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Innovative approaches in colorectal cancer screening: advances in detection methods and the role of artificial intelligence

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***Abstract*:** Colorectal cancer (CRC) is the third most prevalent cancer globally and poses a significant health threat, making early detection crucial. This review paper explored emerging detection methods for early screening of CRC, including gut microbiota, metabolites, genetic markers, and artificial intelligence (AI)-based technologies. Current screening methods have their respective advantages and limitations, particularly in detecting precursors. First, the importance of the gut microbiome in CRC progression is discussed, highlighting how specific microbial alterations can serve as biomarkers for early detection, potentially enhancing diagnostic accuracy when combined with traditional screening methods. Next, research on metabolic reprogramming illustrates the relationship between metabolic changes and CRC, with studies developing metabolite-based detection models that show good sensitivity for early diagnosis. In terms of genetic markers, methylated DNA markers like SEPTIN9 have demonstrated high sensitivity, although further validation across diverse populations is necessary. Lastly, AI technology has shown immense potential in improving adenoma detection rates, significantly enhancing the quality of colonoscopic examinations through image recognition techniques. This review aims to provide a comprehensive perspective on new strategies for CRC screening, emphasizing the potential of noninvasive detection technologies and the prospects of AI and genomics in clinical applications. Despite several challenges, this review advocates for future large-scale prospective studies to validate the effectiveness and cost-effectiveness of these new screening methods while promoting the implementation of screening protocols tailored to individual characteristics.

Keywords: artificial intelligence, colorectal cancer, early screening, genetic markers, gut microbiota, metabolites

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Introduction

Colorectal cancer (CRC) currently has a global incidence rate of 9.6%, ranking third among cancer types, and a mortality rate of 9.3%, ranking second.[1] In China, CRC is the second most prevalent cancer and ranks as the fourth leading cause of cancer-related deaths, posing a significant threat to public health.[2] Most CRC cases in the early stages often present no obvious symptoms, resulting in more than two-thirds being misdiagnosed or diagnosed late, adversely affecting patient prognosis and quality of life.[3] Research indicates that the occurrence and progression of CRC primarily follow an evolution from adenoma or sessile serrated lesions (SSLs), providing ample screening opportunities during the lengthy development process.[4] Regular screening can significantly reduce the long-term incidence and mortality rates of CRC.[5–7]

Screening methods for CRC are mainly classified into invasive and noninvasive types. Colonoscopy remains the gold standard among invasive methods, with the highest sensitivity for all colorectal

lesions, significantly reducing CRC incidence and mortality.[7] Noninvasive approaches primarily rely on fecal occult blood tests, including guaiac-based fecal occult blood tests and fecal immunochemical tests (FIT), which have demonstrated good clinical efficacy.[8–10] In addition, multi-target fecal DNA and RNA testing (MT-DNA, MT-RNA), which combine fecal occult blood and genetic alterations, are progressively being implemented in large-scale CRC screenings, showing better detection capabilities for advanced adenomas compared to FIT.[11–13] Despite the advantages and disadvantages of colonoscopy and fecal-based tests, compliance with colonoscopy is often low, and about a quarter of colorectal tumors may be missed.[14] While fecal-based tests are convenient, safe, and cost-effective, their sensitivity for precursors such as advanced adenomas ranges from 23.3% to 46%, with a particularly low detection rate of only 5.1% for SSLs,[12,15] leading to an increase in interval cancers and affecting screening efficacy. Consequently, current research is widely exploring ways to enhance the detection efficiency of colorectal lesions.

In recent years, the development and application of artificial intelligence (AI) have significantly advanced lesion identification, particularly in improving adenoma detection rates (ADR).[16] Moreover, with a deeper understanding of the mechanisms of CRC, research reveals that the development of precursors such as adenomas and serrated lesions is associated with epigenetic and genetic factors as well as changes in the gut microbiome, providing broad possibilities for developing new noninvasive detection methods.[17] Presently, many studies focus on AI-assisted detection technologies and noninvasive screening biomarkers, such as gut microbiota markers[18–20] and blood markers,[21,22] to enhance the sensitivity and accuracy of CRC screening (Figure 1).[23–25]

In this paper, we undertake a comprehensive review of the latest advancements in detection methods that leverage gut microbiota, metabolic markers, genetic markers, as well as AI-assisted systems. We delve into novel strategies for the early detection and prognostic evaluation of CRC and its precursors within large populations while also considering the potential challenges these emerging methods may face. Our objective is to present a well-rounded perspective on early CRC screening, supplemented by scientific evidence and insights that can inform future strategies and methodologies in this critical area.

Early detection based on gut microbiota

The gut microbiome is a crucial environmental factor in the development of colorectal tumors, influencing the onset of CRC and colorectal adenomas (CRA) through various processes, including metabolic regulation, inflammation control, and epigenetic reprogramming.[26] Increasing evidence suggests that gut microbiota can serve as a tool for identifying high-risk individuals for CRC and early detection.[27,28] This section explores the potential applications and limitations of gut microbiota biomarkers in early CRC screening and provides directions for future research in CRC screening.

Studies indicate that dysbiosis in the gut microbiota may be closely related to the onset and progression of CRC.[29–31] By performing 16S rRNA sequencing on fecal samples from individuals with positive FIT, researchers found a significant increase in the abundance of Proteobacteria in the intestines of CRA patients compared to a control group with normal colonoscopy results, laying the foundation for developing early detection tools based on gut microbiota.[18] McCoy et al. discovered a significant elevation of oral pathogen *Fusobacterium nucleatum* levels in CRA patients.[32] Utilizing receiver operating characteristic curve analysis, they found that this bacterium's DNA levels can effectively distinguish CRC from normal individuals, achieving an area under the curve (AUC) of 0.841, outperforming traditional tumor markers like carcinoembryonic antigen (CEA) and CA-199.[33] In addition, *F. nucleatum* was found to be significantly enriched in the tumor tissues and feces of CRC patients.[34] Research by Mima et al. indicated that patients with positive *F. nucleatum* in CRC tissues have a significantly higher mortality risk compared to negative patients, and there is a positive correlation with *F. nucleatum* DNA levels, suggesting its important role in CRC progression and metastasis, potentially serving in early detection and prognostic evaluation.[35] Wu et al. focused on specific markers for adenomas, developing a classification model that distinguishes CRA, CRC, and healthy individuals through integrative analysis of over 1000 fecal microbiome 16S rRNA data. The model achieved a sensitivity of 82%

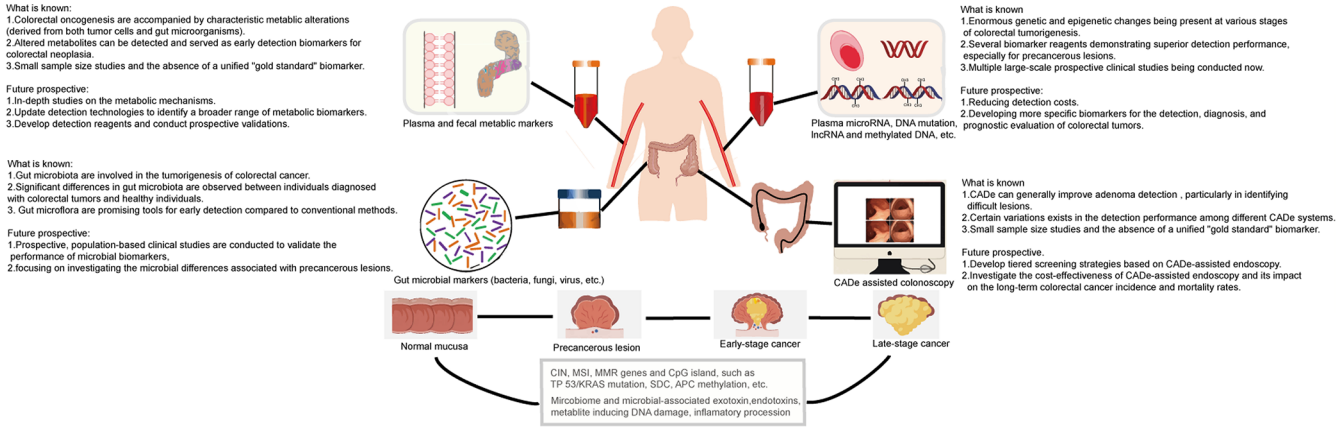

Figure 1. Novel detection methods for CRC screening.
CADe, computer-aided detection; CIN, chromosomal instability; CRC, colorectal cancer; MMR, mismatch repair; MSI, microsatellite instability.

and specificity of 62% for CRA versus healthy individuals, and a sensitivity of 66% and specificity of 90% for adenomas versus CRC,[36] confirming the effectiveness of gut microbiota in the early detection of adenomas.

In addition to these bacterial markers, significant changes have also been observed in the fungal and viral components of the gut microbiome in CRC patients. Nakatsu et al. conducted a metagenomic analysis of fecal samples from CRC and non-CRC patients, finding a notable increase in the diversity of bacteriophage communities in CRC patients. A specific combination of 22 viral taxa effectively distinguished CRC patients from the control group, showing promising application prospects (AUC = 0.802).[37] Lin et al. identified characteristic fungi associated with CRC across multiple cohorts, observing a significant increase in the abundance of six fungal species, while one species showed a notable decrease.[38] Liu et al. performed a metagenomic analysis of 1368 fecal samples from 8 different geographical sources. Their findings revealed that a combination of 11 bacteria, 4 fungi, and 1 archaea created 16 multi-domain microbial signatures with excellent diagnostic value for early CRC detection (AUC = 0.96), validating the potential of fungi in CRC diagnosis and demonstrating that combined detection of multiple microbial domains has higher accuracy than single microbial detections.[39]

Furthermore, microbial biomarkers can effectively enhance the sensitivity of standard fecal occult blood tests for colorectal tumors, especially for detecting CRA. Research by Fan et al. identified significant differences in the presence of *Streptococcus*, *Escherichia*, *Chitinophaga*, *Parasutterella*, *Lachnospira*, and *Romboutsia* between CRC patients and healthy individuals. The incorporation of these differential genera with multi-target stool DNA (MT-sDNA) and CEA testing raised the diagnostic accuracy of MT-sDNA in CRC to 97.1%, with a sensitivity of 98.1% and specificity of 92.3%.[40] Moreover, Malagón et al. conducted microbial biomarker tests on FIT-positive individuals, showing that the incorporation of differential microbes can reduce the false-positive rate of FIT by 16.3%, thereby improving FIT accuracy.[41] Liang et al.'s study focused on a noninvasive test to diagnose adenomas and CRC using gut microbiota biomarkers. Results indicated that combining the gene marker m3 from *Lachnoclastium* sp. with FIT increased the sensitivity of FIT for adenoma detection by 6.0%.[42] These studies collectively suggest that early changes in microbial populations accompany the onset of colorectal tumors, and monitoring these changes can improve the efficiency of early screening and diagnosis for CRC, thereby demonstrating significant research value and application potential in the detection of adenomatous lesions (Table 1).

Transitioning into further implications, modern detection techniques such as 16S rRNA sequencing, qPCR, and next-generation sequencing have identified significant microbial differences between CRC, CRA, and healthy individuals. Preliminary research results indicate that

Table 1. Principle studies of novel markers for CRC detection.

Author	Year	Study design	Participants/ sample	Detection methods	Biomarkers	Outcomes	Sensitivity	Specificity
Guo et al.[43]	2018	Case–control study	Fecal sample	Real-time quantitative PCR, 16s rDNA	Combination of Fn/Bb; Fn/Fp	Sensitivity and specificity for CRC	Fn/Bb for CRC: 84.6% Fn/Bb for CRC: 94.5 % Combination of Fn/Bb and Fn/Fp for CRC: 90.0%	Fn/Bb for CRC: 92.3% Fn/Bb for CRC: 71.28% Combination of Fn/Bb and Fn/Fp for CRC: 60.0%
Zhang et al.[33]	2022	Case–control study	Human Saliva	Multiplex quantitative real-time PCR	Fn DNA	Sensitivity and specificity for CRC	86.7% at a cutoff value of 0.437	67.2% at a cutoff value of 0.437
Shen et al.[44]	2021	Retrospective cohort study	Mucosal sample	16S rRNA sequencing; quantitative PCR	*Lactobacillus-Streptococcus*; the species ETBF; *Peptostreptococcus stomatis* *Parvimonas micra*	Sensitivity and specificity for LST	Combination of *P. stomatis*, *P. micra*, ETBF for CRC: 88.7%	Combination of *P. stomatis*, *P. micra*, ETBF for CRC: 81.4%
Liang et al.[42]	2020	Case–control study	Fecal sample	Quantitative PCR	"m3" from *Lachnoclostrium* sp.	Sensitivity and specificity for adenoma	M3 for adenoma: 44.2%; for advanced adenoma (AA): 50.8% M3 combined with FIT for AA: 56.8%	For adenoma: 79.6%
Fan et al.[40]	2023	Case–control study	Fecal sample	16S rRNA gene sequencing	Intestinal microbiome composition; MT-sDNA	Sensitivity and specificity for CRC	Combination of *Streptococcus*, *Escherichia*, *Chitinophaga*, *Parasutterella*, *Lachnospira*, *Romboutsia*, CEA, and MT-sDNA for CRC: 98.1%	For CRC: 92.3%
Chen et al.[45]	2022	Case–control study	Fecal sample	Liquid chromatography-mass spectrometry; metagenome sequencing	GMSM	Sensitivity and specificity for CRC and adenoma	A GMSM panel including eight metabolites for CRC and adenoma: 83.5%	For CRC and adenoma: 84.9%
Sui et al.[46]	2021	Case–control study	Blood sample	Real-time PCR	ctDNA methylation markers	Sensitivity and specificity for early-stage CRC	For I–III stage CRC: 82.5%	For I–III stage CRC: NA
Zhao et al.[47]	2020	Case–control study	Blood sample	NA	SpecColon test	Sensitivity and specificity for CRC and AA	SpecColon test for CRC: 76.2% For AA: 58.3%	87.9%

(Continued)

Table 1. (Continued)

Author	Year	Study design	Participants/ sample	Detection methods	Biomarkers	Outcomes	Sensitivity	Specificity
Cai et al.[48]	2021	Case–control study	Blood sample	NA	ColonAiQ assay	Sensitivity and specificity for CRC and AA	For CRC: 86% For AA: 42%	92%
Wu et al.[49]	2021	Case–control study	Tissue and blood sample	NA	An 11 cfDNA methylation-based model	Sensitivity and specificity for CRC	For CRC: 84.6%	For CRC: 86.6%
Dai et al.[50]	2023	Case–control study	Tissue and blood sample	NA	Six DNA-marker methylation panel	Sensitivity and specificity for targeted GICs	For CRC: 90.0%–91.7%	For CRC: 86.7%–94.1%
Li et al.[51]	2023	Case–control study	Blood sample	NA	ColoProbe	Sensitivity and specificity for CRC and PL	For CRC: 82.7% For PL: 55.0%	90.1%

AA, Advanced adenoma; Bb, *Bifidobacterium*; CEA, carcinoembryonic antigen; cfDNA, cell-free DNA; CRC, colorectal cancer; ctDNA, circulating tumor DNA; ETBF, *enterotoxigenic Bacteroides fragilis*; FIT, fecal immunochemical test; Fn, *Fusobacterium nucleatum*; Fp, *Faecalibacterium prausnitzii*; GIC, gastrointestinal cancer; GMSM, gut microbiome-associated serum metabolite; LST, laterally spreading tumor; MT-sDNA, multi-target stool DNA; PL, precancerous lesions.

microbial-based detection methods may offer advantages in sensitivity compared to existing methods, but several challenges remain. First, while many microbes—including bacteria, fungi, and viruses—show differences in CRC, CRA, and healthy individuals, it remains difficult to identify a unified and convenient biomarker from the multitude of microbial markers. Although combined multi-microbe detection can enhance accuracy, it also adds complexity and cost to testing, which poses barriers to the development of rapid and low-cost diagnostic tools. Furthermore, most existing studies are retrospective case-control designs or based on database data; while they show high sensitivity and prognostic relevance for CRC detection, there is a lack of prospective, multi-center, large-sample studies to establish diagnostic performance in large populations, as well as comparative data regarding existing screening reagents and predictive capabilities for CRC post-surgical outcomes. Currently, data on specific microbial markers for CRA are still insufficient, necessitating the search for effective biomarkers for precancerous lesions and multi-center clinical validation to address the current limitations in adenoma screening performance.

In summary, there exists an extensive relationship between the microbiota and the mechanisms of CRC. The microbiota modulates the recruitment, activation, and function of immune cells, thereby creating an immunosuppressive and tumor-promoting microenvironment that favors tumor growth. Furthermore, the metabolites produced by the microbiota are capable of regulating gene expression and metabolic processes in intestinal epithelial cells, thus promoting oncogenesis. For instance, metabolites such as short-chain fatty acids (SCFAs) can exert anti-tumor effects by inhibiting histone deacetylases; however, under low-glucose conditions, they may also stimulate the metabolic activity and proliferation of cancer cells. In addition, substances such as exotoxins or endotoxins secreted by microbiota can activate pro-inflammatory signaling pathways, leading to chronic inflammation in intestinal epithelial cells and subsequently inducing and promoting the development of CRC. As research into the mechanisms linking microbes and the progress of CRC and sequencing technologies advances, it is foreseeable that an increasing number of microbes will be identified and validated. Confirming the true diagnostic performance of microbial markers in real large-scale population

Table 2. Abnormal metabolic pathways and serum metabolites in individuals with CRC and polyps.

Group comparison	Abnormal metabolic pathways	Serum metabolites		Implications
		Upregulation	Downregulation	
Individuals with colorectal polyps compared to healthy individuals	The pyruvate metabolism	Lactate	Acetate	ATP generation
	The glycerolipid metabolism	Lipid, polyunsaturated fatty acid	Glycerol	ATP generation
	The amino acid metabolic pathways	Glutamate	Glutamine, amine, aspartate	Oxidative stress, ATP generation, biosynthesis
Individuals with CRC compared to healthy individuals	The glycolysis	Lactate	Citrate, succinate	The "Warburg effect"/ Aerobic glycolysis
	The amino acid metabolism	Glycine, serine, threonine	NA	Cancer cell proliferation
Individuals with CRC compared to individuals with polyps	The glycerolipid metabolism	3-Hydroxybutyrate	NA	ATP generation

CRC, colorectal cancer.

screenings through prospective designs is an urgent task for developing broadly applicable clinical screening tools.

Early detection based on metabolites

Metabolic reprogramming is a crucial physiological process in colorectal tumor cells. By reshaping lipid metabolism, it regulates oncogenic signaling pathways and influences the tumor microenvironment, thereby affecting the onset, progression, and metastasis of tumors.[52,53] Characteristic metabolic changes can provide powerful tools for early detection and clinical diagnosis across different stages of tumor development.[54–56] Zhang et al. investigated the potential of free fatty acids (FFAs) in serum for early CRC detection, revealing that CRC patients had significantly lower levels of FFAs. The combined detection of FFAs such as C16:1, C18:3, C18:2, C18:1, C20:4, and C22:6 achieved a sensitivity of up to 84.6% and specificity of 89.8% for early CRC. Moreover, the combination of C16:1, C18:3, and C18:2 demonstrated a sensitivity of 70% and a specificity of 81% in differentiating benign intestinal diseases from CRC.[57] These findings indicate that changes in FFA levels in early CRC patients carry significant clinical implications for the early detection and assessment of precancerous lesions. In addition to FFAs, Gu et al. utilized H-NMR spectroscopy to compare serum metabolites in 110 individuals, including those with CRC, polyps, and healthy controls. They found that metabolic pathways, including pyruvate metabolism, triglyceride metabolism, glycolysis, and amino acid metabolism, were abnormally activated in patients with polyps and CRC. These abnormalities were associated with energy generation, cancer cell proliferation, and biosynthesis. Furthermore, the study revealed that the lactate/citrate and acetate/glycerol ratios could differentiate CRC patients from healthy individuals and those with polyps, shedding light on the metabolic differences between healthy individuals, polyps, and cancers (Table 2).[58] This underscores the considerable potential of serum metabolic changes in the early diagnosis and prediction of CRC. However, further validation with a larger number of serum samples and more in-depth mechanistic studies are required to solidify these findings.

Moreover, metabolites related to gut microbiota also change with the occurrence of CRC. Chen et al. focused on microbial-related serum metabolites in CRC and CRA, developing a screening model based on eight significantly altered gut microbiota-related metabolites. This model demonstrated a sensitivity of 83.5% and a specificity of 84.9% in independent validation cohorts for CRC and CRA, outperforming traditional tumor markers like CEA.[45] Coker et al. analyzed fecal

samples from 118 CRC patients, 140 CRA patients, and 128 healthy controls, selecting 20, 13, and 4 metabolic markers, respectively, to differentiate CRC from normal individuals, CRC from CRA, and CRA from normal individuals. The AUC values were 0.91, 0.89, and 0.75, respectively.[59] These studies highlight the metabolic changes in microbial-related metabolites at different stages, particularly those associated with advanced adenomas, providing novel noninvasive methods for early detection.

In summary, metabolic changes accompanying the development of colorectal tumors are widespread, involving both cellular metabolic reprogramming and microbial-related metabolic changes. Technological advancements such as gas chromatography–liquid chromatography and deep gene sequencing have enhanced the detection of previously challenging metabolites, expanded the characteristic metabolic profiles of colorectal tumors, and identified biomarkers effective for distinguishing CRC and CRA through metabolomics. Nevertheless, existing studies primarily rely on case–control designs, small sample sizes, and database data, which are insufficient to support direct clinical applications of these biomarkers. Currently, there is a lack of clinical validation from large cohort studies, and there is still some distance to go before metabolite-based detection methods are widely implemented. Moreover, even current technologies have not reliably detected all metabolites, which limits research on the diagnostic value of certain metabolites. Therefore, further investigation into the mechanisms underlying CRC and CRA is needed, alongside the development of more comprehensive or precise technologies to detect broad-spectrum or specific metabolic changes. This should be based on promising biomarkers, especially those applicable for detecting precancerous lesions, to facilitate reagent development and clinical validation.

Early detection based on genetic markers

The occurrence of CRC is associated with DNA mutations and methylation modifications. These genetic changes can enter the bloodstream through tumor cell shedding, lysis, and extracellular vesicle secretion, and can be detected using whole genome sequencing, targeted gene sequencing, and mass spectrometry techniques for early detection, diagnosis, and prognostic evaluation of CRC.[60–62]

In particular, studies have shown that as CRC progresses to more advanced pathological stages, the level of methylated SEPTIN9 in peripheral blood increases. Methylated SEPTIN9 is considered an early diagnostic marker for CRC and has been approved by the FDA as a plasma genetic marker for CRC screening. Research by Church et al. evaluated the detection performance of plasma methylated SEPTIN9 in asymptomatic CRC cases, finding a sensitivity of 48.2% for CRC detection, but only 11.2% for adenomas.[63] Later developments of the next-generation methylated SEPTIN9 assay improved the sensitivity for CRC to 75%–79.3%, but the sensitivity for adenomas remained suboptimal at only 27%.[64,65] In the Chinese population, the sensitivity for adenomas dropped further to 9.8%–17.1%,[66,67] limiting its applicability in that demographic.

Despite the need for improved detection performance of methylated SEPTIN9, this highlights the potential advantages of genetic biomarkers in early screening. A case–control study by Sui et al. aimed to assess the diagnostic value of methylation features of circulating tumor DNA (ctDNA) for CRC, finding that ctDNA methylation models had a sensitivity of 82.5% for stages I–III CRC, with higher sensitivity compared to the SEPTIN9 method while maintaining similar specificity; the positive detection rate for adenomas was 58.3%.[46] To further validate the screening tool potential of this model, the research team launched a prospective multicenter early detection project for CRC (PREDICT, NCT04383353), involving over 14,000 participants, with results still being collected.

Furthermore, in comparison to single-gene testing, multi-gene locus combined testing may further enhance early detection performance. Zhao et al. demonstrated that a new method named SpecColon could detect methylated SFRP2 and SDC2 in blood, significantly increasing sensitivity for adenomas and CRC to 58.3% and 76.2%, respectively, with a specificity of 87.9%.[47] This method requires only 1 ml of plasma for sampling, showcasing its convenience and efficiency for early CRC screening in China. Cai et al.'s research team validated a combined testing method involving six methylated gene markers (SEPTIN9, SEPTIN9 region2, BCAT1, IKZF1, BCAN, and VAV3) called ColonAiQ, finding sensitivity for CRC and adenomas to be 86% and 42%, respectively, outperforming FIT and allowing

monitoring of CRC patient prognosis; further prospective large population studies are needed to validate its performance and clinical utility.[48] Wu et al. conducted targeted methylation DNA sequencing on 187 tissue samples and 489 plasma samples, developing a model based on 11 cell-free DNA (cfDNA) methylation biomarkers, demonstrating higher sensitivity and specificity than traditional tumor markers CEA and CA19-9, with a sensitivity of 84.6% and a specificity of 86.6% for CRC detection.[49] Another study employed bioinformatics and machine learning to identify highly specific and sensitive methylation markers (methylated SEPTIN9, AXL4, and SDC2) to construct a novel detection method called ColoProbe, which was validated in 940 participants, showing a sensitivity of 82.7% and a specificity of 90.1%, with the ability to detect 55% of precancerous lesions.[51] In addition, a study conducted in Brazil indicated that combining blood methylation levels of SEPT9 and BMP3 with patient age (over 60 years) could achieve sensitivity and specificity of 80% and 81%, respectively, with an AUC of 0.845 (Table 1).[68] This suggests that incorporating age into the screening strategy of methylated genetic markers could reduce unnecessary colonoscopies, alleviating healthcare resource burdens.

In summary, blood-based genetic marker detection methods offer higher sensitivity and specificity compared to fecal-based testing, and sampling is more convenient and accepted by the public. Particularly when combined with demographic features such as age and sex for risk stratification, these methods could effectively reduce the frequency of colonoscopies. Therefore, blood-based detection methods exhibit tremendous potential and application prospects for large-scale early detection of CRC. However, several challenges remain: First, despite the excellent detection capabilities of DNA markers, there is a lack of standardized markers applicable across different geographic and ethnic populations, limiting their use in diverse groups. Second, genetic and epigenetic changes related to other gastrointestinal tumors may also lead to false positives and missed diagnoses. Moreover, DNA marker detection relies on technologies such as gene sequencing and qPCR, which could render large-scale screening prohibitively expensive; thus, reducing detection costs is essential to enhance clinical applicability. Finally, while multiple case–control studies have confirmed a high sensitivity of markers for CRC detection, sensitivity for adenomas remains insufficient (42%–58%).[47,48] Considering that approximately one-third of CRC cases evolve from SSLs, which have unique genetic and epigenetic characteristics, research in this area is currently scarce, highlighting the need for greater emphasis on the development and validation of such markers.

Encouragingly, several large prospective studies are currently underway to assess the detection performance of genetic markers, including the ECLIPSE trial in 130 research centers across the United States, evaluating the ctDNA LUNAR-2 test (Guardant Health), and the PREEMPT CRC trial (Prevention of Colorectal Cancer Through Multiomics Blood Testing; NCT04369053), which assesses the sensitivity and specificity of Freenome's detection method in over 35,000 asymptomatic individuals at average risk for CRC. In addition, the BLUE-C CRC observational screening study (NCT04144738) will verify the performance of blood-based ctDNA assays developed by Exact Sciences across 25,000 average-risk participants. Blood-based free DNA detection methods may alter the current landscape, with research results still pending publication (Table 3).

Early detection based on AI

Colonoscopy is the gold standard for diagnosing CRC and its precursors, significantly reducing the incidence and mortality rates of CRC.[69–72] However, approximately one-quarter of colorectal tumors may be missed during examinations, and there are considerable discrepancies in the quality of checks among different medical institutions and endoscopists.[14,73] This low ADR increases the risk of interval cancers, posing a serious threat to patients' survival and quality of life.[74] The challenges in achieving a higher ADR are often due to certain colorectal lesions being difficult to identify, particularly those that resemble the normal mucosal appearance and are relatively smaller in size. Given the importance of improving ADR, the application of AI in detection methods is becoming increasingly widespread. AI-assisted detection systems, through machine learning and deep learning algorithms, can automatically extract lesion features from vast amounts of endoscopic images and surgical videos, effectively identifying colorectal lesions that are difficult to detect by the naked eye.[24,75–77]

Table 3. Ongoing mass blood biomarker-based for CRC screening to date.

Mass CRC screening study	Study type and design	Estimated sample size	Enrollment time (years)	Detection method	Target population	Arm	Primary outcomes	Second outcomes	ClinicalTrials.gov ID
PREDICT	Prospective, multicenter observational	14,000	2	Multi-cancer early detection test (a cell-free DNA methylation-based model)	40–75 Years, participants with newly diagnosed cancer; participants with benign diseases corresponding to the tumor types in the Cancer Arm; healthy individuals	Cancer Arm; Benign Diseases Arm; non-tumor (Healthy) Arm	(1) Sensitivity of early detection of cancer and TOO accuracy of a cfDNA methylation-based model when specificity is 90%, 95%, or 98% in healthy participants; (2) sensitivity and specificity of early detection of cancer and TOO accuracy of a cfDNA methylation-based model	(1) Sensitivity, specificity, and TOO accuracy of a cfDNA methylation-based model in various types of cancer; (2) sensitivity, specificity, and TOO accuracy of a cfDNA methylation-based model in different stages of cancer; (3) sensitivity, specificity, and TOO accuracy of a cfDNA methylation-based model, in combination with clinical characteristics and other biomarkers	NCT04817306
REFLECTION	Prospective multicenter observational	35,000	5	Galleri (multicancer early detection, MCED)	⩾18 Years; any adult	Population receiving the Galleri test; population receiving standard cancer screening	Cancer detection rate; Performance of Galleri: sensitivity, specificity, positive predictive value; cancer signal detected; distribution of cancer stage in those who received a cancer diagnosis following a Galleri cancer signal detected test result	Time from test administration to cancer diagnosis; healthcare resource utilization; adherence to cancer screening guidelines; to describe the repeated use of Galleri test in patients	NCT05205967
ECLIPSE	Prospective multicenter observational	44,400	6	The ctDNA LUNAR 2	45–84 Years; asymptomatic; average risk population; population undergoing screening colonoscopy		Sensitivity of CRC detection; specificity of advanced neoplasia detection	Positive predictive value and negative predictive value of CRC detection; sensitivity and specificity of advanced adenoma detection	NCT04136002
PREEMPT CRC	Prospective multicenter observational	25,000	2	Freenome test	45–85 Years; asymptomatic; average-risk participants who will undergo a routine screening colonoscopy		Sensitivity for CRC of the Freenome test and specificity		NCT04369053

cfDNA, cell-free DNA; CRC, colorectal cancer; ctDNA, circulating tumor DNA; PREEMPT CRC, Prevention of Colorectal Cancer Through Multiomics Blood Testing; TOO, tissue of origin.

Notably, AI-assisted detection systems have shown good sensitivity in adenoma detection. A meta-analysis of randomized controlled trials indicated that, compared to standard colonoscopy, AI-assisted detection can identify 44% more adenomatous lesions.[16] An analysis by Spadaccini et al. of 50 relevant studies also found that AI systems have significant advantages in adenoma detection.[78] In a nationwide randomized controlled study involving over 2000 participants, a computer-aided detection (CADe) system named GI Genius showed an ADR of 56.6%, compared to 48.4% for standard colonoscopy, with the average number of adenomas detected increasing from 1.21 to 1.56 ($p < 0.001$).[79] In a multicenter randomized controlled trial led by Xu's team, the ADR with AI assistance was 39.9%, significantly higher than the control group's 32.4% ($p < 0.001$). The rate of detecting advanced adenomas was also significantly improved (6.6% vs 4.9%; $p = 0.041$).[23] A double-blind randomized trial by Wang et al. found that the CADe system significantly increased the ADR (34% vs 28%; $p < 0.01$), particularly for flat small polyps that were poorly defined and similar to normal mucosa.[80] Results from a prospective cohort study also showed that AI-assisted detection significantly improved the detection of polyp-like lesions (34.0% vs 38.7%; $p < 0.001$), especially for small lesions.[81] In addition, a multicenter study conducted in Spain involving over 3000 high-risk individuals detected by FIT found that while the CADe system did not improve the detection rates of advanced adenomas and adenomas (34.8% vs 34.6% and 64.2% vs 62.0%, respectively), it significantly increased the detection rates of proximal adenomas, small lesions, and non-polypoid lesions that are easily missed.[82] Among average-risk participants, Desai et al.'s study found that the new AI system did not significantly increase the ADR but did lead to an increase in the number of detected adenomas (0.99 ± 1.6 vs 0.85 ± 1.5; $p = 0.02$).[83] Although the effectiveness of AI in adenoma detection varies, potentially linked to the risk level of the subjects and the differences in AI training models, AI remains highly sensitive in identifying small lesions that are challenging for endoscopists to detect, supporting the use of AI-assisted colonoscopy to improve polyp detection.

Approximately 30% of CRC cases develop from SSLs, particularly those larger than 1 cm, which have a high risk of progression.[84] Due to their small and flat nature, and their common location in the proximal colon, detecting these lesions can be challenging.[85] Consequently, more studies are focusing on the impact of AI on the detection and missed diagnoses of SSLs. Hassan et al.'s meta-analysis indicates that AI can improve the detection rate of SSLs.[16] A multicenter randomized controlled study by Kamba et al. demonstrated that using CADe could reduce the missed detection rate of SSLs by about 25%.[86] Another study in the United States found that, compared to separate endoscopic examinations, deep learning-based CADe significantly reduced the missed detection rate of SSLs (7.14% vs 42.11%).[87] In addition, recent research suggests that serrated lesions may be the optimal target for CRC screening,[88] highlighting AI's advantages in improving the detection rate of SSLs, reducing missed diagnoses, and decreasing the occurrence of interval cancers. Therefore, long-term large-scale follow-up studies are necessary to clarify AI's performance in detecting easily missed lesions like SSLs and its impact on CRC incidence and mortality.

Furthermore, AI-assisted detection is regarded as an important tool for enhancing the quality of examinations performed by novice endoscopists. A large multicenter study by Xu et al. indicated that AI significantly improved ADRs among non-expert physicians (37.5% vs 32.1%; $p = 0.023$).[23] Research by Repici et al. found that the AI system (GI Genius) could increase the detection rate of lesions by approximately 10% for non-senior endoscopists,[89] and its effectiveness was independent of the physician's experience, emphasizing AI's supportive role in adenoma detection. Recently, a multicenter non-inferiority study by Yao et al. showed that AI not only significantly improved the lesion detection rate for primary physicians (18.82% vs 43.69%) but also brought their ADRs in line with experts (18.82% vs 26.97%), effectively narrowing the quality gap between physicians.[90] Research in Japan also found that AI-assisted detection systems could significantly reduce the adenoma miss rate among interns (25.6% vs 38.6%) and improve their lesion localization accuracy.[91] While AI applications are becoming more prevalent, endoscopists still need to view CADe as a supportive tool and continually enhance their skills and experience for more effective utilization of AI technology(Table 4).[92]

Table 4. Clinical trial for AI-assisted colonoscopy.

Author	Year	Study design	Subjects	Sample size	Detection method	Primary outcomes	Secondary outcomes	Results
Wang et al.[80]	2020	Prospective single-center double-blind randomized controlled	18–75years old, asymptomatic, average-risk population	1010	CADe	The ADR		The overall ADR (27.6% vs 34.1%) was higher in the AI-assisted colonoscopy
Kamba et al.[86]	2021	Prospective, multi-center, single-blind randomized tandem	40–80Years; screening, surveillance	358	CADe	The AMR	PMR, AMR per patient, PMR per patient, ADR at first pass, PDR at first pass, MAP at first pass	AMR (13.8% vs 36.7%), PMR (14.2% vs 40.6%), SSL miss rate (13.0% vs 38.5%) were lower in the CADe-first group; first-pass ADR (64.5%% vs 53.6%) was higher in the CADe-first group
Glissen Brown[87]	2022	Prospective, multi-center, single-blind randomized tandem	⩾22Years old, asymptomatic, average-risk population	232	CADe (EndoScreener)	The AMR	PMR, hyperplastic PMRs, SSLs miss rates	AMR (20.12% vs 31.25%), SSLs miss rate (7.14% vs 42.11%) were lower in the CADe-first group First-pass ADR (50.44% vs 43.64%) was higher in the CADe-first group
Xu et al.[23]	2023	Prospective multicenter single-blind randomized controlled	45–75Years old, asymptomatic, average-risk population	3059	CADe (Eagle-Eye)	The overall ADR	Mean number of adenomas per colonoscopy, ADR according to the endoscopist's experience, colonoscopy withdrawal time	The overall ADR (39.9% vs 32.4%), advanced ADR (6.6% vs 4.9%), ADR of experts (42.3% vs 32.8%); nonexpert endoscopists (37.5% vs 32.1%), adenomas per colonoscopy (0.59–0.97 vs 0.45–0.81) were higher in the AI-assisted colonoscopy
Mangas-Sanjuan et al.[82]	2023	Multicenter, parallel, randomized controlled	Individuals with a positive fecal immunochemical test	3213	CADe	The advanced colorectal neoplasia (advanced adenoma plus advanced serrated polyp) detection rate	The mean number of advanced colorectal neoplasia; ADR; the mean number of nonpolypoid lesions, proximal adenomas	Advanced colorectal neoplasia detection rate (34.8% vs 34.6%); the mean number of advanced colorectal neoplasia detected per colonoscopy (054 vs 0.52) and ADR (64.2% vs 62.0%) were similar; the mean number of nonpolypoid lesions (0.56 vs 0.47), and proximal adenomas (0.94 vs 0.81) detected per colonoscopy were higher in the CADe group

(Continued)

Table 4. (Continued)

Author	Year	Study design	Subjects	Sample size	Detection method	Primary outcomes	Secondary outcomes	Results
Yao et al.[87]	2024	Prospective, multicenter, randomized, noninferiority tandem	>18 Years old, diagnostic, screening, surveillance	685	CADe	The AMR	Withdrawal and insertion times, APC, PPC, visible AMR, visible PMR, AMR-INV/PMR-INV, PDR, various size and location miss/detection rates	AMR (18.82% vs 43.69%), PMR (21.23% vs 35.38%) were lower in the AI-assisted novice group; AMR (18.82% vs 26.97%), PMR (21.23% vs 24.10%) were similar between the AI-assisted novice group and control expert group
Yamaguchi et al.[91]	2024	Prospective multicenter single-blind randomized controlled	⩾20 Years old, asymptomatic, average-risk population	231	CADe	The trainee's ADR	The trainee's AMR, the ACE tool scores	AMR (25.6% vs 38.6%), number of missed adenomas per patient (0.5 vs 0.9) were lower, and ACE tool scores (2.26 vs 2.07) were higher in the CADe group
Seager et al.[79]	2024	Multicenter, open-label, parallel-arm, pragmatic randomized controlled	⩾18 Years old, gastrointestinal symptoms, surveillance, screening	2032	CADe (GI Genius)	Mean adenomas per procedure (total number of adenomas detected divided by total number of procedures)	ADR (proportion of colonoscopies with at least one adenoma)	Mean adenomas per procedure (1.56 vs 1.21) and ADR (56.6% vs 48.4%) were higher in the CADe group
Desai et al.[83]	2024	Multicenter, prospective, randomized controlled	⩾45 Years old, average-risk subjects; screening; surveillance	1031	CADe (EW10-EC02)	APC	ADR, advanced ADR, SSL detection rate; PDR	APC (0.99 ± 1.6 vs 0.85 ± 1.5, $p = 0.02$) and PPC (1.68 ± 2.1 vs 1.33 ± 1.8, $p < 0.01$) were higher in the CADe group; ADR (46.9% vs 42.8%), advanced adenoma (6.5% vs 6.3%), SSL detection rate (12.9% vs 10.1%) and PDR (63.9% vs 59.3%) were similar

ACE, assessment of competency in endoscopy; ADR, adenoma detection rate; AI, artificial intelligence; AMR, adenoma miss rate; APC, adenoma per colonoscopy; CADe, computer-aided detection; INV, invisible; MAP, mean number of adenomas per procedure; PDR, polyp detection rate; PMR, polyp miss rate; PPC, polyp per colonoscopy; SSL, sessile serrated lesion.

In summary, advancements and applications of AI technology have effectively increased the detection rates of colorectal lesions, particularly in improving ADRs among novice endoscopists, thereby reducing the disparities in performance among different endoscopists. It is anticipated that large-scale CRC screening programs incorporating AI-assisted detection systems will further lower the incidence and mortality rates of CRC in the population. However, several challenges remain for the clinical application of AI-assisted technology: (1) Most current AI studies are small scale and single center, lacking large, multicenter, prospective research to support widespread application; (2) There are numerous existing CADe devices, and further studies are needed to explore the differences in detection efficacy among various training models; (3) Implementing CADe may increase the cost of endoscopic examinations, but research data on the cost-effectiveness of AI remain relatively scarce, particularly regarding its long-term cost-effectiveness in large-scale CRC screening; and (4) Current CRC screening guidelines recommend stratified screening strategies to optimize resource use, but there is a lack of supportive strategies related to CADe. More research is needed to determine whether the existing screening frequency should be adjusted with the widespread adoption of CADe technology. If these barriers can be overcome, AI could become widely used in the screening and diagnosis of population-level CRC.

Conclusion

Early screening is a crucial measure for reducing the incidence and mortality associated with CRC. Several methods, including fecal occult blood tests, multi-target fecal DNA testing, and colonoscopy, have shown positive effects in the early screening and diagnosis of CRC. However, the current screening rate for CRC in the Chinese population remains low, and the existing methods for detecting precancerous lesions require improvement. In addition, with changes in lifestyle and dietary habits, the incidence of CRC is on the rise, and the rate of early-onset CRC is increasing annually. Therefore, it is necessary to develop screening assays that are highly acceptable, accurate, and cost-effective.

Gut microbiota, blood metabolites, and DNA mutation and methylation markers provide new ideas and options for the early detection of CRC and precancerous lesions. With the continuous development of noninvasive testing technologies, these methods demonstrate good sensitivity for CRC and precancerous lesions. Moreover, AI-assisted detection systems show significant advantages in identifying flat, normal-appearing small polyps and enhancing the quality of colonoscopy examinations. It is anticipated that AI-assisted colonoscopy will become a primary means of improving the efficiency of CRC screening and treatment. In the future, there is an urgent need for long-term follow-up in large-scale, prospective CRC screening projects to clarify the detection rates, practical applicability, and cost-effectiveness of these new detection methods. In addition, it will be essential to further promote innovation in gene sequencing technologies to broaden the range of biomarkers for identification and screening, thus seeking better early detection and diagnostic methods.

Despite these advancements, CRC screening still faces numerous challenges. Current noninvasive methods are predominantly studied in small sample sizes and case–control settings, with limited precancerous lesion biomarkers, high detection costs, low prevalence of AI-assisted detection systems, a lack of standardized guidelines, and limitations imposed by regional differences, economic conditions, and screening adherence. With the rising incidence of early-onset CRC, there is an urgent need for innovative screening methods and strategies to adapt to demographic changes in the target screening population. Collaborative efforts from all sectors of society are required to explore ways to lower the costs of new detection methods and increase their technological accessibility, benefiting more regions and populations. Furthermore, individualized healthcare must be promoted, selecting optimal screening strategies based on the specific circumstances of regional populations to enhance targeted screening efficiency. As AI and gene sequencing technologies rapidly advance, there will be ongoing research into these technologies to innovate CRC screening models and improve CRC screening efficiency both nationally and regionally.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication
Not applicable.

Author contributions
Changwei Duan: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Xianzong Ma: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Supervision; Writing – original draft; Writing – review & editing.

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