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REVIEW ARTICLE

Noninvasive Testing for Colorectal Cancer Screening: Where Are We Now?

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Colorectal cancer (CRC) is one of the most prevalent cancers and is the leading cause of cancer-related mortality worldwide. Based on the current screening guidelines by the American Cancer Society and Korean multi-society expert committee, CRC screening is recommended in asymptomatic adults starting at the age of 45 years. Fecal immunochemical test-based screening programs reduce the development of CRC and related mortality in the general population. However, this most popular CRC screening strategy demonstrates a crucial limitation due to modest diagnostic accuracy. Colonoscopy may be considered as an alternative primary method for CRC screening; however, its implementation can still be challenging due to concerns regarding invasiveness, low adherence, cost-effectiveness, and quality assurance. To overcome the limitations of current screening tests, innovative noninvasive tests for CRC screening have been developed with advances in molecular biology, genetics, epigenetics, and microbiomics for detecting CRC, which may enhance the approach to CRC screening and diagnosis in clinical practice in the near future. This review explores the emerging screening methods and discusses their potential for integration into current practice.

Key Words: Colorectal neoplasms; Genetics; Liquid biopsy; Mass screening

INTRODUCTION

Colorectal cancer (CRC) is one of the most prevalent cancers in both men and women. It accounts for approximately 10% of all cancer-related mortality worldwide. In Korea, CRC had the third highest incidence rate among all cancers (the fourth highest for men and the third highest for women). Additionally, Korean patients with CRC exhibited a similar proportion and rank in terms of cancer-related mortality compared to the global statistics. Population-based national programs for CRC screening are widely implemented in the United States (US), as well as in most European, and Asian countries due to the significant reduction of cancer incidence and mortality [1]. In Korea, age-standard incidence rates of CRC have been declining since 2012, mainly attributed to the national screening program. Fecal immunochemical test (FIT)-based screening program is being widely performed, but it has a critical weakness due to modest diagnostic accuracy. Colonoscopy may be considered as an alternative primary method for CRC screening, but colonoscopy-based CRC screening has limitations in terms of compliance, accessibility, cost, risk of adverse events and quality assurance.

With better understanding about the molecular genetic characteristics of CRC and precancerous lesions including adenomas and sessile serrated lesions, noninvasive screening modalities using novel biomarkers have been developed and validated. Some of them are likely to be approved for clinical use as CRC screening and detection in the near future. These emerging tests have the potential to overcome current obstacles and enhance compliance with CRC screening. For them to be widely accepted in practice, however, it is essential that they are affordable, accessible, convenient, and have a low risk of complications as well as high accuracy in

detecting CRC at an early stage. In this review, we discuss pitfalls in current CRC screening modalities and explore promising noninvasive tests which are being developed and evaluated in clinical trials.

MAIN SUBJECTS

CRC Screening: The Present

Currently, there are several types of CRC screening tests available in practice, including both noninvasive and invasive options. Noninvasive tests include FIT, multi-target stool DNA test, plasma methylated septin 9 (*SEPT9*) test, and computed tomography (CT) colonography. Invasive tests including colonoscopy and sigmoidoscopy are utilized. While colonoscopy exhibits the highest sensitivity for detecting CRC and advanced adenomas, it is more invasive, inconvenient, and expensive compared to FIT. Non-invasive tests are advantageous in terms of cost, safety, and convenience. However, it is important to note that the current non-invasive tests have a lower sensitivity for advanced adenomas, with multi-target stool DNA test achieving a sensitivity of 42% [2].

Improving suboptimal compliance with CRC screening programs remains a challenge. In a US longitudinal cohort study from claims database, adherence rates to CRC screening among the general population, aged 50 to 75 years at average risk, increased 50% in 2011 to 70% in 2019 [3]. However, these rates still fall below the target of 80% set by the National Colorectal Cancer Roundtable. Several factors contribute to low compliance with screening colonoscopy, including limited accessibility to healthcare services, particularly for individuals residing in rural areas, psychosocial and socioeconomic factors, such as insurance coverage and income. The coronavirus disease 2019 pandemic has emphasized the need for noninvasive screening strategies because it has revealed the impact of barriers to performing colonoscopy. Emerging noninvasive tests for CRC screening will replace the current strategies aiming to reduce the necessity of invasive colonoscopy in the near future.

Stool-based DNA Tests for CRC Screening

Although noninvasive FIT for hemoglobin in stool samples is available worldwide, the sensitivity is relatively low in detecting CRC, especially at an early stage (73% for stage I CRC) [4]. The suboptimal sensitivity of FIT has led to the development of other stool-based tests using specific molecular biomarkers to detect CRC and adenomas, including genetic mutations, abnormally methylated DNA loci, and microRNAs [5]. CRC and precancerous lesions continuously shed tumor cells into the colonic lumen, in contrast to the intermittent bleeding that can be detected by FIT [6]. Next-generation stool-based tests are able to capture changes in the colonic environment that are associated with the presence of CRC, and detect shed tumor cells in the stool.

Epigenetic changes play an important role in the colorectal carcinogenesis [7]. Several biomarkers of DNA methylation have been explored showing a high accuracy and reproducibility for detecting CRC in noninvasive biosamples. The first multi-target stool DNA test, Cologuard® (Exact Sciences Corporation, Marlborough, MA, USA), was introduced for clinical use in 2014, and have demonstrated its effectiveness as a tool of CRC screening in clinical practice, particularly in the US. It incorporates assays for methylated *DRG4* and *BMP3*, mutant *KRAS*, as well as a FIT assay. In a screening population at average risk, the multi-target stool DNA test had a sensitivity of 92% for detecting CRC [2]. The sensitivity of the multi-target stool DNA test was significantly higher, compared to FIT (sensitivity, 74%) [2]. The sensitivity of the multi-target stool DNA test for detecting advanced colorectal adenomas and sessile serrated lesions were 42%, which was also significantly higher than the 24% sensitivity of FIT ($p < 0.001$) [2]. Compared to FIT, however, the multi-target stool DNA test exhibited a significantly lower specificity for detecting CRC among individuals with negative colonoscopic findings (90% vs. 96%; $p < 0.001$) [2]. Based on the current clinical guidelines by the American College of Gastroenterology (ACG) [8], it is recommended to perform every 3 years for CRC screening in the average-risk population.

However, there are critical limitations of the first-genera-

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tion stool DNA-based test for CRC screening in practice, including much higher cost when compared to FIT and much lower sensitivity for detecting advanced adenomas when compared to colonoscopy. In recent remodeling studies, however, annual FIT and colonoscopy every 10 years were more cost-effective than the multi-target stool DNA testing every 3 years [9,10]. A dilemma faced by physicians occasionally occurs when a multi-target stool DNA test shows a positive result but the subsequently colonoscopy is negative, which carries the risk of overtesting or repeat screening at shorter intervals. This concern is particularly significant due to the higher rate of false positivity associated with the combination of FIT and methylated DNA markers in the multi-target stool DNA test. In a long-term observational cohort study of 1,050 patients with positive multi-target stool DNA tests and negative colonoscopy, 8 cases of lung and gastrointestinal cancers were detected over a 4-year follow-up period [11]. The cumulative incidence did not exceed Surveillance, Epidemiology, and End Results expectations for the general population. According to the current evidence, it is not recommended that asymptomatic individuals with a positive multi-target stool DNA test and a negative high-quality colonoscopy perform additional testing, such as upper endoscopy, CT of the abdomen, or repeat colonoscopy at an interval shorter than recommended [8]. The multi-target stool DNA 2.0 assay was developed to improve the diagnostic accuracy of the previous version. The BLUE-C trial (NCT04144738) is an ongoing prospective observational cohort study that aims to compare the sensitivity and specificity of the multi-target stool DNA 2.0 assay with FIT for detecting CRC.

EarlyTect®-C developed by Genomictree Inc. (Daejeon, Korea) is a stool DNA-based test that detects methylation of syndecan-2 (*SDC2*). It was approved from Korean Ministry of Food and Drug Safety in 2018 for early detection of CRC. This test utilizes a single target stool DNA assay and employs linear target enrichment-quantitative methylation-specific real-time polymerase chain reaction (PCR), a highly accurate technique for detecting *SDC2* methylation in stool samples [12]. There are two pivotal studies to evaluate the sensitivity and specificity of the stool-based methylated *SDC2* test for detecting CRC in screening populations [12,13]. The stool-based methylated *SDC2* test demonstrated an overall sensitivity of 90% for detecting CRC. The sensitivity ranged from 83% to 86% for detecting stage I CRC, and it was 91% for detecting stage II CRC [12,13]. The overall specificity for detecting CRC using the stool-based methylated *SDC2* test ranged from 90% to 91% [12,13]. Currently, the NEXT-CRC trial (NCT05255588) is an ongoing prospective, multicenter, single-blinded, comparative trial aimed at assessing the diagnostic performance of the stool-based methylated *SDC2* test in a high-risk Korean population, based on the Asia-Pacific Colorectal Screening score which is a validated scoring system used to stratify the risk of advanced colorectal neoplasm [14,15].

Next-generation Stool-based Biomarkers for CRC Screening

Recent evidence suggests that other biomarkers may hold promise in improving the effectiveness of current stool-based strategies for CRC screening. An innovative, multi-target stool-based RNA-FIT assay (Geneoscopy, Inc., St. Louis, MO, USA), which combines 8 stool-derived eukaryotic RNA biomarkers, is under investigation for the detection of CRC and advanced adenomas. In a prospective cohort study of 1,300 individuals from an average-risk screening population undergoing colonoscopy, the stool-based RNA-FIT test demonstrated a sensitivity of 95% for detecting CRC and 62% for advanced adenomas, respectively, along with a specificity of 85% for identifying negative colonoscopic findings [16]. This promising stool-based screening test is currently undergoing assessment in a large prospective cohort study called CRC-Prevent (NCT04739722). In a case-control study using novel stool-based protein biomarkers, a panel of proteins enriched in stool samples derived from patients with CRC exhibited a sensitivity of 80% for detecting CRC and 45% for advanced adenomas, respectively. Additionally, the panel showed a specificity of 95%, which was significantly higher compared to FIT alone [17].

Gut microbiome is a major determinant of colorectal carcinogenesis. Feasibility studies suggest that gut microbes

and metabolites serve as promising biomarkers for early detection of CRC and advanced adenoma [18-20]. The fecal microbiome gene signatures associated with CRC were universal, although there was a difference in the microbial community structures among different ethnic cohorts from China, Denmark, Austria, and France [19]. In a Chinese case-control study, *Fusobacterium nucleatum, Lachnoclostridium* species, *Bacteroides clarus*, and *Clostridium hathewayi* were determined as potential screening microbial markers for the detection of CRC and advanced adenoma [20]. The combined score of the four microbial markers exhibited a sensitivity of 85% for detecting CRC and 39% for advanced adenoma in 435 asymptomatic subjects, respectively, which was significantly higher compared to FIT [20]. However, the specificity of the stool microbial DNA markers was lower compared to FIT, with the rates of 83% and 99%, respectively [20]. A recent meta-analysis of eight fecal shotgun metagenomics studies reported a core set of 29 species that were significantly enriched in CRC metagenomes. Training on multiple studies using this set of CRC signatures improved the diagnostic accuracy for detecting CRC [18]. Bacteria such as *F. nucleatum, Porphyromonas, Parvimonas, Peptostreptococcus, Gemella, Prevotella*, and *Solobacterium* were identified as CRC-associated bacteria included in the core set, and functional analysis revealed genes related altered amino acid, carbohydrate, bile acid and mucin metabolism, suggesting a metabolic connection between cancer-associated gut microbes and diet [18]. These findings highlight the potential to incorporate gut microbes and metabolites into CRC screening tests.

Stool-based tests based on the gut microbiome have the potential to improve the accuracy of current stool-based screening strategies, not only in detecting CRC but also in identifying advanced adenoma. To date, however, there is no fecal microbiome-based screening test currently available in practice, in spite of accumulating studies demonstrating the potential of fecal microbial biomarkers for detecting CRC and advanced adenoma. Taking into account the global diversity in microbiome structures, it can be still challenging to determine universally applicable features of the fecal microbiome as biomarkers for detecting CRC and advanced adenoma. Moreover, the novel CRC screening method combining human mutation, bacterial, and metabolic biomarkers should be validated and cost-effective for clinical use. Further large-scale prospective studies are required to determine the diagnostic performance and clinical effectiveness of the fecal microbial biomarkers in detecting both CRC and advanced adenoma in different screening populations.

Novel Blood-based Tests for CRC Screening

The sensitivity of technologies for detecting tumor cell-derived nucleic acids, such as cell-free DNA (cfDNA) and circulating tumor cell DNA (ctDNA), in blood is critical for their utilization in CRC screening. This is due to the fact that the amount of DNA released by cancer cells is directly related to tumor size, and it becomes significantly diluted within the background of normal cell DNA. Therefore, highly sensitive technologies are required to detect and accurately analyze the tumor-specific DNA fragments in circulating blood for clinical use. Recently, there have been rapid advancement in the detection technologies of tumor cell-derived nucleic acids, such as genomic DNA, mRNA, and miRNA in blood. Next generation sequencing (NGS) is a powerful technology capable of profiling billions of DNA fragments in circulation, which allows for comprehensive analysis of the genetic and epigenetic alterations present in cfDNA and ctDNA. In parallel with NGS, advances in PCR-based technologies have expanded the repertoire of methods utilized in emerging blood-based screening tests for CRC. The key questions that still need to be addressed include evaluating the performance of these blood-based biomarker tests in a large-scale screening population, assessing their clinical utility, and demonstrating their cost-effectiveness in real practice.

The plasma methylated *SEPT9* DNA assay, marketed under the names Epi proColon (Epigenomics AG, Berlin, Germany) and ColoVantage (Quest Diagnostics, Secaucus, NJ, USA), employs a PCR-based liquid biopsy test to detect cfDNA derived from methylated *SEPT9* in plasma. It received US Food and Drug Administration (FDA) approval in 2016 as an alternative tool for individuals who decline other CRC

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screening tests. The blood-based screening test addresses limitations associated with convenience and accessibility that prohibit participation in current screening strategies. However, it is not widely utilized in current clinical practice due to its low sensitivity of 48% for detecting CRC and 11% for advanced adenoma, respectively, in a large-scale screening population [21]. A recent systematic review of 39 eligible studies evaluating the performance of the second generation methylated *SEPT9* test reported a pooled sensitivity of 62% for detecting CRC [22]. Given the low sensitivity and limited comparative data on its performance, ACG does not recommend the use of the plasma-based methylated *SEPT9* DNA test for CRC screening.

Another cfDNA-based CRC screening assay developed by Freenome Holdings Inc. (South San Francisco, CA, USA) utilizes a machine learning-based analysis of alterations in genomic, epigenomic, and protein expression pattern for detecting cfDNA in blood [23]. The assay is currently being evaluated in the PREEMPT CRC trial (NCT04369053) which is a prospective multi-center observational study conducted across the US that aimed to validate the cfDNA-based assay for the detection of CRC in 25,000 average-risk individuals aged 45 to 85 years who will undergo a screening colonoscopy. The primary outcomes are sensitivity and specificity of the Freenome test for detecting CRC. The results of this trial are expected to be shown in the near future.

Despite the rising potential of ctDNA and protein-based blood tests for CRC screening from the results of numerous pivotal studies, none of them have demonstrated sufficient sensitivity and specificity to sever as primary screening tools for CRC screening to date. However, there is an ongoing large-scale randomized controlled trial to compare an emerging ctDNA-based assay with colonoscopy and FIT in a screening population. The LUNAR-2 test (Guardant Health, Palo Alto, CA, USA) is a multimodal blood-based assay incorporating ctDNA assessment of somatic mutations and tumor-derived methylation and fragmentomic patterns to maximize sensitivity for detecting CRC at an early stage

Table 1. Summary of commercially available noninvasive tests for CRC screening

Name	Company	Description	Sensitivity (%)	Specificity (%)	Approval	Ongoing clinical trial
Stool-based tests						
Cologaurd®	Exact Sciences	Multi-target DNA assay detecting methylated *DRG4* and *BMP3*, mutant *KRAS*, and FIT in stool	92	90	US FDA (2014)	BLUE-C trial (NCT04144738)*
EarlyTect®-C	Genomictree	Single-target PCR-based DNA assay detecting methylated *SDC2* in stool	90	91	Korean MFDS (2018)	NEXT-CRC trial (NCT05255588)
Geneoscopy	Geneoscopy	Multi-target RNA assay detecting 8 eukaroytic RNA biomarkers in stool	95	85	Not yet	CRC-Prevent (NCT04739722)
Blood-based tests						
Epi proColon/ ColoVantage	Epigenomics AG/Quest Diagnostics	PCR-based assay detecting cfDNA derived from methylated *SEPT9* in plasma	48	92	US FDA (2016)	NA
Freenome test	Freenome	Machine learning-based assay through analysis of alterations in genomic, epigenomic, and protein expression pattern to detect cfDNA in blood	To be reported	To be reported	Not yet	PREEMPT CRC trial (NCT04369053)
Shield (LUNAR-2)	Guardant Health	Multimodal assay using ctDNA, methylation, and fragmentomic patterns in blood	91	94	Not yet	ECLIPSE trial (NCT04136002)

CRC, colorectal cancer; FIT, fecal immunochemical test; US FDA, United States Food and Drug Administration; PCR, polymerase chain reaction; *SDC2*, syndecan-2; MFDS, Ministry of Food and Drug Safety; cfDNA, cell-free DNA; *SEPT9*, septin 9; NA, not available; ctDNA, circulating tumor DNA.
*Using the updated version 2.0 of multi-target stool DNA test.

[24]. In a case-control study of 434 Korean patients with CRC who provided blood samples prior to surgical resection, along with 271 age-matched controls, the LUNAR-2 test exhibited an overall sensitivity of 91%, with high sensitivity across all stages; 88% for stage I and II, and 93% for stage III [24]. Moreover, the specificity of the LUNAR-2 test was 94% [24]. Based on similar performance results for the detection of CRC in a subsquent case-control study from the US, Canada, and the EU, the blood-based ctDNA assay marketed under the name Shield (Guardant Health) has been commercially available in the US since May 2022 although it has not been approved by the FDA. The ECLIPSE trial (NCT04136002) is an ongoing 24-month prospective, observational, multicenter study conducted to evaluate the performance the LUNAR-2 test for detecting CRC in 40,000 average-risk screening participants. The primary endpoints are sensitivity and specificity for the detection of CRC and advanced neoplasm, respectively.

CONCLUSION

Population-based CRC screening is being performed predominantly using stool-based tests such as FIT and colonoscopy, which have been demonstrated to prevent cancer-related mortality. However, the currently available tests for CRC screening have various drawbacks, making the need for noninvasive and accurate diagnostic methods. Emerging stool and blood-based tests have the potential to address the limitations of current modalities and improve compliance for CRC screening. Development of these assays is the product of remarkable advancements in detection and analysis technologies for cell-free nucleic acids and proteins, along with our understanding of the cancer molecular genetics. Data from ongoing large-scale clinical trials are expected to be available in the near future, which will lead to the addition of the emerging noninvasive tests to the current repertoire of diagnostic options for CRC screening in practice (Table 1). The exciting challenge ahead will be to discern the optimal placement of these noninvasive tests in the landscape of CRC screening.

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CONFLICTS OF INTEREST

In addition to what is described in the funding section, no potential conflict of interest relevant to this article was reported.

AUTHOR'S CONTRIBUTIONS

Conceptualization: Jaeyoung Chun. Data acquisition: Jaeyoung Chun. Formal analysis: Jaeyoung Chun. Funding: Jaeyoung Chun. Supervision: Jie-Hyun Kim, Young Hoon Youn, Hyojin Park. Writing—original draft: Jaeyoung Chun. Writing—review & editing: Jie-Hyun Kim, Young Hoon Youn, Hyojin Park.

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