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DISCOVERY SCIENTIFIC SOCIETY

Current evidence on non-invasive methods for colorectal cancer detection

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ABSTRACT

Colorectal cancer (CRC) is the third cause of cancer deaths worldwide. The annual number of diagnosed cases is estimated at 2 million and is expected to increase. Because early detection significantly improves patients' survival, researchers are now looking for new targets for CRC detection strategies. Several strategies for non-invasive CRC detection were analyzed, including stool, blood, urine, saliva, microbiome, and imaging-based ones. Multi-marker studies often reported higher sensitivity than established fecal blood tests and reduced specificity. Another disadvantage was small study cohorts and limited prospective evidence. Evidence from blood-based methods came especially from methylation and circulating miRNA panels. However, promising results are limited by cost and heterogeneity of the studied methods. While studies on saliva, urine, and microbiome-based biomarkers are exploratory, the detection of adenomas and premalignant lesions seems to be neglected.

Keywords: colorectal cancer; non-invasive screening; biomarkers; liquid biopsy; multi-marker panels

1. INTRODUCTION

Observations across North America, Europe, and parts of Asia show rising incidence and mortality of colorectal cancer (Morgan et al., 2023). The biggest burden of colorectal cancer had South Korea, reporting the highest overall incidence rate. The country experiencing the highest annual increase was the United States (Spaander et al., 2023). Globally, 1,9 million people were diagnosed, and 0.9 million people died because of this illness (IARC, 2024).

Colonoscopy is a standard screening, detection, and sometimes therapeutic method. Procedure, however, is expensive, requires specialized personnel, and seems to be hard to accept for many patients. Major international guidelines recognize several effective colorectal cancer screening strategies, including stool-based tests, colonoscopy, CT colonography, and flexible sigmoidoscopy. However, colonoscopy plays a key role because it enables direct visualization, biopsy, and therapeutic removal. Nevertheless, colonoscopy is constrained by its invasiveness,

requirement of bowel preparation, trained personnel, and proper equipment (Adeomi et al., 2025). Survival rate of patients with CRC strongly correlates with the stage of disease upon diagnosis. In the early localized stages, the five-year survival rate exceeds 91%; it decreases to 17% once cancer metastize (National Cancer Institute, 2026). Fecal immunochemical test (FIT) and the guaiac-based fecal occult blood test (gFOBT) are the first established stool-based tests, which paved the way for more studies on a non-invasive approach to CRC screening. However, these stool tests may miss some adenomas or non-bleeding lesions. Positive results of correctly performed tests require a follow-up colonoscopy anyway (Grobbee et al., 2022).

Combining multiple biomarkers into panels has been an increasingly studied topic. Multi-marker and potentially multi-omics panels may improve early detection and risk stratification in the future. The importance of early diagnosis, the continuous rise in incidence, changes in CRC epidemiology, and the established role of gFOBT and FIT have increased interest in new diagnostic strategies.

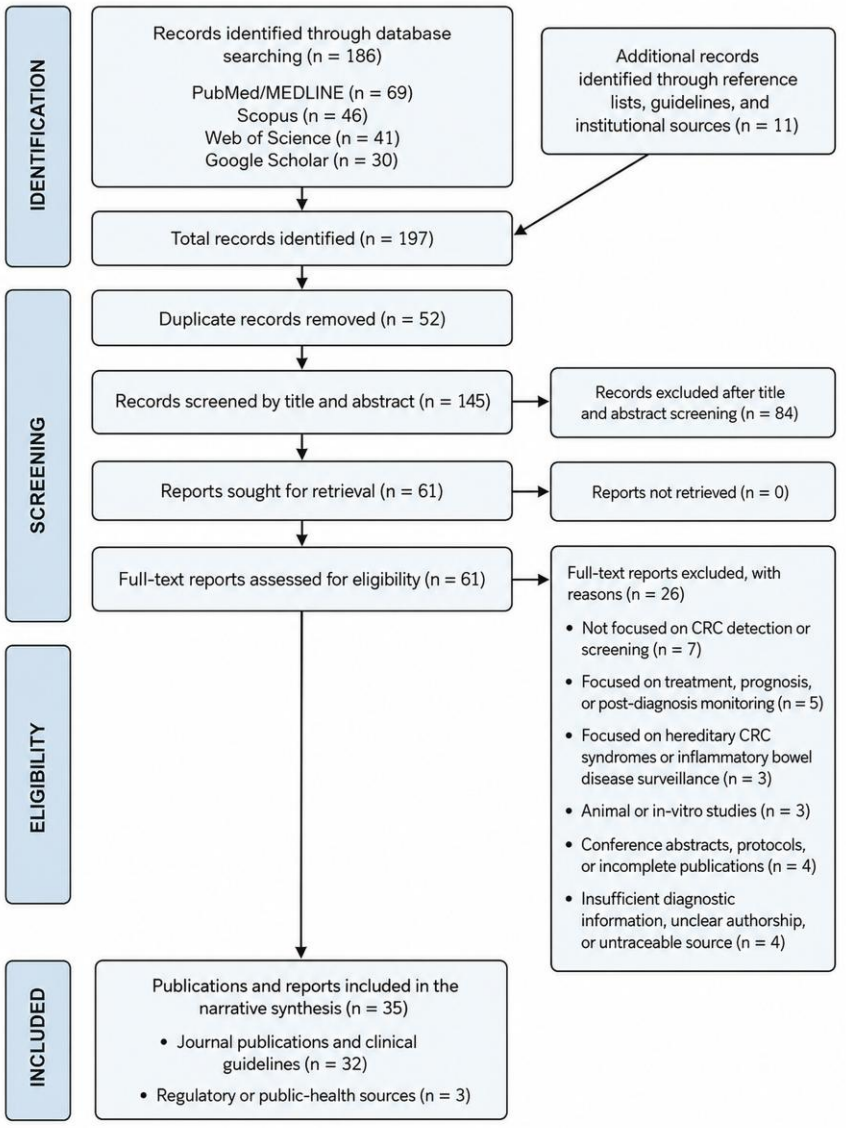

Figure 1. PRISMA-style flow diagram of source identification, screening, eligibility assessment, and inclusion in the narrative review.

2. REVIEW METHODS

A non-systematic search was conducted across medical databases: PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar to find relevant literature. Most of the analyzed articles were primarily published between January 2022 and January 2026, while older

guidelines or landmark studies were included if they were clinically relevant. All studies were carefully analyzed for traceable reference list, journal and publisher credibility, relevance to CRC, study design, and sample size.

This review put most of the focus on systematic reviews, meta-analyses, clinical guidelines, and recent clinical studies. Primary clinical studies, prospective, case-control, pilot, and validation studies, were included when they provided relevant data on the subject or described new potential biomarkers. Molecular or exploratory studies were included to establish the current position of emerging methods and concepts. Clinical guidelines and public health sources, including USPSTF, ESGE/ESGAR, and IARC/WHO, were used to validate the clinical and epidemiological context. Studies were excluded when they did not have a traceable reference list, authors could not be identified, did not undergo a literature review, or had not been fully published yet. Another exclusion criterion belongs to papers focused on CRC treatment, post-diagnosis prognosis, therapeutic monitoring, non-CRC malignancies, or artificial intelligence applied only to colonoscopy image interpretation without relevance to non-invasive detection methods. Studies focused on hereditary CRC syndrome and inflammatory bowel disease surveillance were also excluded. No animal and in-vitro studies were used to support the claims in this review.

As a result of the high heterogeneity of the performed analysis, biological matrices, biomarkers, and diagnostic endpoints, no quantitative meta-analysis was performed. The literature selection process is presented in Figure 1.

3. RESULTS & DISCUSSION

Diagnostic imagining

Computed Tomography Colonography (CTC)

CTC is a diagnostic tool that uses rectal gas insuflation to allow visualization of the colonic lumen, which is not possible using standard computed tomography protocols. This method does not require endoscopic intubation, but bowel preparation is still required (Beniwal et al., 2023). Utano et al., (2025) summarized the trial that reported CTC reached sensitivity for adenomatous polyps ≥10 mm was 90%, and for polyps larger than ≥6 mm, it was 78%. Regarding those findings, CTC may be considered an alternative to colonoscopy in certain situations, such as contraindications to colonoscopy, incomplete examinations, or patient refusal. It should also be noted that CT colonography is recognized in America as a screening tool and advises CTC every 5 years (USPSTF, 2021). Meanwhile, in Europe, it is considered mainly a diagnostic follow-up option when colonoscopy is difficult or incomplete.

MRI and PET-based imaging

ESR Essentials practice recommendations by ESGAR position MRI and CT as a complementary tool to colonoscopy in CRC diagnosis and essential for local and distant staging, restaging, and assessment of treatment response. Current European guidelines do not include MRI and PET as a CRC screening tool. They recognize the use of MRI and PET-based imaging for diagnosis, staging, restaging, and surveillance after cancer diagnosis (Caruso et al., 2024). Further implementation of those methods as a screening tool seems to be low. There is a lack of new studies on this subject.

Stool-based Testing - gFOBT, FIT, and new emerging panels

Fecal occult blood test (gFOBT) and fecal immunochemical test (FIT) are two established stool-based screening methods that detect occult blood in feces, which may reflect bleeding from colorectal neoplasia or other lesions that bleed into the colon lumen. The presence of blood in stool always requires diagnostic evaluation to identify the cause of bleeding. (USPSTF, 2021).

FIT has higher sensitivity than gFOBT for advanced neoplasia in the average-risk population. The authors underline greater expected benefits for mortality of implementing FIT (Săftoiu et al., 2020). Another advantage of FIT over gFOBT is that it uses antibodies specific to the human globin. This reduces false-positive results due to dietary factors, such as red meat consumption (USPSTF, 2021). Those guidelines advise the use of FIT and gFOBT annually, while European recommendations support FIT in population-based CRC screening programs. Those tests are established noninvasive screening methods (Săftoiu et al., 2020).

While FIT and gFOBT remain standard non-invasive screening tools, their effectiveness depends on repeated testing (USPSTF, 2021). Real-world data indicate that patients' compliance with testing varies widely across member states and usually stays suboptimal. (Săftoiu et al., 2020). Moreover, the sensitivity of those methods may be limited for intermittently bleeding lesions, flat neoplasms, early-stage tumors, or advanced adenomas. Additionally, neither FIT nor gFOBT provides anatomical localization, staging information, or a definitive diagnosis (USPSTF, 2021). A positive result is not a diagnosis and requires a follow-up colonoscopy for confirmation and possible intervention. These limitations have turned the attention toward the development of new stool-based panels.

Emerging stool-based panels: multi-target stool DNA (mt-sDNA)

Multi-target stool DNA (mt-sDNA) testing represents an advanced, non-invasive approach to colorectal cancer detection. It detects tumor-derived DNA that is shed into the intestinal lumen. This mechanism targets an important limitation of FIT and gFOBT, namely, that mt-sDNA does not rely on active bleeding caused by neoplasia (Mostafa et al., 2025).

Stool DNA testing shows higher sensitivity than FOBT/FIT for CRC detection, with slightly lower specificity, but both stool DNA and FOBT/FIT have lower sensitivity for advanced precancerous lesions (APL) An analysis of 55 studies has shown mt-sDNA demonstrated higher sensitivity of 93.6% (95% CI 89.0–97.1) versus FIT: 71.6% (95% CI: 64.3–77.9) for detecting CRC. The same meta-analysis has found out 45.6% sensitivity for mt-sDNA and 22.2% for FIT in the diagnosis of advanced precancerous lesions. However, higher sensitivity was accompanied by slightly lower specificity, estimated as 91.6% (95% CI 89.2- 93.7) for mt-sDNA versus 96.3% (95% CI 95.4-97.0) for FIT (Ebner et al., 2025). Those promising findings further increase interest in newer stool-based screening methods.

Cologuard is an example of the real-world implementation of the mt-sDNA test. It is a convenient, at-home stool DNA test that screens for precancerous lesions and CRC by detecting altered DNA markers and hidden blood in stool. However, a positive result test requires follow-up colonoscopy; only 44% of those patients underwent the procedure within 12 months (Kazi et al., 2025).

Patients can perform tests at home, but probes must be processed in a laboratory, which means patients need to send samples back, resulting in low screening completion rates. However, Koseki Senda et al. have attempted to implement interventions to better educate patients and healthcare providers to better utilize tests. Their iterative plan-do-study-act model has shown that, despite a low patient adherence rate, it is possible to improve this test performance. Their results suggest direct patient messaging reaches the highest impact (Koseki Senda et al., 2025). Nevertheless, their effort improved patients' adherence, not test completion.

Stool microRNAs markers

Santos et al. developed two panels consisting of multiple miRNA molecules. Panel A included miR-21-5p, miR-199a-5p, and age, whereas Panel B included miR-21-5p, miR-199a-5p, miR-451a, age, and gender. A combination of two panels gave the best results and reached a sensitivity of up to 92% for CRC plus high-grade dysplasia. Researchers concluded that patients who received positive results of FOBT could have been screened with a miRNA panel as the next diagnostic step. The paper suggests reducing the number of unnecessary colonoscopies by an estimated 40–52% after a positive FOBT result (Santos et al., 2025).

A small cohort study limits strong conclusion, moreover study only analyzed cases already diagnosed, which further discourage too optimistic perspectives of replacing the colonoscopy. Chen and Chang (2025) analyzed studies about fecal miRNAs used as biomarkers for colorectal cancer. They found that MiR-21, miR-92a, miR-135b, miR-144, miR-221, and miR-223 belong to frequently studied molecules, although their combinations vary in different studies. In several analyzed studies, combinations of multiple Fecal miRNAs showed comparable diagnostic performance to FIT. Strong limitations of the analyzed study were the variables of the sample analysis. The subject needs larger prospective studies.

Gut microbiome alterations

Colorectal cancer has been increasingly linked to alterations of the gut microbiome. Those changes can be analyzed and profiled by using gene-sequencing methods. Researchers from China used 16S rRNA gene sequencing to examine microbial signatures consisting of multiple genera. For example, a model of 55 of them distinguished CRC cases from normal controls with high discriminatory performance (AUC = 0.98; 95% CI, 0.96–1.00). However, the CRC group was very small (Li et al., 2025). The same study also developed a model of 27 genera for non-advanced adenomas (AUC = 0.82) and 13 genera for inflammatory lesions (AUC = 0.71). These findings suggest potential discriminatory value, although more evidence is needed.

Different analyses identified distinct changes in microbiota that were associated with tumor localisations. Samples containing Veillonella parvula were associated with right-sided CRC, Streptococcus anginosus with left-sided CRC, and Peptostreptococcus anaerobius with rectal cancer (Lin et al., 2025). Overall, gut microbiome signatures show promising results, but current evidence is exploratory and requires more evidence.

Blood-based biomarkers

Liquid biopsy involves the analysis of blood or other body fluids to isolate circulating cancer biomarkers. Those biomarkers may be a broad group of molecules, including cell-free DNA, circulating tumor DNA (ctDNA), RNA-based markers, and others (Lima et al.,

2023). Methylated ctDNA is considered a promising target of liquid biopsy. In a nested case-control analysis, researchers assessed stored plasma samples of patients before clinical diagnosis. The panel marker they created has reached 43% sensitivity and 86% specificity. While the study can be considered as proof of the concept, ctDNA can be traced before clinical diagnosis; it is not a clinical validation for CRC screening. Further prospective screening trials are needed to find and study the best-performing panel (Brenne et al., 2023).

Another example of such a test is FDA-approved Epi proColon®. This test, based on the detection of methylated gene SEPT9 in patients' plasma, was FDA-approved in April 2016. However, it is important to note that Epi proColon® is not a standard screening tool as FIT and represents lower specificity, while sensitivity was maintained. Indications are limited to average-risk adults ≥50 who have been offered and declined recommended CRC screening tests. Additionally, its use is limited due to high costs (U.S. Food and Drug Administration, 2016).

A different group of researchers studied combining SEPT9 methylation with other methylated genes, such as BMP3, and age >60 years old. Their results supported higher performance for detecting CRC (AUC = 0.845) when all three were combined. Both SEPT9 methylation and BMP3 reached lower AUC when studied alone. However, the study included only a small group of 262 participants (Lima et al., 2023).

Combining even more methylated genes (Septin9, SDC2, KCNQ5, and IKZF1) was the idea of a prospective study that compared the performance of those markers with CEA. Authors showed a positive detection rate of 86.7% for CRC overall, 90.9% for stage I, 87.5% for stage II disease. ROC analysis demonstrated an AUC of 0.809 (95% CI: 0.730–0.888) for the combined panel (Xu et al., 2024). Moreover, both studies included relatively small cohorts. For example, Xu et al., (2024) included only 45 CRC patients, 8 advanced adenoma patients, 34 small-polyp patients, and 37 normal controls. Large, prospective studies are needed to potentially replicate and validate promising findings. High costs and lack of standardization may further limit the implementation of methylated-gene tests.

MiRNA in serum

Changes in microRNA detected in blood are referred to as circulating miRNA. An analyzed systematic review focused on the diagnostic performance of those molecules. Study identifies miR-21, miR-1246, and miR-210 as promising single biomarkers. Most promising molecule seems to be MiR-1246, achieving 100% sensitivity and 80% specificity (AUC = 0.924). The authors underline a broad spectrum of results across different studies (AlZaabi and Shalaby, 2024).

ctDNA

Methylated ctDNA markers are tumor-derived DNA fragments circulating in the bloodstream. In the context of CRC screening, these markers are of interest because methylated ctDNA markers were detectable in some plasma samples collected up to two years before diagnosis. A combination of eight ctDNA markers showed 43% sensitivity and 86% specificity in samples collected from patients who were later diagnosed within 24 months for CRC (Brenne et al., 2023).

Moreover, whether early detection of these molecular changes contributes to long-term survival remains unknown. Currently, it remains unclear how positive, preclinical ctDNA findings could be interpreted. However, blood-based methylation panels for CRC screening remain investigational. Further, large prospective studies are needed to build diagnostic and screening strategies for these markers.

Saliva-based biomarkers

Saliva as diagnostic method experience more and more interest in medical field. It may represent molecular changes in local and systemic tissues, which explain its potential (Swaathi et al., 2024). Salivary microbiota represents a promising area of research in CRC detection. For instance, it has been found that the level of salivary F. nucleatum DNA in the oral cavity is higher among patients with CRC. This marker differentiated CRC patients from individuals with normal colonoscopy results, hyperplastic polyps or adenoma. Moreover, salivary F. nucleatum DNA level outperformed conventional biomarkers: CEA and CA19-9 in CRC diagnosis (Zhang et al., 2022).

MicroRNA in saliva represents another promising target in detection of CRC. Results showed high diagnostic performance for miR-92a (AUC: 0.947) and miR-29a (AUC: 0.978) and high sensitivity and specificity (95.24 % and 84.85 % for miR-92a and 95.20 % and 87.88 % for miR-29a) (Koopaie et al., 2024). However, promising results need to be taken with caution, because those results come from a small case-control study with only 42 CRC cases and an even smaller group of healthy patients.

Waniczek et al., (2022) investigated three salivary proteins: chemerin, α-Defensin 1, and TNF-α as potential non-invasive tools for discriminating CRC patients from healthy controls. All three salivary protein concentrations achieved maximum diagnostic efficiency (100% sensitivity and 100% specificity) in discriminating between CRC patients and healthy controls. However, these results should be interpreted very cautiously because this case-control study was small (39 CRC patients, 40 control group). Moreover, we did not identify studies replicating these results, which would validate the strong diagnostic performance shown by this study.

In a different study, patients with CRC had elevated salivary sHLA-G concentrations compared with healthy controls (18.84 U/ml vs. 6.3 U/ml; $p = 0.036$). Moreover, individuals with stage III–IV CRC had higher salivary sHLA-G levels than those in early stages (24.2 U/ml vs. 8.1 U/ml; $p = 0.019$). Although the study did not track patients over time, these observations suggest a possible association between stage disease and salivary sHLA-G expression. Nevertheless, this study comes from 2020, and we did not identify independent studies reproducing these findings (Lázaro-Sánchez et al., 2020).

In a more recent case-control salivary biomarker study, researchers have analyzed Olink proteomics and untargeted metabolomics in saliva samples from CRC patients and healthy controls. Out of 16 differentially expressed proteins and 40 differentially accumulated metabolites, four biomarkers were selected and validated: succinate, L-methionine, GZMB, and MMP12. A panel of 4 of their molecules achieved AUCs of 0.933 in the discovery group. However, the study had a small cohort of only 49 CRC patients (Su et al., 2025). Nevertheless, salivary biomarkers remain promising as a non-invasive, cost-effective complement to existing tools for the detection of CRC. However, at present, there is a significant lack of large prospective studies that could validate their utility.

Urine-based biomarkers

DNA methylation detected in urine, represents one of the investigated strategies. In one study, urine samples from 92 CRC patients and 63 healthy participants were collected and searched for six methylation markers: SEPT9, TMEFF2, SDC2, NDRG4, VIM, and ALX4. Methylation levels of SEPT9 in urine supernatant were significantly elevated in CRC patients compared to controls ($p < 0.0001$). The combination of SEPT9 and SDC2 methylation achieved up to 70% sensitivity at 86% specificity for discriminating CRC patients from controls. Notably, unfractionated urine did not show encouraging results, which undermined the influence of proper sample processing (Bach et al., 2021).

Beyond DNA methylation, miRNA is another group of studied molecules. Similar to a previously mentioned article, a study has analyzed a panel of two molecules. Urinary microRNA called miR-129-1-3p and miR-566 discriminated CRC patients with an AUC of 0.811 in the training cohort and 0.868 in the validation cohort. Moreover, the panel was analyzed regarding early-stage performance, reaching an AUC of 0.845 for stage 0/I CRC and higher sensitivity than serum CEA or CA19-9 (Iwasaki et al., 2022).

Volatile Organic Compounds (VOCs) are another area of study in the early detection of colorectal cancer. This term refers to small carbon-based molecules that present as gases at room temperature and can be detected by various methods, such as gas chromatography. VOCs are predominantly hydrocarbons, carboxylic acids, aldehydes/ketones, and amino acids. It was shown to reflect tumor-associated changes in metabolism. Detected molecules or their concentrations are linked to metabolic changes of tissues, which are a sign of cancerogenesis (van Liere et al., 2023).

The systematic review analyzed and synthesized data from 16 studies, which included 837 CRC participants, 1618 control group, and 266 adenoma cases. The aim of this research was to evaluate the potential utility of urine VOC as a diagnostic tool. Over 100 VOCs were found to be associated with colorectal cancer, creating a broad pool of studied chemicals. Among individual urinary VOCs, butanal turned out to demonstrate the best results, reaching an AUC of 0.98 in one study. Another promising result evaluated by this study was that combining FIT with urinary VOCs could detect 33% more CRC cases compared to FIT alone. Conclusion need to be cautious; authors underline small cohorts of many studies and large amount of analyzed biomarkers (van Liere et al., 2023).

Urine metabolomics

In a pilot-controlled trial, researchers tested patients' urine samples for hippuric acid, diacetylspermine, and creatinine using point-of-care biosensors. As a reference, all patients underwent colonoscopy, and all cases were histopathologically confirmed. For all respondents, the test showed 91.18% sensitivity and 81.58% specificity. For all respondents, the test showed 91.18% sensitivity and 81.58% specificity, with an AUC of 0.86. With specificity fixed at 50%, sensitivity reached 94.5%. This fixed sensitivity was used to estimate whether the test could halve colonoscopy referrals. This can be especially beneficial in low-income countries with limited access to procedures such as colonoscopy (Adeomi et al., 2025).

The study was designed to triage patients, after measuring metabolite concentrations in urine, the results were combined with clinical features. Generated results were binary: YES/NO for the likelihood of CRC. Crucially, currently, there is not enough evidence for broad implementation. Positive results from this study do not prove benefits for patients' survival and mortality rate. Nevertheless, the study is an example of emerging needs around the world, calling for the development of more affordable diagnostic tools.

Colonoscopy is the reference standard for CRC diagnosis, and thanks to polypectomy and endoscopic mucosal resection (EMR), early-stage treatment. A positive result of non-invasive stool tests requires a subsequent colonoscopy for polyp removal (Ferlitsch et al., 2024). Patients who are over 45 years old and have no absolute contraindications should be encouraged to colonoscopy (USPSTF, 2021). However, many patients hesitate to participate due to the demanding preparation process, fear of pain, or general embarrassment. Nevertheless, many non-invasive tests can be done more frequently than endoscopic interventions; they put less risk to the patient and usually do not require specialized equipment. Endoscopic interventions require substantial resources, particularly for specialized personnel demands. Those are comparably low for most of the analyzed non-invasive methods. The particular role of emerging non-invasive methods lies in complementing high-quality colonoscopy repeated at the frequency recommended by current guidelines.

Established non-invasive methods, such as FOBT and FIT, have lower sensitivity and specificity and cannot fully replace colonoscopy as a diagnostic standard (Yaghoobi et al., 2023). Many studies, like Koseki Senda et al., (2025), are examples of attempts to better utilize tests already existing by educating patients and showing positive results. Table 1 shows the summary of non-invasive colorectal cancer detection methods.

Table 1. Summary of non-invasive colorectal cancer detection methods

Method	Summary
Computed tomography colonography	High sensitivity for larger polyps; bowel preparation and insufflation remain necessary.
MRI and PET imaging	Mainly staging and surveillance tools; not established for population screening.
FIT and gFOBT	Established repeat tests; FIT performs better, but positive results require colonoscopy.
Multi-target stool DNA / Cologuard	More sensitive than FIT but less specific; positive results require colonoscopy.
Stool microRNA panels	High sensitivity was reported; cohorts were selected and methods varied.
Gut microbiome signatures	High AUCs and location-specific taxa were reported; evidence remains exploratory.
Plasma DNA methylation / Epi proColon	SEPT9 and multigene tests showed potential; cost, specificity and small cohorts limit use.
Circulating microRNA	Some markers performed well, but results varied substantially between studies.
Circulating tumor DNA	Some preclinical CRC was detected; the eight-marker panel reached 43% sensitivity.
Salivary Fusobacterium nucleatum	Higher levels were linked to CRC and outperformed CEA/CA19-9 in one study.

Salivary microRNA	High AUCs were reported in a small case-control study.
Salivary proteins and metabolites	Proteins, sHLA-G and multi-omics panels discriminated CRC; replication is limited.
Urinary DNA methylation	SEPT9 plus SDC2 reached 70% sensitivity and 86% specificity; processing mattered.
Urinary microRNA	A two-marker panel reached AUC 0.845 for stage 0/I CRC.
Urinary volatile organic compounds	Butanal reached AUC 0.98; adding VOCs to FIT detected more cases.
Urine metabolomics	A pilot model reached 91.18% sensitivity and 81.58% specificity.
Multi-marker, multi-omics and AI models	Potential for triage was suggested; clinical benefit and validation remain unproven.

Moreover, this new multi-omics approach may provide additional diagnostic information. A combination of epigenomic markers, transcriptomic profiles, metabolomic signatures, and microbiome composition may further improve early CRC detection and patient risk stratification. However, currently, such claims remain speculative. This pattern is widespread across most of the reviewed studies. In the future, we need larger, prospective multi-matrix studies that connect these different panels and integrate findings across multiple biological matrices. Diagnostic performance may vary widely depending on the analyzed matrix. Among the reviewed non-invasive approaches, stool-based testing currently has the strongest evidence and is already widely used for FIT/gFOBT and mt-sDNA testing (USPSTF, 2021).

With the development of algorithms and AI machine learning, new risk-stratifying tools could be introduced. The previously mentioned study analyzed two models: multiple logistic regression and a multilayer feedforward neural network. Interestingly, the logistic regression model performed better than the neural network, suggesting that variable selection and model design may be more important than algorithmic complexity alone (Koopaie et al., 2024).

Nevertheless, most of the studies are in their early stages; importantly, current data do not support the idea of replacing colonoscopy as a primary diagnostic method. However, there are studies that suggest that some screening methods could help differentiate high-risk from low-risk patients and reduce the number of unnecessary diagnostic colonoscopies. Several analyzed studies showed lower sensitivity for advanced adenomas or non-bleeding lesions, which shows potential implementation limitations.

New non-invasive methods may be a more accessible tool in resource-limited settings, where colonoscopy is restricted due to a lack of infrastructure and costs. Point-of-care urine metabolomics may offer triage tools to better prioritize available colonoscopies by identifying higher-risk patients, as illustrated in a pilot study (Adeomi et al., 2025).

However, the study was a small trial from a single Nigerian center; findings should be interpreted very cautiously. Rising incidence rates in low-income and developing countries, combined with limited access to standard diagnostic methods such as colonoscopy, create an additional stimulus for expanding research in this field (IARC, 2024, Morgan et al., 2023).

4. CONCLUSION

Across the many studies and meta-analyses, we examined, there is a clear trend—regardless of whether we are dealing with stool, saliva, blood, or urine. Researchers no longer focus on a single "magic" molecule. Instead, they emphasize panels of multiple markers. This pattern is widespread across most of the reviewed studies. In the future, we need more multi-directional studies that connect these different panels and integrate findings across multiple biological matrices. Nevertheless, most of the studies are in their early stages; what is important is that current data do not support replacing colonoscopy as a primarily used method of detection and treatment. The particular role of emerging non-invasive methods lies in complementing high-quality colonoscopy repeated at the frequency recommended by current guidelines.

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Authors' Contributions
- All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.
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Data and materials availability
All data associated with this study will be available based on the reasonable request to corresponding author.

REFERENCES

1. Adeomi AA, Alatise OI, Wishart D, MacKay S, Olasehinde O, Wuraola F, Adisa A, Mohammed T, Aderounmu A, Betiku OA, Omoyiola OZ, Adeleye AO, Ogunleye SO, Babatunde OJ, Ademakinwa OR, Owoade IA, Mobolaji J, Olcese C, Kahn R, Choonawala NR, Fitzgerald G, Hosgood HD, Kingham TP. Point-of-care urine metabolomics test to diagnose colorectal cancers in low- and middle-income countries: a pilot controlled trial in Southwestern Nigeria. JCO Glob Oncol 2025;11:e2500062. doi:10.1200/GO-25-00062.
2. AlZaabi A, Shalaby A. A systematic review of diagnostic performance of circulating microRNAs in colorectal cancer detection with a focus on early-onset colorectal cancer. Int J Mol Sci 2024;25(17):9565. doi:10.3390/ijms25179565.
3. Bach S, Paulis I, Sluiter NR, Tibbesma M, Martin I, van de Wiel MA, Tuynman JB, Bahce I, Kazemier G, Steenbergen RDM. Detection of colorectal cancer in urine using DNA methylation analysis. Sci Rep 2021;11(1):2363. doi:10.1038/s41598-021-81900-6.
4. Beniwal SS, Lamo P, Kaushik A, Lorenzo-Villegas DL, Liu Y, MohanaSundaram AS. Current status and emerging trends in colorectal cancer screening and diagnostics. Biosensors (Basel) 2023;13(10):926. doi:10.3390/bios13100926.
5. Brenne SS, Madsen PH, Pedersen IS, Hveem K, Skorpen F, Krarup HB, Giskeødegård GF, Laugsand EA. Colorectal cancer detected by liquid biopsy 2 years prior to clinical diagnosis in the HUNT study. Br J Cancer 2023;129(5):861-8. doi:10.1038/s41416-023-02337-4.
6. Caruso D, Polici M, Bellini D, Laghi A. ESR Essentials: imaging in colorectal cancer - practice recommendations by ESGAR. Eur Radiol 2024;34(9):5903-10. doi:10.1007/s00330-024-10645-3.

7. Chen CC, Chang PY. Fecal miRNAs as potential biomarkers for early detection of colorectal cancer: an updated review. Biomed J 2025;48(1):100769. doi:10.1016/j.bj.2024.100769.
8. Ebner DW, Johnson HA, Estes C, Johnson WK, Khan RS, Thompson G, Kong J, Camardo M, Dore M, Vahdat V, Fendrick AM, Limburg PJ, Kisiel JB. Multi-target stool DNA and the fecal immunochemical test: a systematic review and meta-analysis on test performances. Am J Prev Med 2025; 69(2):107654. doi:10.1016/j.amepre.2025.107654.
9. Ferlitsch M, Hassan C, Bisschops R, Bhandari P, Dinis-Ribeiro M, Risio M, Paspatis GA, Moss A, Libânio D, Lorenzo-Zúñiga V, Voiosu AM, Rutter MD, Pellisé M, Moons LMG, Probst A, Awadie H, Amato A, Takeuchi Y, Repici A, Rahmi G, Koecklin HU, Albéniz E, Rockenbauer LM, Waldmann E, Messmann H, Triantafyllou K, Jover R, Gralnek IM, Dekker E, Bourke MJ. Colorectal polypectomy and endoscopic mucosal resection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2024. Endoscopy 2024;56(7):516-45. doi:10.1055/a-2304-3219.
10. Grobbee EJ, Wisse PHA, Schreuders EH, van Roon A, van Dam L, Zauber AG, Lansdorp-Vogelaar I, Bramer W, Berhane S, Deeks JJ, Steyerberg EW, van Leerdam ME, Spaander MCW, Kuipers EJ. Guaiac-based faecal occult blood tests versus faecal immunochemical tests for colorectal cancer screening in average-risk individuals. Cochrane Database Syst Rev 2022;6(6):CD009276. doi:10.1002/14651858.CD009276.pub2
11. International Agency for Research on Cancer (IARC). Colorectal cancer. Lyon: International Agency for Research on Cancer; 2024.
12. Iwasaki H, Shimura T, Kitagawa M, Yamada T, Nishigaki R, Fukusada S, Okuda Y, Katano T, Horike SI, Kataoka H. A novel urinary miRNA biomarker for early detection of colorectal cancer. Cancers (Basel) 2022;14(2):461. doi:10.3390/cancers14020461.
13. Kazi MAI, Qureshi I, Sharma A, Agrawal N, Sarfraz M, Meisenberg B, Singh S. From detection to delay: real-world gaps in post-Cologuard® colonoscopy adherence. J Gastrointest Cancer 2025;56:224. doi:10.1007/s12029-025-01350-5.
14. Koopaie M, Manifar S, Talebi MM, Kolahdooz S, Razavi AE, Davoudi M, Pourshahidi S. Assessment of salivary miRNA, clinical, and demographic characterization in colorectal cancer diagnosis. Transl Oncol 2024;41:101880. doi:10.1016/j.tranon.2024.101880.
15. Koseki Senda M, Chow D, Dev B, DeBroff J, O'Ferrall C, Fliehman R, Jiang R. Improving colorectal cancer screening through Cologuard education: a quality improvement initiative in an urban primary care clinic. BMJ Open Qual 2025;14(4):e003553. doi:10.1136/bmjoq-2025-003553.
16. Lázaro-Sánchez AD, Salces-Ortiz P, Velásquez LI, Orozco-Beltrán D, Díaz-Fernández N, Juárez-Marroquí A. HLA-G as a new tumor biomarker: detection of soluble isoforms of HLA-G in the serum and saliva of patients with colorectal cancer. Clin Transl Oncol 2020;22(7):1166-71. doi:10.1007/s12094-019-02244-2.
17. Li G, Zhao D, Ouyang B, Chen Y, Zhao Y. Intestinal microbiota as biomarkers for different colorectal lesions based on colorectal cancer screening participants in community. Front Microbiol 2025;16:1529858. doi:10.3389/fmicb.2025.1529858.
18. Lima AB, dos Reis MB, Matsushita M, dos Reis MT, de Oliveira MA, Reis RM, Guimarães DP. Combined SEPT9 and BMP3 methylation in plasma for colorectal cancer early detection and screening in a Brazilian population. Cancer Med 2023;12(15):15854-67. doi:10.1002/cam4.6224.
19. Lin Y, Lau HCH, Liu C, Ding X, Sun Y, Rong J, Zhang X, Wang L, Yuan K, Miao Y, Wu WKK, Wong SH, Sung JJY, Yu J. Multi-cohort analysis reveals colorectal cancer tumor location-associated fecal microbiota and their clinical impact. Cell Host Microbe 2025;33(4):589-601.e3. doi:10.1016/j.chom.2025.03.012.
20. Morgan E, Arnold M, Gini A, Lorenzoni V, Cabasag CJ, Laversanne M, Vignat J, Ferlay J, Murphy N, Bray F. Global burden of colorectal cancer in 2020 and 2040: incidence and mortality estimates from GLOBOCAN. Gut 2023;72(2):338-44. doi:10.1136/gutjnl-2022-327736.
21. Mostafa M, Eltaher B, Egiza HA, Gouli S, Mahmoud A, Kharel H, Singh H, Niu C. Use of stool DNA for colorectal cancer screening: a meta-analysis and systematic review. Eur J Cancer Prev 2025;34(4):309-15. doi:10.1097/CEJ.0000000000000937.
22. National Cancer Institute. Cancer Stat Facts: Colorectal Cancer. Bethesda (MD): National Cancer Institute; 2026.
23. Săftoiu A, Hassan C, Areia M, Bhutani MS, Bisschops R, Bories E, Cazacu IM, Dekker E, Deprez PH, Pereira SP, Senore C, Capocaccia R, Antonelli G, van Hooft JE, Messmann H, Siersema PD, Dinis-Ribeiro M, Ponchon T. Role of gastrointestinal endoscopy in the screening of digestive tract cancers in Europe: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy 2020;52(4):293-304. doi:10.1055/a-1104-5245.
24. Santos DAR, Eiras M, Gonzalez-Santos M, Santos M, Pereira C, Santos LL, Dinis-Ribeiro M, Lima L. A preliminary assessment of a stool-based microRNA profile for early colorectal cancer screening. Sci Rep 2025;15(1):28597. doi:10.1038/s41598-025-14485-z.

25. Spaander MCW, Zauber AG, Syngal S, Blaser MJ, Sung JJ, You YN, Kuipers EJ. Young-onset colorectal cancer. Nat Rev Dis Primers 2023;9(1):21. doi:10.1038/s41572-023-00432-7.
26. Su H, Gu X, Zhang W, Lin F, Lu X, Zeng X, Wang C, Chen W, Liu W, Tan P, Zou L, Gu B, Chen Q. Identification of salivary biomarkers in colorectal cancer by integrating Olink proteomics and metabolomics. J Proteome Res 2025;24(5):2542-52. doi:10.1021/acs.jproteome.5c00091.
27. Swaathi R, Narayan M, Krishnan R. Salivary biomarkers in cancer - a narrative review. Oral Oncol Rep 2024;10:100503. doi:10.1016/j.oor.2024.100503.
28. U.S. Food and Drug Administration. Epi proColon: instructions for use. Premarket Approval Application P130001. Silver Spring (MD): U.S. Food and Drug Administration; 2016.
29. US Preventive Services Task Force (USPSTF). Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA 2021;325(19):1965-77. doi:10.1001/jama.2021.6238.
30. Utano K, Aizawa M, Isohata N, Utano Y, Endo S, Togashi K. The potential of CT colonography for colorectal cancer screening in Japan. Jpn J Radiol 2025;43(9):1417-26. doi:10.1007/s11604-025-01798-2.
31. van Liere ELSA, van Dijk LJ, Bosch S, Vermeulen L, Heymans MW, Burchell GL, de Meij TGJ, Ramsoekh D, de Boer NKH. Urinary volatile organic compounds for colorectal cancer screening: a systematic review and meta-analysis. Eur J Cancer 2023;186:69-82. doi:10.1016/j.ejca.2023.03.002.
32. Waniczek D, Świętochowska E, Śnietura M, Kiczmer P, Lorenc Z, Muc-Wierzgoń M. Salivary concentrations of chemerin, α-defensin 1, and TNF-α as potential biomarkers in the early diagnosis of colorectal cancer. Metabolites 2022;12(8):704. doi:10.3390/metabo12080704.
33. Xu Y, Qu H, Liang R, Li M, Li M, Li X, Wang Z. A multi-gene blood-based methylation assay for early diagnosis of colorectal cancer. Transl Cancer Res 2024;13(12):6699-708. doi:10.21037/tcr-24-729.
34. Yaghoobi M, Mehraban Far P, Mbuagbaw L, Yuan Y, Armstrong D, Thabane L, Moayyedi P. Head-to-head diagnostic test accuracy meta-analysis of colonoscopy and fecal immunochemical test in detecting advanced colon neoplasia. Middle East J Dig Dis 2023;15(1):5-11. doi:10.34172/mejdd.2023.313.
35. Zhang X, Zhang Y, Gui X, Zhang Y, Zhang Z, Chen W, Zhang X, Wang Y, Zhang M, Shang Z, Xin Y, Zhang Y. Salivary Fusobacterium nucleatum serves as a potential biomarker for colorectal cancer. iScience 2022;25(5):104203. doi:10.1016/j.isci.2022.104203.