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Potential impact of family history based screening guidelines on early onset colorectal cancer detection

Running head: Impact of family history on CRC detection

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Precis:

Data to support screening at an earlier age based on family history as a strategy for detection and prevention of early onset colorectal cancer are limited. In a population-based case control study of individuals age 40-49, we found 1 in 4 met guideline criteria for earlier screening, and that almost all meeting these criteria could have had CRC diagnosed earlier (or possibly even prevented) if earlier screening had been implemented as per guidelines.

Abstract

Background: Initiating screening at an earlier age based on cancer family history is one of the primary recommended strategies for early onset colorectal cancer (EOCRC) prevention and detection, but data supporting effectiveness of this approach are limited. We assessed performance of family history based guidelines for identifying individuals with EOCRC.

Methods: We conducted a population-based case-control study of individuals age 40 to 49 with (n=2,473) and without (n=772) incident CRC in the Colon Cancer Family Registry, 1998-2007. We estimated sensitivity and specificity of family history based criteria jointly recommended by the American Cancer Society, US Multisociety Task Force on CRC, and the American College of Radiology

in 2008 for early screening, and age at which each participant could have been recommended screening initiation if these criteria had been applied.

Results: Family history based early screening criteria were met by 25% of cases (614/2,473) and 10% of controls (74/772), with 25% sensitivity and 90% specificity for identifying EOCRC cases age 40 to 49. Among 614 individuals meeting early screening criteria, 98.4% could have been recommended screening initiation at an age younger than observed age of diagnosis.

Conclusion: Among CRC cases age 40 to 49, 1 in 4 met family history based early screening criteria, and almost all meeting these criteria could have had CRC diagnosed earlier (or possibly even prevented) if earlier screening had been implemented per family history based guidelines. Additional strategies are needed to improve EOCRC detection and prevention for individuals not meeting family history criteria for early screening.

Keywords: young onset colorectal cancer; sensitivity; specificity; case control; guidelines; family history

Text pages: 16

Tables: 3

Figures: 1

Supporting files: 4

Background:

Colorectal cancer (CRC) is the 2nd leading cause of cancer death in the United States, and the 3rd leading cause of cancer death worldwide [1]. Currently in the United States, 10 to 11% of CRC cases occur under age 50 [1, 2], resulting in CRC being the 3rd leading cause of cancer death among adults younger than age 50 [3]. Further, incidence of CRC under age 50 is rising, with a 1.6% increase per year from 2009 to 2013 [4]. Among early onset CRC (EOCRC) cases (defined in this study as cases under age 50), 72% occur between age 40 and 50 years [4].

A primary strategy for identifying individuals at risk for EOCRC is family history-based. For example, in 2008 the American Cancer Society (ACS), US Multisociety Task Force on Colorectal Cancer

(USMSTF, representing the American Gastroenterological Association, the American Society of Gastrointestinal Endoscopy, and the American College of Gastroenterology), and the American College of Radiology recommended initiating screening at age 40 or 10 years prior to youngest 1st degree relative with CRC for individuals with one or more 1st degree (FDR) or two or more 2nd degree relatives (SDR) with CRC[5]. Other groups offer similar strategies for early screening based on family history (Table 1). Despite widespread promotion of these strategies, there is limited evidence to support effectiveness of current family history-based practice guidelines for EOCRC detection [6, 7]. Specifically, modeling studies suggest application of family history-based criteria to initiate early screening could be effective [8-10], but there are limited empirical data to support these results [7]. Nonetheless, to date, recommendations for early screening based on family history can be justified as clinically rational, based on observation of increased risk associated with family history of CRC [11], as well as knowledge that screening among average risk individuals can reduce incidence and mortality. To address gaps in evidence to support early screening based on family history, our aim was to assess the sensitivity and specificity of family history-based practice guidelines for identifying individuals with EOCRC utilizing a large, population-based case-control study, with a focus on individuals age 40 to 50 years. To estimate the potential impact of full implementation of family history-based guidelines for screening initiation, we also compared the observed age of CRC diagnoses with age at which screening initiation could have been recommended based on family history based guidelines.

Methods:

Study Population

We conducted a retrospective case-control study of population-based cases and controls age 40 to 49 with and without incident CRC, enrolled 1998-2007 in the multisite Colon Cancer Family Registry. Design of the Colon Cancer Family Registry and process of evolution into the Colon Cancer Family Registry Cohort are described in detail elsewhere [12, 13]. Briefly, the Colon Cancer Family Registry was established to support studies on etiology, prevention, and management of CRC. Recruitment included population- and clinic-based recruitment from multiple centers around the world. Cases and unaffected controls were identified from population and clinical based registries representing the spectrum of colorectal cancer risk. Baseline data collection for CRC cases and non-cancer cases included detailed family history, diet/lifestyle questionnaires, clinical records, and biospecimens, also detailed elsewhere [12, 13]. Currently, the Colon Cancer Family Registry Cohort includes data from 42,489 participants from 15,049 families. For this analysis we included population-based cases and controls age 40 to 49 with and without CRC, enrolled 1998-2007 [12, 13]. Population-based cases were identified from population

cancer registries, with some sites oversampling case families with stronger family history of CRC. Population-based controls were randomly sampled from the general population living in the population recruitment area using resources including: Medicare and driver's license files, telephone subscriber lists, or electoral roles [12, 13]. Non-population-based cases and controls, as well as participants missing age at diagnosis were excluded. Access to data for the current project was granted through the Colon Cancer Family Registries formal review process. The research analysis was designated as exempt from IRB review under 45 CFR 46.1010(b) by the UC San Diego Human Research Protections Program.

Analysis

Our primary aim was to determine sensitivity and specificity of family history-based guidelines for early initiation of screening for the identification of EOCRC cases age 40-49 years. A secondary aim was to estimate the age at which each CRC case could have been recommended to initiate screening if family history-based criteria had been applied. Cases and controls were characterized with respect to enrollment center, age, sex, and family history of CRC. Family history was characterized in several ways: 1) any family history of CRC; 2) number of FDRs with CRC (1 or ≥2); number of SDRs with CRC (1 or ≥2); 3) meeting practice guideline criteria for early age of screening initiation based on family history based early age of screening initiation. Practice guidelines from the ACS in conjunction with the American College of Radiology (ACR) and the USMSTF from 2008 (referred to hereafter as family history based criteria)[5], National Comprehensive Cancer Network (NCCN) from 2017 [14], the USMSTF from 2017 (not in conjunction with ACS or ACR [15]), and the Canadian Association of Gastroenterology endorsed by the American Gastroenterological Association (CAN guidelines) from 2018 [16] were applied, since all of these guidelines include recommendation for early screening for patients meeting specific family history criteria (Table 1). This project was initiated 2017-2018, thus guidelines available at that time were initially used. We note at time of revision preparation 12/23/2019, that no new joint ACS/ACR/USMSTF guideline had been issued, and that the NCCN has issued an updated 2019 guideline which differs only slightly (Table 1).We also considered applying guidelines from Cancer Council Australia [17], but for simplicity did not do so because these recommendations take a hybrid approach in which FIT is initially recommended at younger years with a transition to colonoscopy, making them distinct from the other practice guidelines which were generally more similar in strategy. In primary analyses, we characterized cases and controls with respect to meeting family-history based criteria for early screening recommended jointly by the ACS, USMSTF, and ACR in 2008. Results based on application of practice guidelines from NCCN, USMSTF, and CAN are presented as secondary analyses. Some of the population-based CCFR sites oversampled cases that had a family history of CRC. To examine whether this might have biased estimates of criteria sensitivity and specificity, we conducted

a sensitivity analysis restricted to CCFR sites that did not purposefully oversample CRC cases with a family history of colorectal cancer. We used descriptive statistics, including means, and proportions with associated 95% confidence intervals to characterize data; all analyses were performed using SAS version 9.4.

Results

We included 2,473 CRC cases and 772 controls age 40 to 49 (Table 2). Cases and controls were similar with respect to age (mean 45.4 vs. 44.8 years) and sex (48% vs. 46% male). Any family history of CRC was more prevalent among cases than controls (37% vs. 17%). Joint ACS/USMSTF/ACR family history-based criteria had 25% sensitivity (614/2473, 95% CI: [0.23, 0.27]), and 90% specificity (698/772, 95% CI: [0.88, 0.92]) for identifying individuals with CRC diagnosed between ages 40 to 49 (Table 3).

Among the 614 individuals with CRC diagnosed between ages 40 to 49 meeting early screening criteria, 98.4% (n=604) could have been recommended screening initiation at an age younger than observed age of diagnosis, if family history-based criteria had been fully implemented (Figure 1). Ten of 614 individuals with CRC (1.6%) did not meet criteria to begin screening younger than age of actual diagnosis. One hundred and forty-nine (24%) individuals with CRC diagnosed ages 40 to 49 had a first degree relative present with CRC younger than their age of diagnosis, suggesting earlier screening could have been recommended based on family history. The mean age that could have been recommended based on guidelines for screening among CRC cases was nearly 10 years younger than the observed age of diagnosis (mean 36±5 vs 45±3 years), and 62.2% (382/614) could have been recommended screening initiation prior to age 40 (frequency distribution of guideline recommended potential age to initiate screening is provided in Supplemental Table A). Observed age of CRC diagnosis was the same as youngest affected FDR for 44% (271/614) of cases, suggesting many cases may not disclose family history or seek evaluation until reaching age of youngest affected relative (Supplementary Figure 1).

Secondary analyses of the potential impact of other practice guidelines for early age of screening initiation were qualitatively similar: sensitivity for identification of CRC cases age 40 to 49 years was 21% for NCCN, 21% for USMSTF, and 21% for CAN criteria (Table 3). Overall proportion of cases age 40 to 49 who had a first degree relative diagnosed with CRC at a younger age was estimated to be 20% for the NCCN, USMSTF, and also the CAN guidelines (Supplemental Table B). Additional secondary

analyses restricted to the 1597 subjects (n=990 cases, 607 controls) from three CCFR sites that did not by design oversample CRC cases with a family history of CRC also showed qualitatively similar results: ACS criteria had 23% sensitivity, and 92% specificity for identification of CRC cases age 40 to 49 (Supplementary Table C).

DISCUSSION

In this population-based analysis of 2,473 CRC cases and 772 cancer-free controls, we found that application of family history criteria identified 1 in 4 individuals age 40 to 49 with EOCRC for early age of screening initiation, suggesting substantial yield, but also an opportunity for develop improved strategies for identifying individuals at risk for EORCRC diagnosis. Importantly, if the recommended age of screening initiation had been applied to the 1 in 4 cases meeting criteria for early screening, our data suggest that over 98% of these CRC cases could have had their cancer detected (or possibly even prevented) before at an age younger than the observed age of CRC diagnosis, underscoring the potential importance of early initiation of screening in persons with a positive family history. Our results also show that 44% of all CRC cases meeting criteria for early age of screening initiation had their CRC diagnosed at the same age as their youngest FDR with CRC, perhaps suggesting that some CRC cases did not make healthcare providers aware of their family history until they reached near age of their youngest FDR with CRC.

A primary strategy for identifying patients at risk for early onset cancer is family history-based. This approach has been informed by epidemiologic studies, which demonstrate that having any FDR with CRC increases cancer risk about 2-fold; risk is even higher among relatives of individuals with younger onset CRC and among family members where multiple family members are affected [11]. Accordingly, family history-based CRC guidelines recommend early initiation of screening, based on the observation that age-specific CRC incidence appears to being to increase at younger ages among FDRs of individuals with CRC compared to individuals without a family history of CRC [18].

Despite widespread promotion of family history-based criteria as the primary strategy for identifying individuals for EOCRC, to our knowledge, no population-based study has evaluated sensitivity and specificity of this strategy for identifying individuals with EOCRC. Further, while a modeling study has suggested implementation of family history based early screening could be effective and cost effective at a population level [9], to our knowledge, no population-based study has assessed potential impact of family history-based criteria for early screening initiation if recommendations were to be fully implemented, as we have done by comparing age of CRC diagnosis to age of youngest FDR with

CRC among CRC cases. We found that the sensitivity of family history-based criteria, as recommended jointly by the ACS/ACR/USMSTF in 2008, was 25%. As such, while family-history based criteria appear to have substantial yield for identifying individuals at risk for EORCRC, our observation also underscores the need for developing new approaches for identifying the other 75% of individuals at risk for EOCRC. In contrast, we found that 98% of the 1 in 4 individuals who met family history criteria could have been recommended an earlier age of screening initiation than actual observed age of CRC diagnosis. Further, the mean age when screening could have been initiated based on practice guidelines was nearly 10 years earlier than observed age of diagnosis, with 62.2% meeting criteria to initiate screening before age 40. As such, these results suggest that for patients who meet family history criteria, full implementation of current recommendations represents an opportunity for early detection, and perhaps prevention. Our observation that 44% of all CRC cases meeting early screening criteria were diagnosed at the same age as their youngest FDR with CRC is intriguing, and may have several explanations. We speculate that in usual clinical practice, providers may not be systematically asking about family history and acting on this information, or perhaps in some cases that patients may be seeking screening evaluations when they reach the age their relatives had cancer, rather than well before this age. Alternatively, presentation with signs/symptoms of CRC may have led clinicians to elicit family history of CRC, and, upon discovering a family history of CRC at same age as the proband's presentation, led them to place greater urgency on diagnostic work ups resulting in CRC diagnosis. Similarly, probands with CRC experiencing signs/symptoms of CRC such as rectal bleeding might have been motivated to seek more urgent work up with the knowledge of having a FDR diagnosed with CRC at the same age.

Achieving full implementation of current family history-based recommendations is a challenge. Family history, particularly under age 50, is collected with suboptimal frequency, with one study estimating that just 39% of patients under age 50 had been asked about family history of CRC [19]. Even when family history is collected, age of cancer onset in a relative is also often not recorded, and the accuracy family history of CRC reported by patients is often suspect [20, 21]. CRC family history is poorly recalled (versus other cancers) and recall of details such as age of affected relatives is limited [22]. Among relatives of patients with CRC, adherence to recommended guidelines for age of screening initiation and frequency of screening is low, estimated as ranging from 31 to 47% in one review [11]. Physician recommendation may be a key factor that can foster screening adherence. Increased promotion of awareness of family cancer history in the population, and elicitation of family history with guideline-appropriate recommendations by medical providers may help identify more candidates for early screening [11]. Despite these challenges, our observation that nearly all of the 1 in 4 CRC patients meeting family history based criteria could have had a recommendation for screening initiation younger than their age of

diagnosis, suggests that efforts to collect and act on family history of CRC should be intensified. Indeed, our findings underscore and emphasize that failure to collect and act on family history of CRC in usual practice may represent a significant missed opportunity for early detection and prevention.

Currently, there are few alternative options for early identification and prevention of CRC among individuals at risk for early onset disease. Widespread genetic screening, such as with a multi-gene panel screening for mutations associated with increased risk for EOCRC might be considered [23]. Experience to date with applying these panels to patients with CRC suggest that many of the mutation carriers identified did not have a family history of cancer, raising potential for a strategy of population-based germline testing to complement family history-based identification. However, it is notable that even among patients with EOCRC, a multi-gene panel including most of the genes currently available for evaluation by most commercially available tests found an identifiable mutation in only 16% of individuals with CRC younger than age 50 [24]. Expense, management of variants of uncertain significance, and challenge of identifying mutations for which natural history and ideal management strategies are unclear may dampen enthusiasm for using population-based multigene testing as a strategy for identifying individuals with pathogenic germline mutations in rare moderate to high penetrance genes that may confer increased risk for EOCRC.

Another alternative would be to lower the age of screening initiation for the entire population. The modeling study used to support the 2016 US Preventive Services Task Force (USPSTF) on Colorectal cancer suggested initiation of screening at age 45 instead of 50 could result in more life years gained at the population level [25]. However, the USPSTF elected to keep the recommendation to start at age 50, mainly noting that the gain in life years was modest, and citing concerns that the models were discordant with respect to ideal repeat screening intervals with a lower cutoff, and the lack of evidence of the impact of earlier initiation of population screening at age 45. An analysis commissioned by the ACS using the same models, updated to include the increasing population risk for colorectal cancer in individuals younger than age 50, concluded that initiating screening at age 45 could be favorable relative to age 50 [26]. This resulted in the ACS' recent conditional recommendation to initiate screening for all risk groups at age 45 [27]. However, a population-strategy of starting screening earlier may be too aggressive and inefficient for addressing the challenge. For example, the model suggested that an additional 810 lifetime colonoscopies would be required to prevent 3 incident and 1 fatal cancers for every 1000 people screened with colonoscopy every 10 years beginning at age 45 instead of 50 years. Further, lowering the age to 45 would still miss a substantial number of people with EOCRC. Recognizing that neither the USPSTF 2016 nor ACS 2018 recommendations were meant to address early detection and prevention of CRC among individuals with increased CRC risk, more targeted approaches

utilizing a combination of genetic, lifestyle, and family-history based factors may be promising. For example, a study by the Genetics and Epidemiology of Colorectal Cancer Consortium and the Colorectal Trans-disciplinary study of CRC cases of all ages found that the combination of an environmental risk score, a genetic risk score, and presence/absence of any family history of CRC showed improved accuracy for identification of CRC cases compared to family history alone [23]. Though accuracy was improved compared to family history alone, it was still estimated to be suboptimal (Area Under the Curve = 0.62 to 0.63 for the combined model vs. 0.53 to 0.54 for presence of family history alone), suggesting more work is needed to identify additional factors for risk stratification.

Potential limitations of our study include the possibility of "spectrum bias", in which the CRC cases may have been more likely to have family history of cancer than CRC cases in the general population. This could have biased results towards finding increased sensitivity of family history-based guidelines and overestimation of the proportion of individuals meeting criteria for early initiation. We focused on individuals age 40 to 49, which represent the bulk (72%) of EOCRCs. Genetic factors were not directly assessed because the focus was on impact of the general phenotype of first-degree family history guidelines in the absence of known germline genetic mutation. Mode of CRC detection (e.g. asymptomatic screening versus based on work up for signs/symptoms of CRC) was not available, thus we are unable to quantify precisely how many individuals with signs/symptoms of disease could have been detected through earlier, asymptomatic screening. Strengths of our study include the use of a large, population-based sample of cases and controls, and application of multiple different clinical guidelines to assess sensitivity and specificity. Further, the study fills a gap in the literature with respect to assessment of the potential impact of changing family-history based guidelines on clinical practice. Oversampling could have been a potential source of bias. However, sensitivity analyses did not show oversampling to have been a bias in our study.

In conclusion, our results suggest that current family history-based guidelines have low sensitivity for identification of individuals at risk for CRC age 40 to 49 years. However, among individuals who do meet family history criteria for early screening, our data suggest that the vast majority might have an opportunity to have early detection or even prevention of CRC. Thus, while novel strategies to optimize identification of individuals at risk for EOCRC are required, until these become available for usual clinical practice, ensuring awareness of family cancer history, and implementation of recommendations for family-history based screening have the potential to improve early detection and prevention of CRC.

Figure Legends

Figure 1: Potential impact of family history-based guidelines on time of CRC diagnosis
Legend: Of 2,473 CRC cases, 25% met criteria for early screening. Among 614 CRC cases meeting criteria for early screening, 98% could have been recommended screening initiation younger than actual age of CRC diagnosis.

Supplementary Figure 1: Proportion of CRC cases diagnosed at same age as their youngest FDR with CRC, overall, and stratified by age of cases at diagnosis. Among the 614 cases, 44% had CRC diagnosed at the same age as the earliest CRC diagnosis in their youngest first degree relative. The proportion diagnosed at same age as the youngest first degree relative varied from 34 to 55% across age categories of CRC diagnosis between 40 and 49 years. Note that the age range of cases at diagnosis is 40 to 49 because the study sample was restricted to cases diagnosed in this age range.

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Table 1: Sample of practice guidelines recommending early initiation of CRC screening before age 50 based on family history of CRC

	Criteria	Recommendation
Joint Guideline by American Cancer Society, US Multi-Society Task Force on Colorectal Cancer (USMSTF[a]) and American College of Radiology, 2008[5]	CRC or advanced adenoma in 2 first degree relatives at any age OR CRC or adenoma in a single first degree relative < age 60 years	Colonoscopy every 5 years beginning 10 years prior to age of first degree relative diagnosis or age 40
	CRC or adenoma in single first degree relative diagnosed age >=60 OR CRC in 2 second degree relatives at any age	Begin screening at age 40 with any test
USMSTF 2017[b, 15]	CRC or advanced adenoma in 2 first degree relatives at any age OR CRC or advanced adenoma in a single first degree relative < age 60 years	Colonoscopy every 5 years beginning 10 years prior to age of first degree relative diagnosis or age 40
	CRC or advanced adenoma in single first degree relative diagnosed age >=60	Begin screening at age 40 with any test
National Comprehensive Cancer Network 2017 [c,14]	CRC >=1 first degree relative with CRC at any age	Colonoscopy at age 40 or 10 years before earliest diagnosis of CRC, repeat every 5-10 years
Canadian Association of Gastroenterology, endorsed by American Gastroenterological Association[16]	CRC in 2 or more first degree relatives	Colonoscopy every 5 years at age 40 or 10 years younger than age of diagnosis of earliest diagnosed first degree relative, whichever is earlier
	CRC in 1 first degree relative	Colonoscopy every 5-10 years at age 40-50 years or 10 years younger than age of diagnosis of first degree relative, whichever is earlier. FIT every 1-2 years is suggested as 2nd line option
	1 or more first degree relative with documented advanced adenoma	No recommendation for a preferred test. Colonoscopy or FIT are both options.

		Colonoscopy every 5-10 years at age 40-50 years or 10 years younger than age of diagnosis of first degree relative, whichever is earlier. FIT every 1-2 years is suggested as 2nd line option
Cancer Council Australia 2018[17]	CRC in 1 first degree relative diagnosed <55, or in 2 first degree relatives at any age, or in 1 first degree relative and at least 2 second degree relatives with CRC at any age	FIT every 2 years from age 40-49 and colonoscopy every 5 years from age 50-74
	>=3 first degree or second degree relatives with CRC, with at least 1 diagnosed under 55 years, or >=3 first degree relatives with CRC at any age	FIT every 2 years from age 35-44 and colonoscopy every 5 years from age 45-74

[a] USMSTF, US Multi-Society Task Force on Colorectal Cancer, represents the American Gastroenterological Association, the American Society for Gastrointestinal Endoscopy, and the American College of Gastroenterology

[b] In 2017, USMSTF issued updated recommendations for colorectal cancer screening, without the American Cancer Society or the American College of Radiology, which differed from the 2008 joint recommendations only by excluding the prior reference to specialized screening for individuals with 2 SDRs with CRC at any age

[c] Update to the National Comprehensive Cancer Network Guidelines in 2019 specified every 5 year follow up instead of every 5-10 years

Table 2. Demographic characteristics and family history of the study population (N=3,245)

	CASES (n=2,473)	**CONTROLS (n=772)**
Age (years)/Mean (SD)	45.3 (2.8)	44.8 (2.8)
	n (%)	n (%)
Center		
Sinai Health System, Ontario, CAN	674 (27%)	165 (21%)
Cedars-Sinai/USC Consortium	427 (17%)	
University of Melbourne, AUS	377 (15%)	87 (11%)
University of Hawaii	85 (3%)	

Mayo Clinic	297 (12%)	
Fred Hutchinson Cancer Research Center	591 (24%)	520 (67%)
University of California, San Francisco (formerly Cancer Prev. Inst. Of California-CPIC)	22 (1%)	
Male Sex	1191 (48%)	354 (46%)
Family history of CRC	917 (37%)	133 (17%)
First degree relative (FDR) with CRC		
One FDR	423 (17%)	63 (8%)
Two or more FDR	84 (3%)	2 (0.1%)
Second degree relative (SDR) with CRC		
One SDR	409 (17%)	68 (9%)
Two or more SDR	179 (7%)	15 (2%)
Any ACS criteria met	614 (25%)	74 (10%)
CRC in 2 first degree relatives at any age*	84 (3%)	2 (0.3%)
CRC in a single FDR< age 60 years*	301 (12%)	9 (1%)
CRC in single FDR diagnosed age >=60*	100 (4%)	43 (6%)
CRC in 2 SDRs at any age*‡	107 (4%)	9 (1%)
CRC in single FDR with missing Dx age for the FDR*	22 (1%)	11 (1%)

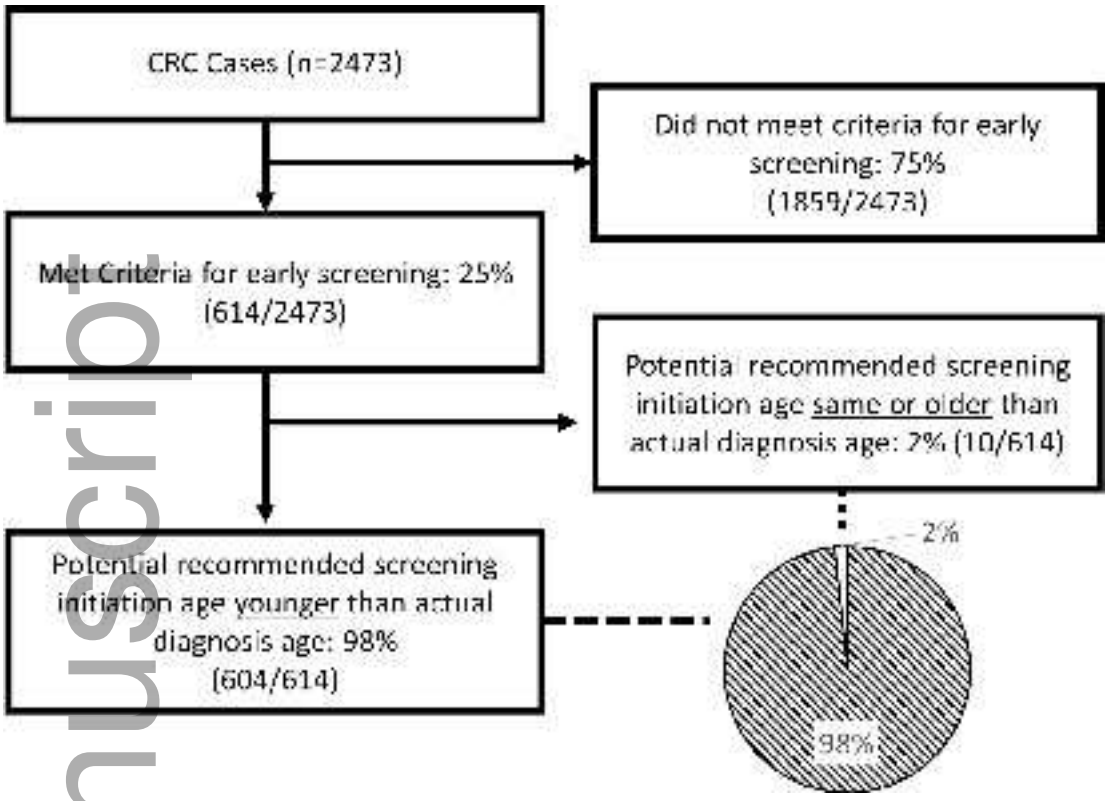
*% of those with ACS criteria; ‡excludes those with history of either 1 or more FDR ; CRC, colorectal cancer

Table 3. Sensitivity and specificity of family history based criteria issued by the ACS, NCCN, USMSTF, and CAN for identifying early onset CRC cases age 40 to 49.

	Sensitivity	Specificity
ACS 2008*	25%	90%
NCCN 2017	21%	92%
USMSTF 2017	21%	92%

CAN 2018	21%	92%

ACS, American Cancer Society; NCCN, National Comprehensive Cancer Network; USMSTF, US Multi society Task Force on Colorectal Cancer; CAN; Joint Canada/American Gastroenterological Association; *Joint recommendations by ACS, USMSTF, and American College of Radiology in 2008



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