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REVIEW

# Colorectal cancer screening: Opportunities to improve uptake, outcomes, and disparities

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## Abstract

Colorectal cancer screening has become a standard of care in industrialized nations for those 50 to 75 years of age, along with selected high-risk populations. While colorectal cancer screening has been shown to reduce both the incidence and mortality of colorectal cancer, it is a complex multi-disciplinary process with a number of important steps that require optimization before tangible improvements in outcomes are possible. For both opportunistic and programmatic colorectal cancer screening, poor participant uptake remains an ongoing concern. Furthermore, current screening modalities (such as the guaiac based fecal occult blood test, fecal immunochemical test and colonoscopy) may be used or performed suboptimally, which can lead to missed neoplastic lesions and unnecessary endoscopic evaluations. The latter poses the risk of adverse events, such as perforation and post-polypectomy bleeding, as well as financial impacts to the healthcare system. Moreover, ongoing disparities in colorectal cancer screening persist among marginalized populations, including specific ethnic minorities (African Americans, Hispanics, Asians, Indigenous groups), immigrants, and those who are economically disenfranchised. Given this context, we aimed to review the current literature on these important areas pertaining to colorectal cancer screening, particularly focusing on the guaiac based fecal occult blood test, the fecal immunochemical test and colonoscopy.

**Key words:** Fecal occult blood test; Fecal immunochemical test; Colonoscopy; Neoplasia; Polyp

**Core tip:** Colorectal cancer (CRC) screening has become a standard of care in industrialized nations for those aged 50 to 75 years. While CRC screening has been shown to reduce the incidence and mortality of CRC, it is a complex multi-disciplinary process that frequently presents challenges to implementation. This is a focused review on 3 pivotal areas of CRC screening that require improvement: (1) suboptimal uptake of CRC screening; (2) poor outcomes manifesting as missed lesions and adverse events during the screening process; and (3) ongoing disparities among marginalized populations.

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## INTRODUCTION

Colorectal cancer (CRC) is a critical health concern. It is the second most commonly diagnosed cancer in women and the third most commonly diagnosed cancer in men[1,2], with North America, Europe and Australia having the highest incidence rates worldwide[2,3]. In part due to the increasingly widespread adoption of Western dietary and lifestyle behaviors, the incidence of CRC is also rising in developing nations[3,4]. Therefore, CRC represents a significant economic burden globally, with Medicare treatment costs within the United State estimated at over $7 billion dollars[5]. This highlights the importance of effective CRC screening with the intent to minimize the CRC disease burden through the removal of adenomatous neoplasia and the detection of CRC at an earlier stage at which point treatment is more successful. CRC screening has been shown to be effective at reducing the incidence and mortality of CRC[6-13]. In addition, economic analyses[14-18] evaluating CRC screening have highlighted it as a cost-effective, and possibly cost-saving, intervention[18]. Consequently, many North American organizations including the Canadian Association of Gastroenterology (CAG)[19], the American College of Gastroenterology (ACG)[20], the Canadian Task Force on Preventative Health Care (CTFPHC)[21], the United States Preventative Services Task Force (USPSTF)[22] and the United States Multi-Society Task Force[23] have endorsed multiple different screening methods including: Fecal occult blood tests (FOBTs) such as the guaiac-based (gFOBT) as well as fecal immunochemical (FIT) tests, fecal DNA tests, flexible sigmoidoscopy (FSIG), colonoscopy (CSPY), and computed tomographic colonography (Table 1).

Although the concept of screening is intuitively simplistic, the implementation of population-based CRC screening is a complex interdisciplinary process. Most notably, participation in initial and subsequent CRC screening have still not reached well-recognized benchmarks[24,25]. Moreover, screening test performance is an ongoing area of concern, given the potential for missed neoplasia as well as procedure-related adverse events. These issues are further exacerbated by persistent disparities in CRC screening among marginalized populations[26]. Considering these issues, we sought to review these important areas and propose opportunities for optimization. For the purposes of this article, we will focus on the two predominant methods for CRC screening used in Canada and the United States, namely FOBTs (including gFOBT and FIT) and CSPY.

## UPTAKE AND RETENTION

For CRC screening to be effective, high levels of participation in initial and subsequent CRC screening are required. Likewise, when gFOBT or FIT are used, abnormal results must be promptly followed by an evaluation with CSPY[27]. Failure at any of these steps carries with it the potential to impair the effectiveness of CRC screening.

### *Initial CRC screening*

In the United States, CRC screening uptake appears to be increasing[28]. Unfortunately, estimates still remain below national targets[28]. Based on findings derived from the 2010 National Health Interview Survey, a United States-based survey assessing a representative sample of the United States civilian population, only 59% of those aged 50 to 75 years were up-to-date with CRC screening as per the 2008 USPSTF recommendations (high-sensitivity FOBT every year; or FSIG every 5 years and high-sensitivity FOBT every 3 years; or CSPY every 10 years)[24]. In comparison, estimates gathered from the 2012 Behavioral Risk Factor Surveillance System survey, another United States-based survey assessing a representative sample of the United States civilian population, close to 65% of those aged 50 to 75 years were up-to-date with CRC screening as per the same USPSTF recommendations[28]. Of note, a concerning finding was that 28% stated they had never been screened for CRC.

In Canada, CRC screening rates also appear to be increasing, but they are similarly below current national benchmarks[27]. Estimates from the 2012 Canadian Community Health Survey, a Canadian-based survey assessing a representative sample of the Canadian population, only 55% of those aged 50 to 74 years were up-to-date with CRC screening (FOBT every 2 years; or FSIG or CSPY every 10 years)[25]. In recent years, Canada has made a concerted effort to transition to nationwide programmatic screening. Emerging data from 5 Canadian provinces between 2009 and 2011 collated by the Canadian Partnership Against Cancer (CPAC) revealed that participation in programmatic CRC screening (either gFOBT or FIT) ranged from 5% to 37% only[27]. These estimates captured programmatic CRC screening alone whereas CRC utilization considers both programmatic and non-programmatic CRC

**Table 1 Colorectal cancer screening recommendations for guaiac-based fecal occult blood test, fecal immunochemical test and colonoscopy among asymptomatic average-risk adults**

| | USPSTF[22] | CTFPHC[21] | CAG[19] | USMSTF[23] | ACG[20] |
|---|---|---|---|---|---|
| Publication year | 2016 | 2016 | 2010 | 2008 | 2008 |
| Country | United States | Canada | Canada | United States | United States |
| Age cut-off | 50 to 75[2] | 50 to 74 | 50 to 75[2] | Start at 50 | Start at 50 |
| gFOBT | Every year | Every 2 yr | Every 1 or 2 yr[3] | Every year | Every year |
| FIT | Every year | Every 2 yr | Every 1 or 2 yr[3] | Every year | Every year |
| CSPY | Every 10 yr | Not recommended | Not recommended[4] | Every 10 yr | Every 10 yr |
| Preferred test[1] | No preference | No preference | FIT[5] | CSPY | CSPY |

[1]Preferred test considering gFOBT, FIT and CSPY as potential CRC screening tests; [2]CRC screening can be considered between ages 76 to 85 years on an individual basis; [3]Frequency of testing dependent on jurisdictional resources; [4]Recommendation against CSPY for population-based CRC screening. CSPY was a recommended option for opportunistic screening; [5]Preference in the setting of programmatic CRC screening. ACG: American College of Gastroenterology; CAG: Canadian Association of Gastroenterology; CRC: Colorectal cancer; CSPY: Colonoscopy; CTFPHC: Canadian Task Force on Preventative Health Care; FIT: Fecal immunochemical test; gFOBT: Guaiac-based fecal occult blood test; USMSTF: United States Multi-Society Task Force; USPSTF: United States Preventative Services Task Force.

screening. FIT or gFOBT utilization ranged from 6% to 44% in 2009, and increased to 12% to 58% in 2011[27].

### *Confirmatory testing with CSPY*

Follow-up CSPY after an abnormal gFOBT or FIT result has also been highlighted as an area requiring further optimization. In 2001, a prospective study of 2410 participants aged ⩾ 70 years were assessed, of which 212 has a positive gFOBT result[29]. After 6 mo and 1 year, only 22% and 42%, respectively, had undergone endoscopic evaluation. In Canada between 2009 and 2011, 45% of subjects participating in programmatic screening underwent CSPY within 60 d and 81% underwent CSPY within 180 d after an abnormal gFOBT or FIT[27]. There were significant variations between provinces whereby estimates ranged from 68% to 90%.

### *Serial screening at subsequent intervals*

To benefit from CRC screening, retention during subsequent screening cycles is required. In a United States-based cohort of 11110 participants who had undergone gFOBT for CRC screening, only 44% completed repeat testing in the next 2-year follow-up period[30]. In another large United States-based retrospective cohort of over 1 million participants across 136 Veteran Affairs medical centers, only 41% of men and 44% of women received adequate screening over a 5-year period (FOBT in 4 of the 5 years or ⩾ 1 FOBT as well as CSPY, FSIG or double-contrast barium enema)[31]. When stratifying outcomes based on the 384527 men and 10469 women who only used FOBT, only 14% (both groups) completed FOBT testing in 4 of the 5 years.

While findings from programmatic screening are more optimistic, they are still not ideal. Two studies from the Netherlands that assessed gFOBT and/or FIT showed that participation in the second round of testing ranged between 63% to 86%[32,33]. In the evaluation of an Italian FIT-based CRC screening program over 4 rounds in a 7-year period, participation ranged between 56% to 63%[34].

## POOR OUTCOMES

Test performance is a major determinant of health outcomes, especially considering the potential clinical and economic implications of false positive and false negative results. In the setting of CRC screening, false negative findings equate to missed neoplastic lesions. This delay in diagnosis can have a profound impact on outcomes whereby potentially curable disease is rendered palliative. Likewise, false positive results can lead to additional healthcare resource use in the form of unnecessary CSPYs. Although CSPY is a generally safe procedure, it is not without adverse events, specifically post-polypectomy bleeding and perforation.

### *Fecal occult blood test performance*

In comparing FIT and gFOBT, FIT has clearly emerged as the superior option for CRC screening[35,36], which is now reflected in both national[19] and international[37] guidelines. However, FIT still has some inherent limitations. In a recent meta-analysis of 19 unique evaluations, FIT sensitivity was 79%[38]. However, with adjustment of the FIT cut-off, sensitivity ranged from 67% to 86%. Interestingly, single sample FIT had similar sensitivity as several sample FIT. Aside from modifying the quantitative threshold to define test positivity, other factors have been identified that affect FIT sensitivity. For example, the version of FIT being used has been implicated in test performance variability. In the Taiwanese nation-wide screening program, 956005 participants underwent CRC screening using either OC-Sensor (Eiken Chemical Co, Tokyo, Japan) or HM-Jack (Kyowa Medex Co Ltd, Tokyo, Japan). Even though identical positive test cut-offs (20 μg hemoglobin/g feces) were used[39], significant differences between the two quantitative FITs were found when examining the positive predictive value for cancer and rates of interval cancer. Additional factors that affect FIT performance include processing time and temperature. As FIT is based on the detection of the protein globin, it is susceptible to false-negative results secondary to protein degradation. In a 2009 study, van Rossum

*et al*[40] compared FIT performance based on time between sampling and laboratory delivery (< 5 d *vs* ⩾ 5 d). There was a significant reduction in adenoma detection rate (ADR) when samples were returned after ⩾ 5 d. Moreover, it was found that mean fecal hemoglobin values decreased by 29 ng hemoglobin/mL buffer solution per day. In regards to the effect of temperature on FIT result, an Italian FIT CRC screening program found that an increase in temperature of one degree Celsius reduced the likelihood of FIT positivity by 0.7%[41]. Similarly, there was a 13% reduction in detecting CRC or advanced adenomas in the summer compared to the winter.

### *Missed lesions on CSPY*

It is well documented that CSPY may not reliably prevent CRC[42-47] because of the potential of missed lesions[47,48] or incomplete polypectomy[49,50] at initial procedure. This is further compounded by variations in CRC tumorigenesis[51]. In a recent meta-analysis that characterized the miss rates of polyps which were corroborated by tandem CSPY, the pooled miss rate for polyps of any size was 22%[48]. For adenomas, the pooled miss rates were 2.1% for adenomas ⩾ 10 mm, 13% for adenomas 5 to 10 mm and 26% for adenomas 1 to 5 mm. Moreover, there is marked variability in ADR between endoscopists[52-55] in which estimates have ranged from 7% to 44%[52-55]. In a 2010 study that evaluated 186 endoscopists alongside 45026 patients (188788 person-years), ADR was significantly associated with the risk of interval cancer[56]. In comparing ADR < 20% *vs* ADR ⩾ 20%, the hazard ratios were > 10 for interval CRC. In a 2014 study of 136 endoscopists, it was determined that a 1% increase in ADR was associated with a 3% decrease in risk of CRC[57]. The aforementioned evidence underscores the importance of ADR and reinforces its value as an important CSPY quality indicator. This has been endorsed by multiple societies[58,59], with the American Society for Gastrointestinal Endoscopy (ASGE) recommending an ADR of ⩾ 25% (⩾ 30% in men, ⩾ 20% in women) among asymptomatic average-risk individuals[59].

Another limitation of CSPY pertains to proximal CRC (lesions proximal to the splenic flexure)[42,45,60]. Proximal lesions are different from those that are distal in many ways. For instance, proximal masses can be missed secondary to inadequate bowel preparation[59], complicated by incomplete CSPY[61], and prone to suboptimally removed lesions. Further, CRC tumorigenesis between proximal and distal lesions can be different[51,62]. In a 2009 study of 10292 patients who died of CRC and 51460 matched-controls, it was shown that receipt of a complete CSPY was significantly associated with less death secondary to left-sided CRC; however, a similar relationship was not found for right-sided CRC[42]. In a subsequent 2010 study, amongst 54803 patients who underwent index CSPY, a 29% reduction in overall CRC mortality was identified[45]. However, there was no reduction in CRC mortality for proximal CRC. In another 2010 study that investigated 3287 individuals undergoing screening CSPY, a preceding CSPY within 10 years decreased the prevalence of advanced colorectal neoplasms, but this had little, if any, effect on reducing the prevalence of proximal advanced colorectal neoplasms[60].

### *CSPY - adverse events*

Serious adverse events secondary to CSPY are well-recognized. Although they are relatively infrequent, they remain a concern, particularly in settings where CSPYs are performed outside current recommendations for screening and surveillance[63]. It is estimated that the risk of serious adverse events, specifically perforation and post-polypectomy bleeding, is approximately 1 per 1000 CSPYs[64,65].

Perforation is the most serious adverse event associated with CSPY. In a 2008 study[64], using administrative-level data among 97091 individuals who underwent outpatient CSPY, the rate of perforation was 0.85/1000 and the rate of death was 0.074/1000. Factors associated with increased risk of perforation were older age, male sex, polypectomy, and having the CSPY performed by a low-volume endoscopist. These findings were supported by a 2009 study[65] of 53220 CSPYs performed in a Medicare population, highlighting a perforation rate of 0.6/1000. In terms of post-polypectomy bleeding, two studies described rates to be 1.64/1000[64] and 6.4/1000[65] respectively. Similar risk factors were observed to increase the likelihood of post-polypectomy bleeding, including older age, male sex, polypectomy and having the CSPY performed by a low-volume endoscopist[64]. In addition, large polyp size, proximal location, and use of anti-coagulation[66] worsened the risk

In the recent ASGE quality indicators for colonoscopy guidelines, performance targets for perforation have been set at < 1:500 (all examinations), < 1:1000 (screening examinations) and < 1% for post-polypectomy bleeding. As per the ASGE, it was recommended that rates exceeding these recommendations should prompt a review of CSPY technique of the endoscopist in question.

## ONGOING DISPARITIES

Disparities in CRC screening are an unfortunate reality. With an estimated 49190 deaths due to CRC within the United States in 2016, a disproportionate burden will occur within marginalized populations[1]. People of specific ethnic minorities, immigrants, and those in lower socioeconomic backgrounds are less likely to receive screening[24,67]. For United States and Canada to successfully achieve their respective screening targets, these disparities need to be addressed and minimized.

### *Ethnic and immigrant minorities*

Ethnic minorities have been found to have lower CRC screening uptake. This is apparent across multiple ethnicities including African Americans[68], Hispanics[1],

Asians[69], and Indigenous populations (American Indians and Alaska Natives within the United States; First Nations and Metis within Canada)[70]. Multiple factors have been implicated as drivers of this disparity. A lack of knowledge concerning CRC and poor awareness of the concept and importance of CRC screening are key drivers, but fear of discomfort, anxiety of waiting for results, and general mistrust of healthcare professionals have been cited in the literature as reasons why selected patient subgroups fail to seek screening[71-73]. The latter is especially concerning since it can lead to decreased physician engagement and poor continuity of care. Similar to other factors associated with treatment disparities, ethnic populations may also be more vulnerable to the effects of lower socioeconomic status[74], a lack of health insurance[75] and barriers in communication[75]. Lastly, differences in CRC tumorigenesis[76] may play a further role whereby a CRC diagnosis affects patients at younger ages when screening is generally not recommended. Likewise, immigrants[75,77] represent another subgroup of patients who are less likely to undergo CRC screening. In a 2013 study[75] that compared United States-born citizens to non-citizens who participated in the California Health Interview Survey, 67% *vs* 46% underwent CRC screening. Potential factors contributing to this disparity were living in rural areas, a lack of health insurance, and not being proficient in the English language.

### *Socioeconomic status*

There is notable interplay between drivers of disparity and socioeconomic status. Individuals with low socioeconomic status have poorer uptake of CRC screening[78,79]. In a 2009 study assessing Medicare enrollees ages 65 to 80 years, individuals less educated or belonging to low-income groups were less likely to undergo CRC screening[80]. Unfortunately, even when the cost of CRC screening is alleviated, disparity still persists[81]. In England, the Bowel Cancer Screening Program does not pose any financial costs to participants because it is operated by the National Health Service since 2006. Despite this fact, there were marked variations in CRC screening uptake among the first 2.1 million participants. In the least socially and economically deprived areas, uptake was highest at 61% whereas uptake was lowest at 35% in the most deficient areas[81,82]. To a large extent, the ongoing drivers of these differences remain unclear within this subgroup; however, it is postulated that stress, low social supports, competing life demands, and literacy are strongly implicated[72,83] and thus challenging to mitigate systematically.

## CONCLUSION

In conclusion, while CRC screening has clearly proven its ability to reduce the incidence and mortality of CRC, there are critical areas requiring further improvements. For the benefits of CRC screening to materialize, increased uptake and retention during subsequent screening cycles is paramount. Additionally, refinement of current screening test performance measures along with optimization of CSPY quality to prevent procedure-related adverse events are essential as an increasing number of jurisdictions continue to introduce and implement programmatic CRC screening. Lastly, effective interventions that target and consider the unique needs of the marginalized subsets of our population is crucial if our goal is to enhance outcomes for all. With universal adoption of programmatic CRC screening and continued advances in screening modalities, it is our hope that CRC screening can provide meaningful morbidity and mortality benefits to patients in an equitable and cost-effective manner.

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