screening rates in these high-risk populations?
6. What types of tools are available for assessing cancer FH to inform CRC screening?

Data Sources and Inclusion Criteria

Medline, Embase and National Guidelines Clearinghouse databases were searched for articles published from January 1, 2004 to July 15, 2015. Sentinel articles published more than 10 years prior were included as appropriate. The search was limited to English-language articles, and excluded editorials, letters, conference papers, comments, opinions or abstracts only. For Questions 1, 3, 4 and 5, we restricted our search to randomized controlled trials or observational studies and included only studies that specifically focused on persons with a FH of CRC (non-hereditary forms). For question 2, we limited our search to guidelines based in the United States. For Question 6, we selected a convenience sample of existing tools available in the U.S that include FH of CRC as publication is limited in the field since the majority of these tools are newly and/or commercially developed; final selection of tools presented was guided by experts on the Task Group. The search strategy and terms are provided in the Supplemental Materials.

Data Abstraction

Data was abstracted into separate data tables for each key question. The tables were reviewed and discussed by members of the FH Task Group of the NCCRT, as well as several nationally recognized experts who were invited to the Symposium on FH and CRC in September 2014 that was organized and sponsored by the NCCRT.

Data Synthesis and Analysis

Results were summarized for each key question. The FH Task Group and key experts evaluated the results of the literature search and identified gaps in knowledge, opportunities for improving CRC screening rates in persons with a FH. The Task Group also provided recommendations for next steps to address these gaps and optimize opportunities for improving identification and management of this group. These recommendations are presented in the Discussion section.

Results

A total of 5,780 articles were identified and screened for inclusion. A sequential review of titles, abstracts and full-text articles resulted in a final set of 76 articles that were included in this review. A summary of results for each key question are presented below in terms of what is known, based on current evidence, and what is not known or uncertain due to lack of evidence in a specific area.

Question 1: What are the risks for CRC associated with FH of CRC or adenomatous polyps (adenomas)?

What is Known: FH of CRC—Four meta-analyses and 12 original studies were identified that evaluated risk of CRC associated with having a FH of CRC.[17–32] Results from these studies consistently show that the risk of developing CRC is about 2 times higher in persons with *at least one* affected FDR than in those without a FH, and that risk increases with the number of affected FDRs and with earlier age of diagnosis (Table 1). The risk of CRC is more than 3-fold higher among persons with a FDR diagnosed under age 50 (pooled relative risk (RR) from meta-analysis =3.55; 95% confidence interval =1.84–6.83), and between 2 and 3-fold higher if a FDR is diagnosed under the age of 60 (RR range=1.81–3.30). Although CRC risk among FDRs of persons diagnosed with CRC at older ages (≥60 or ≥70 years) is slightly attenuated, it is still significantly higher (nearly 2-fold) than that for persons of similar age without a FH. The risk of CRC has also been shown to be higher for younger (<50 years) unaffected family members of persons with CRC.[17,23]

Six studies assessed risk of CRC associated with having an affected second (SDR) or third-degree relative (TDR).[17,21,26,28–30] These studies indicate that the risk of CRC among persons with ≥1 affected SDR is about 75% higher than persons with no FH and the risk associated with having a single affected TDR is elevated but much less (12%–15% higher) (Table 1). A study by Taylor et al (2010) that assessed risk of CRC based on various combinations of family history concluded that the number of FDRs is the most important predictor of risk, but that a single FDR in combination with a SDR or TDR, can also increase risk by 2-fold or more.[21] Among seven studies that compared risk of CRC according to the relationship of the affected FDR, five cited higher risk associated with having an affected sibling compared to a parent. [17–19,22,25] Of six studies that assessed risk according to cancer site (colon vs. rectum), four report higher risks of CRC among persons with an FDR with colon (2–3 fold) vs. rectal cancer (generally less than 2-fold increased risk); [19,23,25,30] two studies reported no difference in risk according to the sub-site of the primary CRC in the affected relative. [26,32]

What is Known: FH of adenomas—One meta-analysis and three original studies were identified that assessed the risk of CRC associated with having an FDR with colonic adenomas. [18,33–35] Results from these studies suggest that the relative risk of CRC associated with having a FDR with an adenoma compared to persons with no FH of adenomas is less than 2.0 (RR range=1.35–1.99) (Table 1). The risk of CRC is somewhat higher if the adenoma was 'large' (>10mm; (RR= 1.68; 1.29–2.18) or 'advanced' (with villous histology; RR=3.90; 0.89–17.01) and if the FDR was diagnosed with an adenoma under age 60 (Table 1).

What is Not Known—It is not known to what degree inclusion of families with undiagnosed hereditary CRC syndromes (eg. Lynch syndrome) or those with Familial CRC Type X may have impacted estimates of CRC risk among persons with a family history of CRC. Further, although population-based risk estimates associated with having a FDR affected with CRC are fairly consistent, little is known about the extent to which environmental factors influence risk at the individual level or how these modify risk of developing CRC in persons with a FH.

Relatively few studies have examined risk of CRC associated with a FH of adenomas. Further, the definition of adenomas was variable across studies, and most did not distinguish adenomas according to histologic features or size (e.g., advanced versus non-advanced) making it difficult to assess risk by adenoma subtype. With improvements in screening adherence and shrinking family size, the definition of high-risk based on FH of CRC will likely change. In the future, we will have to rely more on diagnoses of polyps to identify families that are at increased risk. Thus knowing the histology and size of polyps and understanding the attendant CRC risk conferred upon family members will become increasingly important.

In recent years, it has become clear that sessile serrated polyps and traditional serrated adenomas are also CRC precursors and that they arise through a different molecular pathway than conventional adenomas.[36] These polyps are particularly important because they are more difficult to identify and remove than conventional adenomas. Further, they appear to contribute disproportionately to interval CRCs (CRCs that develop in the interval between routine screening exams).[37] There are essentially no data related to CRC risk based on a FH of serrated polyps. These unresolved issues highlight the need for more studies to refine our understanding of familial risk associated with both adenomas and serrated lesions.

Question 2: What are the existing screening recommendations for persons with a FH of CRC or adenomas?

Existing Guidelines—Seven organizations were identified that currently provide guidelines for CRC screening for persons with a FH (Table 2). [38–44] The one group for whom the guidelines are consistent across organizations are persons with 1 FDR with CRC <60 years of age or 2 or more FDRs with CRC at any age; the recommendation in this group is to start colonoscopic screening at 5 year intervals at age 40 or 10 years earlier than the earliest CRC in the family. For persons who have 1 FDR with CRC ≥60, the recommendations differ ranging from average risk screening (start at age 50 with any

screening option) to colonoscopy every 5–10 years starting at age 40 (Table 2). Three organizations have guidelines for persons with affected SDRs. With respect to FH of polyps, two organizations specify recommendations only for history of ‘advanced adenoma’, while the other five organizations specify a history of ‘adenoma’; none of them include serrated polyps specifically.

What is Not Known—Although guidelines exist, it is not known to what degree these guidelines are followed. Little is known about whether provider specialty (primary care vs specialty care), patient insurance type or reimbursement rates determine what guidelines are followed by providers for their high-risk patients. Studies have demonstrated that both primary care providers and specialists lack sufficient knowledge to accurately assess risk and implement appropriate guidelines for persons with familial risk.[45–48] Since the guidelines have changed in recent years, new studies are needed to assess current knowledge and practices among providers and whether inconsistencies in the guidelines influence provider adherence.

It is notable that two of the seven organizations specify a history of ‘advanced adenoma’ versus simply ‘adenoma’ for defining risk and recommendations. The evidence to support more intensive screening in persons who have a relative with an ‘advanced adenoma’ is limited. It is estimated that, with improvements in endoscopic imaging and greater attention to colonoscopy quality and adenoma detection, nearly one half of the population that is age-eligible for screening might have an adenoma detected. Thus, adherence to guidelines that support more intensive screening in relatives of persons with any adenoma would greatly increase the number and costs of screening as well the potential for harm and unnecessary workup, with seemingly little impact on CRC burden. [49] Moreover, studies show that a patient’s knowledge about polyps in family members is limited.[50] Thus, full implementation of the guidelines will require better communication about polyps between providers and patients and within families.

Finally, though the guidelines generally support more frequent screening for persons with an FDR with CRC or an adenoma under age 60, there is a paucity of evidence supporting these intervals; statistical modeling studies are ongoing (personal communication Anne Zauber, CISNET). There is also limited empiric data to evaluate the cost-benefit ratio for more intensive screening in this group though results from decision analytic modeling suggest that colonoscopy every 5 years is cost-effective in persons at increased CRC risk.[51]

Question 3: What are the rates of adherence to screening recommendations among persons with a FH of CRC or adenomas?

What is Known—Twenty articles including two meta-analyses, one review article and 16 original studies were identified that evaluated endoscopic screening adherence in persons with a FH of CRC.[2,6,8,10,52–67] These studies generally show that adherence in this group to recommended guidelines for age of screening initiation and screening interval is relatively low, less than 50 percent (range =31%–47%).[8–10,52,60,64,68] A meta-analysis of 17 studies from 1995 to 2012 reported that the percentage of persons with at least 1 FDR with CRC that had *ever* had colonoscopy was 40% (range =26–54%), but the percent who had

colonoscopy per the recommended interval (within 5 years) was only 31% (range =12–51%) [53]. The estimates for *ever* having colonoscopy, though higher than those 'per guidelines', are somewhat lower than those reported in an earlier review by Rees et al (2008) of 16–69%.[54] However, the Rees review included studies of persons who had received genetic counseling, a population known to have higher adherence rates. The review by Rees also found that studies that had surveyed unaffected FDRs that had been referred by a CRC-affected relative report higher screening rates (generally greater than 50%).

Only one study identified (from Australia) had assessed adherence as defined by age at initiation of colonoscopy and compliance with recommended intervals over time (every 5 years from age 50 forward). This study found that only 6% of persons with a FDR with CRC diagnosed at <55 years of age were fully adherent. [52]

Eight studies identified analyzed data from U.S. or state-based population surveys to assess adherence to CRC screening according to recommendations from the U.S. Preventive Services Task Force that would be applicable to average risk persons (colonoscopy every 10 years). More recent studies (using survey data from 2005 forward) report rates of adherence of 65% to77%, [2,56,58,67] which are significantly higher than those reported in earlier studies using data from 2000 of 28% for persons over 40 years [62] or limited to persons 40–49 years of age.[63] A recent study by Tsai et al (2015) using national data showed that although adherence to colonoscopy screening among persons with a FDR with CRC has improved overall with time, from 25% in 2000 to nearly 66% in 2010, adherence remains low in persons aged 40–49 (38% in 2010).[2] In another study, adherence was also found to be lower among Hispanics (44%) compared to Asians (83%), non-Hispanic Whites (79%) or non-Hispanic Blacks (72%).[67] One study that was able to assess adherence to colonoscopy within five years using data from the 2009 California Health Interview study, reported adherence rates of 60% among persons with a FDR with CRC.[65] These studies also generally show that adherence to USPSTF guidelines, was 2–3 times higher among persons with FH of CRC compared to those with no FH.[2,6,57,58,63]

What is Not Known—The majority of studies have evaluated screening adherence at one point in time rather than adherence with the recommended age of initiation and screening interval. Thus there is limited data to evaluate adherence to current recommendations. Further, many studies do not discern between 'screening' vs. 'diagnostic' colonoscopies, and most rely on self-reported screening behaviors, which may overestimate adherence. It is also difficult to compare estimates across studies given the variability in the populations studied (accrued via an affected family member vs. clinic or population-based settings), how FH is defined (any vs. FDR vs. FDR under a certain age), and what guidelines are used with which to measure adherence.

One of the major challenges to assessing screening adherence in high-risk populations is the lack of population-based surveillance systems to capture sufficient FH information and risk appropriate screening behaviors. To adequately measure adherence, a system would need to collect both. The National Health Information Survey (NHIS) added a cancer control module in 2000 and some states have added questions to their Behavioral Risk Factor Surveillance Surveys to periodically collect cancer FH and screening history. However, the

sampling strategy for these surveys results in relatively small numbers of persons with a significant FH and these surveys cannot measure adherence over time. Further, the age category for affected FDRS (<50 vs. >50) that is used to stratify respondents by risk group does not align with current guidelines (FDR <60). Thus, while useful for assessing adherence at a population level, these surveys have limited ability to measure adherence to risk-based guidelines.

Question 4: What are the known predictors and barriers to screening in these high risk populations?

What is Known—One systematic review, one review article and 10 original studies were identified for this question.[54,69–79] A recent systematic review found that the most important predictors of screening adherence were having a doctor recommendation (increased likelihood of screening by 5 to 27-fold), and multiple affected family members (3.7 times more likely to screen if >1 FDR affected).[69] The closeness of the relationship of the affected family member and social influence of family and friends were also found to be consistent, though more modest predictors of screening (up to 3-fold higher). [69] Additional studies cited having private insurance, perceived CRC risk, having knowledge of their relative's diagnosis and having discussed FH with their provider and/or having this documented in the medical record as predictors of screening and or intentions to screen.[54,59,70–73,75,76] The evidence is mixed across studies with respect to the influence of gender, age, income, and education on adherence. [54,77]

Common barriers to CRC screening reported by patients across studies include lack of symptoms, anticipation of pain from the test, and not having a doctor recommendation.[54] One qualitative study assessed barriers to screening in patients with a FH of CRC from the providers' (primary care providers and specialists) perspective. [74] Provider-related barriers included a lack of availability of educational materials for high-risk patients and the lack of systematic means for collecting FH. Patient and systems-related barriers cited were patient inability to provide complete FH, challenges in communicating with family members about screening, and systems that do not allow providers to talk with family members of CRC patients or monitor screening in family members. Facilitators cited were having access to simple messages about risk with practical rules for applying recommendations, educating patients on the importance of screening based on their personal or FH of CRC, and having educational materials available that are targeted to high-risk patients.

Inadequate collection of FH and lack of knowledge of the importance of FH to inform screening were also cited as patient and systems barriers to screening in a study by Fletcher et al (2007). [73] The authors interviewed 1870 patients under age 55 who were enrolled in a group medical practice and reported that 39% of patients <50 years of age had *never* been asked about their FH of CRC; 46% of patients with a strong FH (1FDR<60 or 2+FDRs) did not know that they needed to start screening before age 50; and although FH was documented in 59% of patient charts, only 54% of records included the relative's age of diagnosis. Further, only 45% of patients less than age 50 who had a strong FH had been screened appropriately (start at age 40; repeat every 5 years). This study highlights the need

for educational efforts for both providers and patients about the importance of FH as a risk factor for CRC.

What is Not Known—There is limited data on best practices for mitigating modifiable barriers to screening among persons at increased risk. In considering perceived risk, an important question is whether the primary goal is to provide education about risk, promote shared decision-making or improve screening uptake. In general, the literature shows that personalized risk communication increases the rate of informed decision-making, but yields only a modest increase in uptake of screening. [80] Thus it must be appreciated that accurate risk perception does not necessarily lead to screening. If increasing screening uptake is the goal, it remains unclear whether messages on risk should be qualitative or quantitative, whether absolute or relative risk should be emphasized, and how uncertainty should be acknowledged. More research in this area is needed.

With respect to family communication, few studies have focused on communication about CRC risk and screening outside of the context of disclosure of genetic test results in families with a known inherited predisposition. This literature suggests that notification of CRC risk occurs most frequently with closer (i.e., first-degree) relatives versus more distant relatives.[81] Less is known about how CRC screening is communicated in these families. Following genetic testing, the available data suggest that communicating with a greater proportion of family members about CRC risk, and receiving encouragement for CRC screening from a greater proportion of relatives, is associated with more recent colonoscopies[81] . Although limited, these data suggest that family communication and encouragement of CRC screening, especially from affected family members, may be important in promoting screening within high-risk families. There is a need for research focused on interventions to improve family communication about CRC risk and screening in these families including determining effective intervention elements, timing of intervention delivery, and family engagement strategies.

Despite strong evidence that providers' recommendation is positively associated with colonoscopy intention or utilization,[9,70] there is little evidence that provider recommendation directly impacts CRC screening uptake in persons at increased risk. Members of high-risk families could play an important role in initiating such discussions with providers, as they are responsible for communicating FH and family genetic risk information that, in turn, is used to generate screening recommendations. In hereditary CRC families, disclosure of genetic test results from patients to their healthcare provider was significantly associated with endoscopy in the year following testing.[81] However, both descriptive and intervention research is lacking with regard to the influence of provider-patient communication on CRC screening in those at increased familial risk.

Question 5: What interventions have proven effective for improving screening rates in these high risk populations?

What is Known—There were eight studies identified that tested interventions to promote CRC screening in persons with a FH of CRC (n=7) or adenoma (1).[9,82–88] All studies specifically targeted FDRs of CRC cases; one study focused on minority groups.[82] These

studies used various means for recruiting subjects (cancer registry, medical practices, family registries, hospitals), used different intervention approaches (print/mail, telephone, in-person), and assessed various outcomes in terms of screening type (any vs. colonoscopy only) and time since intervention (3 to 24 months). The most common theoretical model used for framing the intervention was the Health Belief Model.

In all but one study,[88] moderate increases in screening adherence were noted for both the intervention and control groups (range = 11–30%). In six studies, adherence was significantly higher in the more 'intensive' intervention group(s) (range of effect size= 1.3–7 times greater) than in the control groups.[9,82–85,87] In these studies, the intervention was delivered by phone or in-person, was tailored to the individuals' risk and perceived barriers and incorporated strategies for overcoming barriers. The two studies that reported no intervention effects offered a one-time print intervention that was tailored or not tailored to the individual. [86,88]

What is Not Known—Relatively few controlled studies have been done and the different approaches used make comparison of results across the published studies difficult and recommendations for the most effective approaches impossible. Though almost all studies showed significant yet moderate effects within a controlled trial setting, it is not known whether these interventions would be effective in practice or population-based settings. There is a need for research in this area to determine the feasibility of implementing these interventions, or components of these interventions into real world settings, and for evaluating their impact in various patient populations.

One of the major obstacles for conducting targeted interventions for persons at increased CRC risk due to FH is identifying and contacting these individuals within the health care system or the population at-large. The studies reviewed herein recruited FDRs from CRC cases who allowed researchers to contact them or who had enrolled in family registries. Screening compliance among these FDRs and their motivations to get screened are likely skewed. The challenge, if these interventions are to be implemented in clinical practice, is to develop systems to reliably identify persons with a FH of CRC and have the ability to contact them.

Question 6: What types of tools are available for assessing cancer FH to inform CRC screening?

What is Known—Publication is limited on this topic since the majority of FH tools are newly and/or commercially developed. Thus, a convenience sample of both publically-available and private/commercially-available cancer FH tools was selected and described here (n=10 supporting articles); final selection of tools included was guided by experts on the Task Group.

Free-standing tools that assess cancer FH vary broadly in their intended use, inputs, and endpoints. Several publicly-available, patient-oriented tools focus solely on CRC risk assessment (e.g. estimating lifetime risk for CRC). These tools generally provide personalized guidance on CRC screening based on patient self-report of personal and family health history, for example the presence/absence of one or more FDRs with CRC before age

60. These tools can be very brief (e.g., Columbia University's three question Familial CRC Risk Assessment Tool, http://columbiasurgery.org/news/2015/03/03/3-questions-assess-your-familial-colorectal-cancer-risks) or more elaborate (e.g., The Ohio State University Family Health*Link*, https://familyhealthlink.osumc.edu/) and many include personal health history and lifestyle choices in addition to FH in their risk assessment (e.g., Cleveland Clinic's Score Against Colon Cancer, http://digestive.ccf.org/scores/go). These tools can be completed by patients or facilitated by an affiliated health care provider. Additionally, there are publically-available, clinician-oriented tools that focus solely on CRC risk assessment available that also employ limited, focused data sets for risk assessment (e.g., NCI's Colorectal Cancer Risk Assessment Tool, http://www.cancer.gov/colorectalcancerrisk/).

There are also several publically-available tools that collect broader cancer FH, some of which also provide risk estimates. Two examples are the Surgeon General's My Family Health Portrait (https://familyhistory.hhs.gov/FHH/html/index.html) and the CDC's Family Healthware (https://www.familyhealthware.com/). Both are patient-oriented, allowing entry of family structure and health history, and have undergone some clinical validation. [89–91] Additionally, both tools provide personal risk estimates.[91,92] However, these tools differ from those focused solely on CRC risk assessment in that they capture the structure of a patient's family and not just individuals affected by CRC, allowing for the number, age, and relation of unaffected relatives to inform risk and appropriate screening recommendations.

In addition to publically-available tools, there is a growing suite of private and/or commercially available broader cancer FH collection tools, many of which offer risk assessment. These tools generally allow for patient self-entry of FH and many provide clinical decision support directly to clinicians. Several have undergone formal scientific assessment. [93–97] Included in the Supplemental Materials is an inventory of 15 tools that can be used for cancer FH collection/risk assessment and their attributes that was developed in conjunction with the Global Alliance for Genomics and Health.

In contrast to free-standing tools, electronic health records (EHRs), which are becoming increasingly available and widely adopted in the US, present an opportunity to collect FH directly into the patient medical record. To assess current utility of EHRs to collect and use FH data, the NCCRT commissioned a survey of community health centers across the U.S. (2014).[98] Key findings from this study indicate that all EHRs surveyed had a FH section but it was variably completed and not regularly updated; this section typically, but not uniformly, includes structured fields for relative relation (up to 2nd or 3rd degree) and type of cancer, but not for other variables like age at diagnosis. Many of these observations are in striking contrast to published suggested core data sets for family health history in EHR systems.[99] None of the EHRs surveyed link FH information to medical decision making.

What is Not Known—Few tools have been evaluated in terms of reach (how many patients and/or providers are using them), acceptability (what do patients/providers think about these?), and ease of use. There is also little information available on how best to link free-standing tools with existing EHRs and/or how to incorporate these data fields directly into EHR systems. Few effectiveness studies and no comparative effectiveness studies have been done on these tools. Further, though the value of collecting FH is recognized, there is

little direct evidence that taking comprehensive FH changes clinical practice or improves patient outcomes.

Discussion

This review summarizes what is known and not known, and what questions remain in terms of quantifying CRC risk, improving screening adherence, and identifying persons at increased risk of CRC due to their FH. Based on these findings and expert opinion from members of our national panel, we highlight below four priority opportunities to reduce the burden of CRC in these at-risk populations and provide some specific recommendations.

1). Improve how we collect and utilize cancer FH information

As revealed herein, FH it is not routinely collected nor used to inform risk and screening in practice. Further, although cancer screening is a required reporting metric in primary care, risk-appropriate screening based on familial risk is not. Two strategies for improving collection of FH are expanding use of existing FH tools and enhancing the capability of EHR systems to collect these data in standardized formats and link them with clinical decision making. Having these data available electronically should enable providers to identify patients at increased risk, and monitor screening rates and outcomes in these groups, a combination that is currently lacking. The NCCRT has begun efforts to work with several EHR vendors in the U.S. to discuss if/how to enhance collection of FH in primary care. It is recognized that in order to operationalize this broadly, there must be both provider demand for this functionality and support from EHR vendors.

Recommendation #1: Establish a clinical consensus regarding the essential elements of a high quality FH section of the EHR that could be entered directly into EHRs, or integrated into the EHR from free-standing FH tools

Recommendation #2: Advocate for including the collection and updates of FH as a quality metric in primary care

2). Establish consensus across organizations for CRC screening guidelines by FH status

The only group for whom the guidelines are consistent are those with an FDR with CRC <60 years of age or those with>1FDR with CRC; there is substantial variability in the recommendations for those with a single CRC or adenoma > age 60. As noted earlier, there are limited data on risk of CRC associated with a FH of polyps. Further, it is recognized that the evidence to support more intensive screening regimens in high-risk groups is lacking, though modeling studies are on-going.

Recommendation #3: Catalyze an effort to come to consensus on screening guidelines for individuals with a single FDR with CRC > age 60

Recommendation #4: Conduct additional studies to assess risk of CRC associated with a FH of adenomas (specified according to size, histology of polyp), and efficacy of interval screening in persons at increased risk

3). Enhance provider-patient knowledge of guidelines and communication about CRC risk

This review clearly demonstrates that providers play a significant role in promoting screening. Although guidelines exist for persons at increased risk, many providers are unaware of them. Important challenges identified are limited FH data available to identify high-risk patients (addressed above), and poor knowledge and communication about polyps to inform risk.

Recommendation#5: Educate primary care providers on appropriate application of guidelines for high-risk patients

Recommendation #6: Develop standard reporting metrics for disclosing endoscopy findings (specifically information about polyps) and screening recommendations for their at-risk relatives to patients

4). Encourage cancer survivors to promote screening within their families, and partner with existing CRC screening programs to expand reach to high-risk groups

Encouragement from family members, and in particular those affected with CRC, can facilitate screening in unaffected family members. The CRC survivor community is growing yet it remains an untapped resource for promoting screening in their own families and in others. Further, there are many organizations that promote CRC awareness and screening in average risk persons including the NCCRT, 80% by 2018 campaign and the CDC's Colorectal Cancer Control Program (CRCCP). The CRCCP, now in 25 states and expanding, uses evidence-based interventions to increase rates of provider recommendations and adherence to screening guidelines. Strategies and resources from these programs can be leveraged to promote screening in high-risk groups.

Recommendation #7: Enlist efforts from patient advocate groups and state cancer registries to promote CRC screening in family members of persons affected by CRC

Recommendation #8: Collaborate with national/local organizations that promote and/or monitor CRC screening (ex. CRCCP, NCCRT, BRFSS, NHIS) to expand efforts in high-risk groups

This review has some limitations. It is recognized that although the search strategy was comprehensive and broad, some relevant articles may have been missed. There is also the possibility for publication bias, as only studies that were published in peer-reviewed journals were reviewed for inclusion.

Conclusion

Having a FH of CRC or adenomas is an important risk factor for CRC. The lifetime risk of developing CRC for an individual with just one affected FDR is about twice that of persons without an affected family member and the risk is even higher with more affected relatives and younger age of CRC diagnoses in the family. Moreover, the population at-risk is sizeable; over 10% of the adult population in the U.S. has one or more family members who have been diagnosed with CRC. Routine screening with colonoscopy can prevent CRC through removal of polyps and can detect CRC in its early stages, which saves lives; [100] 5-

year survival following CRC diagnosis is markedly better if detected at a local vs. distant stage (90% vs. 13%).[101] Despite the proven efficacy of screening and the existence of consensus guidelines for persons at increased risk due to FH, adherence to screening in this population remains low, particularly for persons less than age 50. This is an important group as it has been estimated that 7% of the population under age 50 will have a FH of CRC that would warrant early (age 40 or younger) and more frequent screening.[102]

In summary, persons with a FH of CRC or adenomas represent a large, at-risk population that is not receiving guideline recommended screening for CRC. The collective efforts described above by providers, researchers, policy-makers and patient advocates to improve how we identify, manage and communicate with these individuals about their risk can have a significant impact on reducing CRC burden in these families and in the population at-large.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. American Cancer Society. Cancer facts and figures--2015. Atlanta, Georgia: American Cancer Society; 2015.
2. Tsai MH, Xirasagar S, Li YJ, de Groen PC. Colonoscopy screening among US adults aged 40 or older with a family history of colorectal cancer. Prev Chronic Dis. 2015; 12:E80. [PubMed: 25996988]
3. de Jong AE, Vasen HF. The frequency of a positive family history for colorectal cancer: a population-based study in the Netherlands. Neth J Med. 2006; 64(10):367–370. [PubMed: 17122453]
4. Mai PL, Wideroff L, Greene MH, Graubard BI. Prevalence of family history of breast, colorectal, prostate, and lung cancer in a population-based study. Public Health Genomics. 2010; 13(7–8):495–503. [PubMed: 20389042]
5. Mitchell RJ, Campbell H, Farrington SM, Brewster DH, Porteous ME, Dunlop MG. Prevalence of family history of colorectal cancer in the general population. Br J Surg. 2005; 92(9):1161–1164. [PubMed: 15997443]
6. Henrikson NB, Webber EM, Goddard KA, et al. Family history and the natural history of colorectal cancer: systematic review. Genet Med. 2015
7. CDC. [Accessed August 2015] Behavioral Risk Factor Surveillance System. Survey Data. 2014. www.cdc.gov/brfss/
8. 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):629–637. [PubMed: 23546820]
9. 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):601–610. [PubMed: 24501379]

10. 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):737–743. [PubMed: 21555945]
11. Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015; 110(2):223–262. quiz 263. [PubMed: 25645574]
12. Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-society Task Force on colorectal cancer. Am J Gastroenterol. 2014; 109(8):1159–1179. [PubMed: 25070057]
13. Vasen HF, Tomlinson I, Castells A. Clinical management of hereditary colorectal cancer syndromes. Nat Rev Gastroenterol Hepatol. 2015; 12(2):88–97. [PubMed: 25582351]
14. Rubenstein JH, Enns R, Heidelbaugh J, Barkun A, Committee CG. American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Lynch Syndrome. Gastroenterology. 2015; 149(3):777–782. quiz e716-777. [PubMed: 26226577]
15. Hampel H, Bennett RL, Buchanan A, Pearlman R, Wiesner GL. Guideline Development Group AeCoMGaGPPaGCaNSoGCPGC. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. Genet Med. 2015; 17(1):70–87. [PubMed: 25394175]
16. Lindor NM, Rabe K, Petersen GM, et al. Lower cancer incidence in Amsterdam-I criteria families without mismatch repair deficiency: familial colorectal cancer type X. JAMA. 2005; 293(16): 1979–1985. [PubMed: 15855431]
17. 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):216–227. [PubMed: 16338133]
18. Johns LE, Houlston RS. A systematic review and meta-analysis of familial colorectal cancer risk. Am J Gastroenterol. 2001; 96(10):2992–3003. [PubMed: 11693338]
19. 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):114–124. [PubMed: 16426946]
20. Johnson CM, Wei C, Ensor JE, et al. Meta-analyses of colorectal cancer risk factors. Cancer Causes Control. 2013; 24(6):1207–1222. [PubMed: 23563998]
21. Taylor DP, Burt RW, Williams MS, Haug PJ, Cannon-Albright LA. Population-based family history-specific risks for colorectal cancer: a constellation approach. Gastroenterology. 2010; 138(3):877–885. [PubMed: 19932107]
22. 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): 1195–1198. [PubMed: 17702662]
23. Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Speizer FE, Willett WC. A prospective study of family history and the risk of colorectal cancer. N Engl J Med. 1994; 331(25):1669–1674. [PubMed: 7969357]
24. Turati F, Edefonti V, Bosetti C, et al. Family history of cancer and the risk of cancer: a network of case-control studies. Ann Oncol. 2013; 24(10):2651–2656. [PubMed: 23884440]
25. Hemminki K, Chen B. Familial risks for colorectal cancer show evidence on recessive inheritance. Int J Cancer. 2005; 115(5):835–838. [PubMed: 15704173]
26. Maul JS, Burt RW, Cannon-Albright LA. A familial component to human rectal cancer, independent of colon cancer risk. Clin Gastroenterol Hepatol. 2007; 5(9):1080–1084. [PubMed: 17625976]
27. Murphy G, Shu XO, Gao YT, et al. Family cancer history affecting risk of colorectal cancer in a prospective cohort of Chinese women. Cancer Causes Control. 2009; 20(8):1517–1521. [PubMed: 19418234]
28. Safaee A, Moghimi-Dehkordi B, Pourhoseingholi MA, et al. Risk of colorectal cancer in relatives: a case control study. Indian J Cancer. 2010; 47(1):27–30. [PubMed: 20071786]

29. 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
30. Andrieu N, Launoy G, Guillois R, Ory-Paoletti C, Gignoux M. Estimation of the familial relative risk of cancer by site from a French population based family study on colorectal cancer (CCREF study). Gut. 2004; 53(9):1322–1328. [PubMed: 15306593]
31. Wei EK, Colditz GA, Giovannucci EL, Fuchs CS, Rosner BA. Cumulative risk of colon cancer up to age 70 years by risk factor status using data from the Nurses' Health Study. Am J Epidemiol. 2009; 170(7):863–872. [PubMed: 19723749]
32. 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):573–580. [PubMed: 25604623]
33. Tuohy TM, Rowe KG, Mineau GP, Pimentel R, Burt RW, Samadder NJ. 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. [PubMed: 24150925]
34. 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):1086–1092. [PubMed: 17919484]
35. Winawer SJ, Zauber AG, Gerdes H, et al. Risk of colorectal cancer in the families of patients with adenomatous polyps. National Polyp Study Workgroup. N Engl J Med. 1996; 334(2):82–87. [PubMed: 8531963]
36. Baron TH, Smyrk TC, Rex DK. Recommended intervals between screening and surveillance colonoscopies. Mayo Clin Proc. 2013; 88(8):854–858. [PubMed: 23910411]
37. Obuch JC, Pigott CM, Ahnen DJ. Sessile serrated polyps: detection, eradication, and prevention of the evil twin. Curr Treat Options Gastroenterol. 2015; 13(1):156–170. [PubMed: 25623474]
38. NCCN. [Accessed July 2015] Clinical Practice Guidelines for Oncology. Colorectal Cancer Screening, V 1.2015. 2015. 2015; http://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf
39. Rex DK, Johnson DA, Anderson JC, et al. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol. 2009; 104(3):739–750. [PubMed: 19240699]
40. American Cancer Society. [Accessed 081514] American Cancer Society recommendations for colorectal early detection. 2014. 2014; www.cancer.org
41. Qaseem A, Denberg TD, Hopkins RH, et al. Screening for colorectal cancer: a guidance statement from the American College of Physicians. Ann Intern Med. 2012; 156(5):378–386. [PubMed: 22393133]
42. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology. 2008; 134(5):1570–1595. [PubMed: 18384785]
43. Davila RE, Rajan E, Baron TH, et al. ASGE guideline: colorectal cancer screening and surveillance. Gastrointest Endosc. 2006; 63(4):546–557. [PubMed: 16564851]
44. Management IfCS. [Accessed July 2015] Preventive Services for Adults. Colorectal Cancer Screening. 2015. 2014; https://www.icsi.org/guidelines
45. Barrison AF, Smith C, Oviedo J, Heeren T, Schroy PC 3rd. Colorectal cancer screening and familial risk: a survey of internal medicine residents' knowledge and practice patterns. Am J Gastroenterol. 2003; 98(6):1410–1416. [PubMed: 12818289]
46. Gennarelli M, Jandorf L, Cromwell C, Valdimarsdottir H, Redd W, Itzkowitz S. Barriers to colorectal cancer screening: inadequate knowledge by physicians. Mt Sinai J Med. 2005; 72(1):36–44. [PubMed: 15682261]
47. Schroy PC 3rd, Barrison AF, Ling BS, Wilson S, Geller AC. Family history and colorectal cancer screening: a survey of physician knowledge and practice patterns. Am J Gastroenterol. 2002; 97(4):1031–1036. [PubMed: 12008667]

48. White PM, Sahu M, Poles MA, Francois F. Colorectal cancer screening of high-risk populations: A national survey of physicians. BMC Res Notes. 2012; 5:64. [PubMed: 22272666]
49. Austin GL, Fennimore B, Ahnen DJ. Can colonoscopy remain cost-effective for colorectal cancer screening? The impact of practice patterns and the Will Rogers phenomenon on costs. Am J Gastroenterol. 2013; 108(3):296–301. [PubMed: 23208273]
50. 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. [PubMed: 22244866]
51. Ladabaum U, Ferrandez A, Lanas A. Cost-effectiveness of colorectal cancer screening in high-risk Spanish patients: use of a validated model to inform public policy. Cancer Epidemiol Biomarkers Prev. 2010; 19(11):2765–2776. [PubMed: 20810603]
52. Ait Ouakrim D, Boussioutas A, Lockett T, et al. Screening practices of unaffected people at familial risk of colorectal cancer. Cancer Prev Res (Phila). 2012; 5(2):240–247. [PubMed: 22030089]
53. Ait Ouakrim D, Lockett T, Boussioutas A, Hopper JL, Jenkins MA. Screening participation for people at increased risk of colorectal cancer due to family history: a systematic review and meta-analysis. Fam Cancer. 2013; 12(3):459–472. [PubMed: 23700069]
54. Rees G, Martin PR, Macrae FA. Screening participation in individuals with a family history of colorectal cancer: a review. Eur J Cancer Care (Engl). 2008; 17(3):221–232. [PubMed: 18419625]
55. Lowery JT, Marcus A, Kinney A, et al. The Family Health Promotion Project (FHPP): design and baseline data from a randomized trial to increase colonoscopy screening in high risk families. Contemp Clin Trials. 2012; 33(2):426–435. [PubMed: 22101228]
56. Ponce NA, Tsui J, Knight SJ, et al. Disparities in cancer screening in individuals with a family history of breast or colorectal cancer. Cancer. 2012; 118(6):1656–1663. [PubMed: 22009719]
57. Zlot AI, Silvey K, Newell N, Coates RJ, Leman R. Family history of colorectal cancer: clinicians' preventive recommendations and patient behavior. Prev Chronic Dis. 2012; 9:E21. [PubMed: 22172188]
58. Bostean G, Crespi CM, McCarthy WJ. Associations among family history of cancer, cancer screening and lifestyle behaviors: a population-based study. Cancer Causes Control. 2013; 24(8): 1491–1503. [PubMed: 23681471]
59. Carney PA, O'Malley JP, Gough A, et al. Association between documented family history of cancer and screening for breast and colorectal cancer. Prev Med. 2013; 57(5):679–684. [PubMed: 24029558]
60. Courtney RJ, Paul CL, Carey ML, et al. A population-based cross-sectional study of colorectal cancer screening practices of first-degree relatives of colorectal cancer patients. BMC Cancer. 2013; 13:13. [PubMed: 23305355]
61. Lin OS, Gluck M, Nguyen M, Koch J, Kozarek RA. Screening patterns in patients with a family history of colorectal cancer often do not adhere to national guidelines. Dig Dis Sci. 2013; 58(7): 1841–1848. [PubMed: 23371014]
62. Longacre AV, Cramer LD, Gross CP. Screening colonoscopy use among individuals at higher colorectal cancer risk. J Clin Gastroenterol. 2006; 40(6):490–496. [PubMed: 16825930]
63. Murff HJ, Peterson NB, Greevy RA, Shrubsole MJ, Zheng W. Early initiation of colorectal cancer screening in individuals with affected first-degree relatives. J Gen Intern Med. 2007; 22(1):121–126. [PubMed: 17351851]
64. Ruthotto F, Papendorf F, Wegener G, et al. Participation in screening colonoscopy in first-degree relatives from patients with colorectal cancer. Ann Oncol. 2007; 18(9):1518–1522. [PubMed: 17761708]
65. Almario CV, May FP, Ponce NA, Spiegel BM. Racial and Ethnic Disparities in Colonoscopic Examination of Individuals With a Family History of Colorectal Cancer. Clin Gastroenterol Hepatol. 2015; 13(8):1487–1495. [PubMed: 25737445]
66. Hogan NM, Hanley M, Hogan AM, et al. Awareness and uptake of family screening in patients diagnosed with colorectal cancer at a young age. Gastroenterol Res Pract. 2015; 2015:194931. [PubMed: 25688262]

67. Perencevich M, Ojha RP, Steyerberg EW, Syngal S. Racial and ethnic variations in the effects of family history of colorectal cancer on screening compliance. Gastroenterology. 2013; 145(4):775–781. e772. [PubMed: 23796457]
68. Lin OS. Colorectal cancer screening in patients at moderately increased risk due to family history. World J Gastrointest Oncol. 2012; 4(6):125–130. [PubMed: 22737273]
69. Ait Ouakrim D, Lockett T, Boussioutas A, et al. Screening participation predictors for people at familial risk of colorectal cancer: a systematic review. Am J Prev Med. 2013; 44(5):496–506. [PubMed: 23597814]
70. Boonyasiriwat W, Hung M, Hon SD, et al. Intention to undergo colonoscopy screening among relatives of colorectal cancer cases: a theory-based model. Ann Behav Med. 2014; 47(3):280–291. [PubMed: 24307472]
71. Bronner K, Mesters I, Weiss-Meilik A, et al. Determinants of adherence to screening by colonoscopy in individuals with a family history of colorectal cancer. Patient Educ Couns. 2013; 93(2):272–281. [PubMed: 23916675]
72. Courtney RJ, Paul CL, Sanson-Fisher RW, et al. Individual- and provider-level factors associated with colorectal cancer screening in accordance with guideline recommendation: a community-level perspective across varying levels of risk. BMC Public Health. 2013; 13:248. [PubMed: 23514586]
73. Fletcher RH, Lobb R, Bauer MR, et al. Screening patients with a family history of colorectal cancer. J Gen Intern Med. 2007; 22(4):508–513. [PubMed: 17372801]
74. Ingrand I, Dujoncquoy S, Beauchant M, Letard JC, Migeot V, Ingrand P. General practitioner and specialist views on colonoscopic screening of first-degree relatives of colorectal cancer patients. Cancer Epidemiol. 2009; 33(3–4):223–230. [PubMed: 19683486]
75. Gili M, Roca M, Ferrer V, Obrador A, Cabeza E. Psychosocial factors associated with the adherence to a colorectal cancer screening program. Cancer Detect Prev. 2006; 30(4):354–360. [PubMed: 16963195]
76. Gimeno Garcia AZ, Quintero E, Nicolas Perez D, Hernandez M, JimenezSosa A. Colorectal cancer screening in first-degree relatives of colorectal cancer: participation, knowledge, and barriers against screening. Eur J Gastroenterol Hepatol. 2011; 23(12):1165–1171. [PubMed: 21989122]
77. Madlensky L, Esplen MJ, Goel V. Reasons given by relatives of colorectal cancer patients for not undergoing screening. Prev Med. 2004; 39(4):643–648. [PubMed: 15351528]
78. Manne SL, Coups EJ, Winkel G, et al. Identifying cluster subtypes for intentions to have colorectal cancer screening among non-compliant intermediate-risk siblings of individuals with colorectal cancer. Health Educ Res. 2009; 24(5):897–908. [PubMed: 19654222]
79. Koc S, Esin MN. Screening Behaviors, Health Beliefs, and Related Factors of First-Degree Relatives of Colorectal Cancer Patients With Ongoing Treatment in Turkey. Cancer Nurs. 2014
80. Edwards AG, Naik G, Ahmed H, et al. Personalised risk communication for informed decision making about taking screening tests. Cochrane Database Syst Rev. 2013; 2:CD001865.
81. Ersig AL, Hadley DW, Koehly LM. Colon cancer screening practices and disclosure after receipt of positive or inconclusive genetic test results for hereditary nonpolyposis colorectal cancer. Cancer. 2009; 115(18):4071–4079. [PubMed: 19536903]
82. Bastani R, Glenn BA, Maxwell AE, et al. Randomized trial to increase colorectal cancer screening in an ethnically diverse sample of first-degree relatives. Cancer. 2015
83. Glanz K, Steffen AD, Taglialatela LA. Effects of colon cancer risk counseling for first-degree relatives. Cancer Epidemiol Biomarkers Prev. 2007; 16(7):1485–1491. [PubMed: 17627015]
84. Kinney AY, Boonyasiriwat W, Walters ST, et al. Telehealth personalized cancer risk communication to motivate colonoscopy in relatives of patients with colorectal cancer: the family CARE Randomized controlled trial. J Clin Oncol. 2014; 32(7):654–662. [PubMed: 24449229]
85. Manne SL, Coups EJ, Markowitz A, et al. A randomized trial of generic versus tailored interventions to increase colorectal cancer screening among intermediate risk siblings. Ann Behav Med. 2009; 37(2):207–217. [PubMed: 19418107]
86. Rawl SM, Champion VL, Scott LL, et al. A randomized trial of two print interventions to increase colon cancer screening among first-degree relatives. Patient Educ Couns. 2008; 71(2):215–227. [PubMed: 18308500]

87. Rawl SM, Christy SM, Monahan PO, et al. Tailored telephone counseling increases colorectal cancer screening. Health Educ Res. 2015; 30(4):622–637. [PubMed: 26025212]

88. Stephens JH, Moore JW. Can targeted intervention in CRC patients' relatives influence screening behaviour? A pilot study. Colorectal Dis. 2008; 10(2):179–186. [PubMed: 17459064]

89. Yoon PW, Scheuner MT, Jorgensen C, Khoury MJ. Developing Family Healthware, a family history screening tool to prevent common chronic diseases. Prev Chronic Dis. 2009; 6(1):A33. [PubMed: 19080039]

90. Facio FM, Feero WG, Linn A, Oden N, Manickam K, Biesecker LG. Validation of My Family Health Portrait for six common heritable conditions. Genet Med. 2010; 12(6):370–375. [PubMed: 20479646]

91. O'Neill SM, Rubinstein WS, Wang C, et al. Familial risk for common diseases in primary care: the Family Healthware Impact Trial. Am J Prev Med. 2009; 36(6):506–514. [PubMed: 19460658]

92. Feero WG, Facio FM, Glogowski EA, et al. Preliminary validation of a consumer-oriented colorectal cancer risk assessment tool compatible with the US Surgeon General's My Family Health Portrait. Genet Med. 2014

93. Wu RR, Himmel TL, Buchanan AH, et al. Quality of family history collection with use of a patient facing family history assessment tool. BMC Fam Pract. 2014; 15:31. [PubMed: 24520818]

94. Doerr M, Edelman E, Gabitzsch E, Eng C, Teng K. Formative evaluation of clinician experience with integrating family history-based clinical decision support into clinical practice. J Pers Med. 2014; 4(2):115–136. [PubMed: 25563219]

95. Ozanne EM, Loberg A, Hughes S, et al. Identification and management of women at high risk for hereditary breast/ovarian cancer syndrome. Breast J. 2009; 15(2):155–162. [PubMed: 19292801]

96. Pritzlaff M, Yorczyk A, Robinson LS, et al. An internal performance assessment of CancerGene Connect: an electronic tool to streamline, measure and improve the genetic counseling process. J Genet Couns. 2014; 23(6):1034–1044. [PubMed: 24916850]

97. Hulse NC, Ranade-Kharkar P, Post H, Wood GM, Williams MS, Haug PJ. Development and early usage patterns of a consumer-facing family health history tool. AMIA Annu Symp Proc. 2011; 2011:578–587. [PubMed: 22195113]

98. Aeffect, I. [Accessed December, 2014] Summary Report: Use of electronic medical records to facilitate colorectal cancer screening in community health centers. 2014. nccrt.org/wp-content/uploads/NCCRT-Summary-/EMR-Report-Final.pdf

99. Feero WG, Bigley MB, Brinner KM. Community FHHM-SWotAHI. New standards and enhanced utility for family health history information in the electronic health record: an update from the American Health Information Community's Family Health History Multi-Stakeholder Workgroup. J Am Med Inform Assoc. 2008; 15(6):723–728. [PubMed: 18755994]

100. Doubeni CA, Weinmann S, Adams K, et al. Screening colonoscopy and risk for incident late-stage colorectal cancer diagnosis in average-risk adults: a nested case-control study. Ann Intern Med. 2013; 158(5 Pt 1):312–320. [PubMed: 23460054]

101. National Cancer Institute. [Accessed 01/07/2016, 2016] SEER Stat Fact Sheets: Colon and Rectum Cancer. 2015. www.seer.cancer.gov/statfacts/html/colorect.html

102. Ziogas A, Horick NK, Kinney AY, et al. Clinically relevant changes in family history of cancer over time. JAMA. 2011; 306(2):172–178. [PubMed: 21750294]

Table 1

Risk of CRC among unaffected persons with a family history of CRC or adenomas compared to persons with no family history.

Family History Category	Risk Measure	References
FDR with CRC		
≥1[+] FDR	Pooled= 2.24 (2.06–2.43); 2.26 (1.86–2.73); 2.25 (2.00–2.53); 1.80 (1.61–2.02); Range = 1.55–2.80	17–21, 23–24,27–31
2+ FDRs	Pooled=3.97 (2.60–6.06); 4.25 (3.01–6.08);3.95 (2.49–6.26); Range = 2.75–3.01	17–19 21,23,28
≥1 FDR <50	Pooled=3.55 (1.84–6.83); Range=1.65–3.31	17,21,22
≥1 FDR <60	Pooled (if FDR 45–59) = 2.25 (1.85–2.72); Range = 1.81–3.30	18,24,29,30
1 FDR ≥60	Pooled=1.83 (1.47–2.25); Range = 1.43–2.50	21,24,29,30
1 FDR ≥70	RR: 1.97 (1.86–2.08)	21
SDR or TDR with CRC		
≥1 SDR	Pooled=1.73 (1.02–2.94); Range=1.05–2.49	17,21,28–30
1 TDR	Range=1.12–1.15	26,29
FDR or SDR with Adenoma		
≥1 FDR ‘any’ adenoma	Pooled = 1.99 (1.55–2.55); Range=1.35–1.78	16,33, 35
≥1 FDR with ‘large’ or ‘advanced adenoma’ (AA)	Range=1.68–3.90	33,34
FDR <60	RR: 1.41 (1.27–1.56)	33
FDR ≥ 60	RR: 1.23 (1.07–1.42)	33
FDR <60 with AA	RR=1.54 (1.06–2.24); OR:3.83 (0.92–15.87)	33, 34
FDR≥60 with AA	RR: 2.04 (1.35–3.08)	33
1 SDR	RR: 1.15 (1.07–1.23)	33
1 SDR with AA	RR: 0.85 (0.63–1.13)	33

Definitions:
Pooled = risk estimates from meta-analyses with 95% confidence intervals
Range = risk estimates (relative risk (RR) or odds ratio (OR)) from multiple original studies identified
RR = risk estimate if only original study identified
FDR = first degree; SDR=second degree; TDR=third degree relative

[+] interpreted as ‘at least one FDR with CRC’

Table 2

Summary of current guidelines for CRC screening for persons with a family history of CRC

Organization	Family History	Recommendation
ACS [36]	1 FDR with CRC or adenoma <60 OR in 2+ FDRs at any age	Start colonoscopy at 40 or 10 yrs before earliest CRC (whichever is earlier); repeat every 5 years
	1 FDR with CRC or adenoma >=60 OR 2+ SDRs with CRC at any age	Start screening at 40 (any modality); repeat as average risk
NCCN [34]	1 FDR with CRC <60 or 2+ FDRs with CRC at any age	Start colonoscopy at 40 or 10 yrs before earliest CRC (whichever is earlier); repeat every 5 yrs
	1 FDR with CRC >= 60	Start colonoscopy at 50 or 10 yrs before earliest CRC; repeat every 5–10 yrs
	1 SDR <50	Start colonoscopy at 50; repeat every 5–10 yrs
	1 FDR with **advanced** adenoma	Start colonoscopy at 50 or age of adenoma (whichever is earlier); repeat every 5–10 yrs
Multi-society Task Force on CRC (AGA, ACS, ACR)[38]	1FDR with CRC or adenoma <60 OR in 2+ FDRS at any age	Start colonoscopy at 40 or 10 yrs before earliest CRC (whichever is earlier); repeat every 5 years
	1 FDR with CRC or adenoma >=60 OR 2+ SDRs with CRC at any age	Start screening at 40 (any modality); repeat as average risk
ACG [35]	1 FDR with CRC or **advanced** adenoma <60 or 2+ FDRs with CRC or advanced adenoma	Start colonoscopy at 40 or 10 yrs before earliest CRC; repeat every 5 years
	1 FDR with CRC or advanced adenoma >=60	Start colonoscopy at 50; repeat every 10 yrs
ASGE [39]	1 FDR with CRC or adenoma <60	Start colonoscopy at 40 or 10 yrs before earliest CRC; repeat every 3–5 years
	1 FDR with CRC >= 60	Start colonoscopy at 40; repeat every 10 yrs
	1 FDR with adenoma >60	Start colonoscopy (age of initiation individualized); repeat every 10 yrs
American College of Physicians [37]	1 FDR with CRC or adenoma <60 OR in 2+ FDRS at any age	Start colonoscopy at 40 or 10 yrs before earliest CRC in family; repeat every 5 years
Institute for Clinical Systems Improvement [40]	1 FDR with CRC or adenoma <60 OR 2+ FDRs with CRC or adenoma at any age	Start colonoscopy at 40 or 10 yrs before earliest case in family; repeat every 5 years
	FDR with CRC or adenoma >=60 or 2+ SDR with CRC	no specific recommendation supported