World Journal of Gastroenterology

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*World J Gastroenterol* 2024 July 28; 30(28): 3361-3366

DOI: 10.3748/wjg.v30.i28.3361

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

# Optimization of colorectal cancer screening strategies: New insights

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**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**

**Scientific Quality:** Grade C
**Novelty:** Grade C
**Creativity or Innovation:** Grade C
**Scientific Significance:** Grade C

**P-Reviewer:** Qiu Y

**Received:** March 16, 2024
**Revised:** June 7, 2024
**Accepted:** June 28, 2024
**Published online:** July 28, 2024
**Processing time:** 129 Days and 12.9 Hours

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## Abstract

In this editorial, we discuss the article by Agatsuma *et al*. We concentrate specifically on the current routinely used screening tests recommended by society guidelines and delve into the significance of early diagnosis of colorectal cancer (CRC) and its substantial impact on both incidence and mortality rates. Screening is highly recommended, and an early diagnosis stands out as the most crucial predictor of survival for CRC patients. Therefore, it is essential to identify and address the barriers hindering adherence to screening measures, as these barriers can vary among different populations. Furthermore, we focus on screening strategy optimization by selecting high-risk groups. Patients with comorbidities who regularly visit hospitals have been diagnosed at an early stage, showing no significant difference compared to patients undergoing regular screening. This finding highlights the importance of extending screening measures to include patients with comorbidities who do not routinely visit the hospital.

**Key Words:** Colorectal neoplasms; Early diagnosis; Barriers to adherence; Cancer screening guidelines; Screening tests

**Core Tip:** Despite the proven mortality benefits, adherence to colorectal cancer (CRC) screening guidelines remains low in many regions worldwide. Because nation-wide screening is not feasible due to limited financial and human resources, it is crucial to identify high-risk groups that ought to participate in screening measures. However, variation in each population is to be considered when implementing screening procedures, and barriers affecting adherence to screening guidelines should be addressed in each specific population. Finally, patients with comorbidities who regularly schedule visits to the hospital are diagnosed at an early stage similar to those who undergo periodic screening. This underscores the importance of encouraging patients with comorbidities who do not attend routine visits to undergo screening to reduce the burden of late-stage CRC diagnosis.

**Citation:** Tamraz M, Al Ghossaini N, Temraz S. Optimization of colorectal cancer screening strategies: New insights. *World J Gastroenterol* 2024; 30(28): 3361-3366
**URL:** https://www.wjgnet.com/1007-9327/full/v30/i28/3361.htm
**DOI:** https://dx.doi.org/10.3748/wjg.v30.i28.3361

## INTRODUCTION

Globally, colorectal cancer (CRC) ranks third following breast and lung cancer. It is expected that the incidence of CRC will increase 1.6-fold by the year 2030[1], and in 2040, it is estimated that there will be approximately 3.2 million cases diagnosed worldwide[2]. The 5-year relative survival rate of CRC has shown a notable increase of 15% from the mid-1970s to the years 2012-2018[3,4]. This trend is primarily attributed to advancements in earlier detection facilitated by routine clinical examinations and screening strategies. Early-stage diagnosis is the most significant predictor of survival among CRC patients mounting to a 5-year survival rate of 91% in early-stage cases compared to a 5-year survival rate of 14% in metastatic cases[5].

Various screening tests are provided for the early detection of CRC and adenomatous polyps. These tests vary in terms of sensitivity and specificity, effectiveness, convenience, safety, accessibility, and cost. Screening tests could be categorized into four groups: Stool-based tests, endoscopic visualization, radiologic visualization, and blood-based markers. Stool-based tests include fecal immunochemical test (FIT) for blood, which directly detects hemoglobin in stool samples, and Guaiac-based fecal occult blood test (gFOBT), which recognizes hemoglobin by altering guaiac reactant-permeated paper to blue due to a peroxidase reaction, multitarget stool DNA tests with FIT that combines molecular assays to test for DNA (KRAS) mutations in addition to FIT. Endoscopic visualization methods include colonoscopy, sigmoidoscopy, sigmoidoscopy plus FIT or gFOBT[6], and colon capsule endoscopy[7]. Available blood-based markers typically identify CRC at a more developed stage instead of premalignant lesions, and thus, their part in identifying early-stage disease remains uncertain and has not been incorporated in main society guideline recommendations. Presently employed blood-based markers, particularly in the United States, are the septin 9[8], which is a plasma assay that identifies circulating hypermethylated septin 9 DNA in CRC, and the 7-gene biomarker test (*ANXA3*, *CLEC4D*, *LMNB1*, *PRRG4*, *TNFAIP6*, *VNN1*, and *IL2RB*)[9]. Table 1 summarizes the specificity and sensitivity of the abovementioned tests as well as the recommended frequency of each screening test.

Another technique of defining screening tests for CRC is by distinguishing between 1-step or 2-step approaches. The 1-step approach such as colonoscopy simultaneously serves both diagnostic and therapeutic purposes. Colonoscopy is effective in diagnosing early lesions or polyps and enables their removal during the same procedure. Polypectomy can reduce the risk of mortality from CRC by 53%[10]. Consequently, the European Society of Gastrointestinal Endoscopy recommendation involves the removal of all polyps, with the exception of miniscule rectal and rectosigmoid polyps that are known to be hyperplastic[11]. In contrast, the 2-step approaches (FIT, gFOBT, CTC, and colon capsule) will require a follow-up colonoscopy if the initial test results are positive. This requirement is a drawback of the 2-step tests, contributing to why colonoscopy remains the gold standard approach for screening[12].

Screening tests are efficient in the context of increased adherence of the population to screening guidelines. Candidates for screening include adults with no signs or symptoms of CRC who are at an average risk of developing CRC and have no personal or family history of genetic disorders such as Lynch syndrome or familial adenomatous polyposis. However, patients with risk factors for CRC are included in high-screening programs. Furthermore, individuals with abnormal findings such as cancer or polyps should undergo surveillance colonoscopy regardless of their age[13]. Figure 1 summarizes the most updated societal recommendations for the screening of CRC.

Screening has significantly impacted the incidence and mortality rates of CRC. The use of gFOBT screening resulted in a reduced incidence of CRC by 20% in the United States and 60% in Japan. Flexible sigmoidoscopy reduced the incidence of CRC by 26% in the United Kingdom and 10% in Italy[14]. Regarding mortality rates, a gFOBT screening led to reductions in the mortality rate of 31.7% in China, 30% in Japan, 18% in Denmark, 16% in France, 16% in Sweden, 15% in the United Kingdom, and 13% in Italy. However, 1-year screening with gFOBT resulted in a higher reduction of mortality rates compared to 2-year screening (32% *vs* 18%)[3]. It is without a doubt that screening is crucial in addressing the high incidence and mortality rates of CRC.

**Table 1 Comparison between different screening tests for colorectal cancer**

| Test type | Specificity, % | Sensitivity, % | Frequency, years | Ref. |
|---|---|---|---|---|
| Stool-based tests | | | | |
| FIT | 90-95 | 71-91 | 1-2 | [23] |
| gFOBT | 88-98 | 50-75 | 1-2 | [24-26] |
| MT-sDNA | 92.70 | 93.90 | 1-3 | [27] |
| Endoscopic visualization | | | | |
| Colonoscopy | 86 | 95 | 10 | [28] |
| Sigmoidoscopy | 87 | 95[1] | 5 | [28] |
| Colon capsule | 76-98.2 | 81-87 | 5 | [29,30] |
| Radiologic visualization | | | | |
| CTC | 88 | 84 | 5 | [28] |

[1]Examining the distal part of the colon that is within reach of the sigmoidoscope.
CTC: Computed tomography colonography; FIT: Fecal immunochemical test; gFOBT: Guaiac-based fecal occult blood test; MT-sDNA: Multitarget stool DNA.

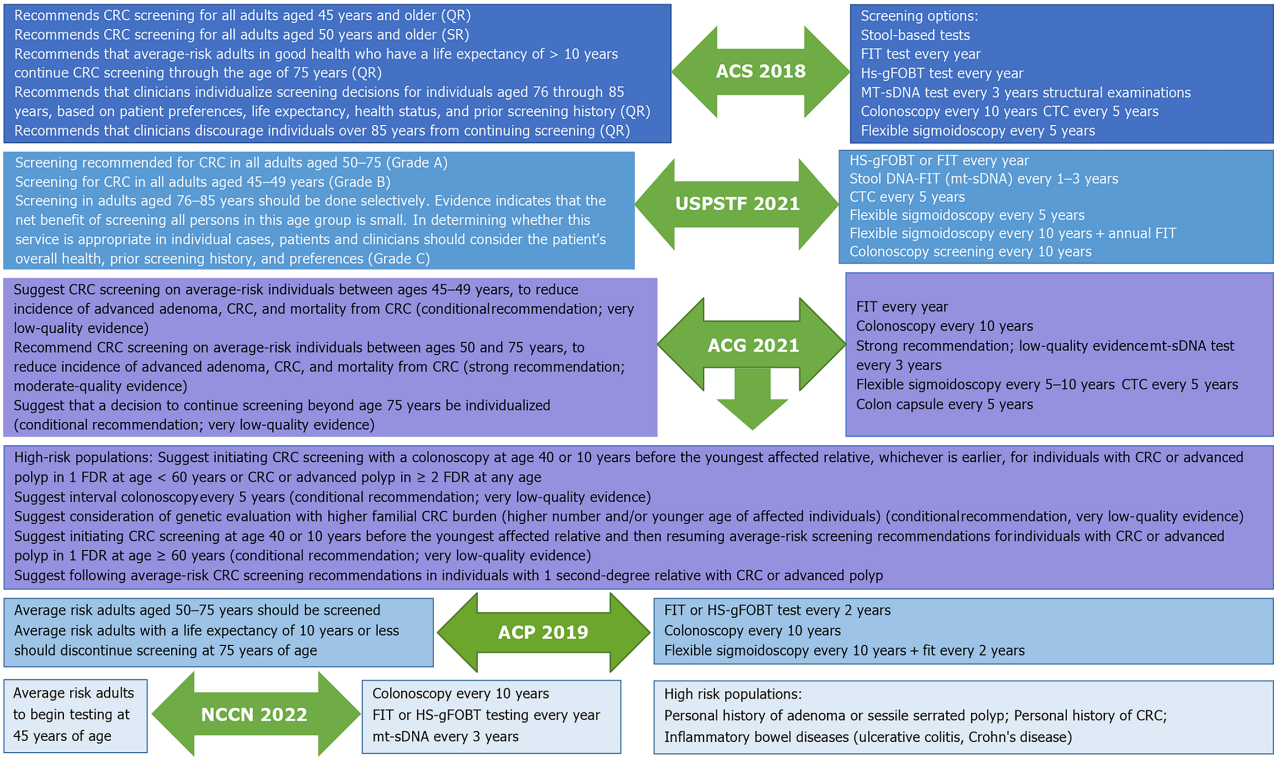


**Figure 1 Colorectal cancer screening guideline recommendations from several societies.** ACG: American College of Gastroenterology; ACP: American College of Physicians; ACS: American Cancer Society; CRC: Colorectal cancer; CTC: Computed tomography colonography; FDR: First-degree relative; FIT: Fecal immunochemical test; gFOBT: Guaiac-based fecal occult blood test; MT-sDNA: Multitarget stool DNA; NCCN: National Comprehensive Cancer Network; QR: Qualified recommendation; SR: Strong recommendation; USPSTF: United States Preventative Service Task Force.

## BARRIERS TO APPROPRIATE SCREENING STRATEGIES

Despite the proven mortality benefits, adherence to screening guidelines varies significantly between countries. In Europe, the Netherlands has the highest adherence to screening guidelines, with a rate of 71.3%. Another 12 European countries reported an adherence rate greater than 50% and Italy reported an adherence of 45.7%. However, Poland and Belgium had an adherence rate below 20%[3]. Barriers affecting patient adherence include inadequate information and consciousness about CRC and its screening measures, absence of doctor recommendations, emotional factors such as anxiety, distress, and disgrace, in addition to social, spiritual, and sociodemographic factors including decreased income

and feminine gender[15]. Ideally, total population screening based on clinical recommendations would be the most efficient screening strategy to combat CRC; however, barriers to achieving total population screening are also limited by human and financial resources, in addition to the aforementioned barriers.

Furthermore, establishing clear guidelines regarding who should be screened is still challenging, particularly with an erratic disease such as CRC. For instance, previous recommendations involved screening adults who were older than 50 years. However, recent updates from the American Cancer Society and the United States Preventive Service Task Force have extended screening recommendations to include individuals aged 45 and older due to an increase in the incidence of CRC among younger adults[3]. Furthermore, in a recent systematic review of 24 clinical practice guidelines and five consensus statements, the median overall quality and reporting were 54.0% and 42.0% and the applicability had low quality in 83% of guidelines (24/29) which necessitates a revision and an enhancement of the current guidelines[16].

## SCREENING STRATEGY OPTIMIZATION

In their retrospective study recently published in *World J Gastroenterol*, Agatsuma *et al*[17] elucidate the different stages of CRC at the point of diagnosis according to the diagnostic routes by utilizing cancer registries from two Japanese hospitals. They report that CRCs identified during hospital visits for comorbidities were diagnosed earlier, similar to cancer screening, and emphasize that patients with comorbidities without periodic visits to the hospital should be encouraged to undergo screening. With the high rate of CRC cases diagnosed *via* non-screening routes detected during hospital visits for comorbidities, it is practical to also consider the population of patients with comorbidities who are not routinely and periodically visiting the hospital, as this population of patients does not obtain early CRC recognition benefits due to lesser number of hospital visits. However, the challenge of assessing the burden of comorbidities remains unaddressed. Several studies have found that patients with chronic comorbid conditions harboring lower scores are more likely to adhere to screening compared to patients with higher burden comorbidities. In a population-based study conducted in Spain, it was found that patients with multiple minor chronic diseases were more inclined to participate in screening compared to those with three or more major chronic diseases who were likely to participate less in screening programs[12]. Wellbeing systems elaborated in the Population-Based Research Optimizing Screening by Personalized Regimens consortium observed that with increased comorbidity, diagnosis with fecal blood testing only was less common[18]. These patterns indicate a competing emphasis on morbidities and the notion of poor screening benefits for patients with comorbidities[19]. Another factor contributing to the lower adherence of patients with comorbidities to screening guidelines could be attributed to not being provided or suggested a screening measure by their healthcare providers. It was reported that individuals with a chronic disease index score equal to 1 had 8%-9% chance of being given a FIT, whereas those with a score greater than 4 identified as having an elevated disease burden were 13%-23% less likely to be offered a FIT[20]. Thus, tackling adherence to screening in patients with comorbidities not visiting the hospital for their routine check-ups should be addressed in the context of disease burden and screening emphasis.

Screening programs must be tailored to risk groups to provide approaches formulated to their risk of developing CRC [21]. Furthermore, to determine whether screening is suitable in individualized cases, both patients and practitioners ought to take into account the overall health of the patient, previous screening measures, and preferences[22]. In addition to the comorbidity burden, which is highly valuable in identifying patients less likely to adhere to screening, certain risk factors have been linked to tumorigenesis including smoking, lack of activity, excess fatness, and alcohol, which should also be considered when selecting high-risk individuals. However, protective factors such as aspirin and nonsteroidal anti-inflammatory drug use, and dietary interventions such as Mediterranean diet, high intake of fiber from fruits and vegetables, and intake of certain nutraceuticals such as curcumin, resveratrol, and quercetin may play a preventive role. Furthermore, the age at which CRC screening should begin needs to be identified to seize critical CRC cases while at the same time considering the cost-effectiveness of these tests, looking at regional epidemiology, and weighing the anticipated benefits *vs* harms.

## CONCLUSION

Screening guidelines with limited adherence will not be effective in reducing CRC mortality and incidence. It is thus crucial to address barriers limiting patient adherence to screening guidelines and target patients with comorbidities who are not receiving routine clinical check-ups. Patients with comorbidities undergoing routine check-ups are diagnosed early similar to patients who undergo regular screening tests. The reason behind this finding is that patients with comorbidities undertake imaging studies and colonoscopies due to an abnormal test result or after experiencing certain symptoms, which might result in an earlier diagnosis. Comorbidities are categorized into two; those with a high burden and those with a low burden. High-burden comorbidities are inversely related to screening measures and should therefore be targeted. As for physician recommendations for screening, this should also be tailored to high-burden comorbidities

## FOOTNOTES

**Author contributions:** Tamraz M contributed to manuscript drafting and writing; Al Ghossaini N contributed to critical revision; Temraz

S contributed to conception and design.

**Conflict-of-interest statement:** The authors report no relevant conflicts of interest for this article.



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**S-Editor:** Li L
**L-Editor:** Filipodia
**P-Editor:** Zheng XM

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