Review Article

Non-Invasive Stool- and Blood-Based Biomarkers in Colorectal Cancer: A Review of Emerging Alternatives

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ABSTRACT

Colorectal cancer (CRC) remains a leading cause of cancer-related morbidity and mortality worldwide. Colonoscopy is the gold standard for screening, but its invasiveness, cost, and limited acceptance highlight the need for non-invasive alternatives. Stool- and blood-based biomarkers have emerged as promising tools for early detection, surveillance, and minimal residual disease (MRD) monitoring. This review evaluates the current evidence on stool- and blood-based biomarkers for CRC, focusing on their diagnostic performance, clinical utility, challenges, and future prospects in comparison with colonoscopy. A comprehensive review of recent literature (2010–2025) was conducted using PubMed, Scopus, and Web of Science databases. Studies evaluating fecal immunochemical tests (FIT), multitarget stool DNA (mt-sDNA), circulating tumor DNA (ctDNA), methylated SEPT9, protein biomarkers, and microRNAs were included, with emphasis on sensitivity, specificity, and clinical applications. FIT and mt-sDNA demonstrate sensitivities of 70–92% and specificities of 87–90% for CRC detection, though their effectiveness in identifying advanced adenomas is lower. Blood-based assays, particularly methylated SEPT9 and ctDNA, show moderate sensitivity (60–75%) but provide unique value in MRD detection and recurrence monitoring. Combination strategies integrating stool and blood biomarkers improve diagnostic yield. However, limitations include variability across populations, high cost, limited access in low- and middle-income countries (LMICs), and lack of assay standardization. Stool- and blood-based biomarkers are important complements to colonoscopy, enhancing CRC detection and surveillance while improving patient compliance. FIT remains the most cost-effective for large-scale screening, while ctDNA coupled with standardization and global accessibility efforts, could transform CRC prevention and management. Wider implementation of biomarkers in risk-stratified screening, investment in cost-effective approaches for LMICs, assay standardization, and adoption of multi-omics innovations are essential for equitable global CRC care.

Keywords: Biomarkers, Blood-based biomarkers, Circulating tumor DNA (ctDNA), Colorectal cancer, Early detection, Fecal immunochemical test (FIT), Stool DNA, Methylated SEPT9, Minimal residual disease (MRD), Non-invasive screening

INTRODUCTION

Colorectal cancer (CRC) is one of the most significant public health concerns worldwide. It ranks among the top three most frequently diagnosed malignancies and remains a leading cause of cancer-related mortality, with the global burden projected to rise further as populations age and adopt increasingly Westernized lifestyles [1,2]. While incidence rates have historically been highest in

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high-income countries, recent data show rapid increases in many low- and middle-income regions, including parts of Africa [3]. Moreover, a disturbing trend of early-onset CRC (diagnosis before the age of 50 years) has been reported in several countries, adding complexity to existing screening strategies [4].

Early detection substantially reduces CRC mortality, as removal of premalignant polyps interrupts progression to invasive disease and earlier-stage cancers have more favorable outcomes. Colonoscopy remains the reference standard for detection and prevention because it allows direct visualization, biopsy, and polypectomy during the same procedure [5]. However, despite its strengths, colonoscopy has important limitations. Evidence from systematic reviews indicates that conventional white-light colonoscopy may miss up to one in three adenomas, particularly flat and diminutive lesions, which contributes to the occurrence of interval cancers [6].

Beyond performance issues, colonoscopy is resource intensive, requiring endoscopy suites, skilled personnel, and pathology support. It is also associated with low but clinically relevant risks of adverse events such as bleeding, perforation, and sedation-related complications [7,8]. These risks are accentuated in older individuals and those undergoing therapeutic procedures. Furthermore, patient acceptability is limited by bowel preparation, perceived invasiveness, and logistical barriers, leading to suboptimal participation even in countries with established screening programs [9]. In many low- and middle-income countries, including much of sub-Saharan Africa, limited infrastructure and workforce shortages further restrict access to colonoscopy-based screening [10].

Histopathology, though indispensable as the diagnostic reference, is reliant on invasive sampling and thus cannot be scaled for primary population screening. Taken together, these limitations highlight the need for accurate, cost-effective, and non-invasive biomarkers to complement colonoscopy. Stool- and blood-based assays have emerged as promising alternatives, capable of expanding screening coverage, improving early detection, and facilitating non-invasive disease monitoring, including detection of minimal residual disease (MRD) and recurrence [11].

Stool-Based Biomarkers

Stool-based biomarkers represent the most widely adopted non-invasive approach for colorectal cancer (CRC) detection. Because colorectal neoplasia sheds DNA, proteins, and blood products into the intestinal lumen, stool analysis provides a convenient, repeatable, and population-level screening option. Several stool-based tests are currently in clinical use or under investigation, including fecal occult blood tests, fecal DNA assays, and microbiome-derived markers.

Faecal Occult Blood Tests (FOBT): FOBTs remain the cornerstone of stool-based CRC screening. The guaiac-based test (gFOBT), one of the earliest methods, detects peroxidase activity of hemoglobin but has limited sensitivity for adenomas and early-stage cancers, in addition to being affected by dietary and medication interference [12]. The fecal immunochemical test (FIT) has largely replaced gFOBT in high-resource settings due to its greater sensitivity, improved specificity, and ease of use. FIT specifically detects human hemoglobin using monoclonal antibodies, thereby reducing dietary false positives and allowing quantitative threshold adjustment [13]. Large population-based trials have demonstrated FIT to have sensitivities of 70–80% for CRC and 25–40% for advanced adenomas [14]. Despite these advantages, FIT performance varies by lesion size, location, and patient adherence, and it requires repeated periodic testing to maintain effectiveness [15].

Fecal DNA Testing: Molecular stool testing has expanded the biomarker spectrum beyond hemoglobin detection. Neoplastic cells exfoliated into stool can be interrogated for genetic and epigenetic alterations. The most widely validated test is the multi-target stool DNA assay (mt-sDNA, e.g., Cologuard®), which combines FIT with assays for KRAS mutations, aberrant methylation of NDRG4 and BMP3, and β-actin as a reference gene [16]. In a pivotal multicenter trial, mt-sDNA achieved a sensitivity of 92.3% for CRC and 42.4% for advanced adenomas, outperforming FIT alone,

although with slightly reduced specificity [17].

Epigenetic markers, particularly DNA methylation, are increasingly recognized as promising stool biomarkers. Hypermethylation of genes such as SEPT9, SDC2, and VIM has been consistently associated with CRC [18,19]. Commercial assays detecting methylated SDC2 and VIM in stool samples have demonstrated sensitivities of 80–90% for CRC with high specificity, though performance in detecting advanced adenomas remains moderate [20].

Microbiome-Based Biomarkers: The gut microbiome plays an important role in CRC pathogenesis through mechanisms involving inflammation, metabolism, and genotoxicity. Advances in metagenomic sequencing have enabled stool-based microbial signatures to be evaluated as diagnostic markers. Studies have shown enrichment of Fusobacterium nucleatum, Peptostreptococcus anaerobius, and Parsimonies micra in CRC patients compared with controls [21]. Integrating microbial signatures with FIT has been reported to significantly improve sensitivity for adenoma detection [22]. While promising, microbiome-based assays face challenges including variability across populations, technical complexity, and lack of standardization.

Advantages and Limitations

Stool-based biomarkers offer substantial advantages: they are non-invasive, relatively inexpensive, and suitable for repeated large-scale population screening. However, challenges remain in optimizing sensitivity for advanced adenomas, ensuring compliance with repeated testing, and establishing uniform diagnostic thresholds across diverse populations. Emerging multi-target stool assays and integration with microbial markers may provide a more comprehensive approach to non-invasive CRC screening.

Blood-Based Biomarkers

Blood-based biomarkers for colorectal cancer (CRC) have gained considerable attention as minimally invasive alternatives to colonoscopy and stool testing. These "liquid biopsy" approaches offer opportunities not only for screening but also for disease monitoring, prognostication, and detection of minimal residual disease (MRD). The main categories include circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), protein markers, and multi-analyte blood-based assays.

Circulating Tumor DNA (ctDNA): Fragments of tumor-derived DNA can be detected in plasma and analyzed for genetic and epigenetic alterations. The methylated SEPT9 (mSEPT9) assay is the most widely validated ctDNA biomarker for CRC. Multiple clinical studies and meta-analyses have shown sensitivities of 48–72% for CRC, with specificity exceeding 90% [23,24]. Although sensitivity for advanced adenomas remains low (<20%), mSEPT9 testing has been approved for CRC screening in some jurisdictions [25]. Beyond screening, ctDNA assays can detect minimal residual disease after curative resection and predict recurrence earlier than imaging, making them powerful tools for disease monitoring [26,27].

Circulating Tumor Cells (CTCs): CTCs are malignant cells shed into the bloodstream from primary tumors or metastases. Their detection relies on immunoaffinity-based enrichment (e.g., EpCAM antibodies) or size-based separation. Although CTCs have limited sensitivity for early-stage CRC, they are useful as prognostic markers in advanced disease. Studies show that higher CTC counts are associated with poor survival outcomes and treatment resistance [28,29]. Current limitations include technical variability, low abundance in early CRC, and lack of standardized detection platforms [30].

Protein Biomarkers: Carcinoembryonic antigen (CEA) is the most widely used serum biomarker in CRC, mainly for postoperative surveillance rather than screening, as its sensitivity and specificity for early detection are suboptimal [31]. CA19-9 has limited standalone value but may complement CEA in metastatic settings [32]. Recent advances have led to development of multi-analyte protein panels incorporating markers such as TIMP-1, AREG, and MIC-1, which demonstrate improved diagnostic performance over single-analyte tests [33].

Multi-Analyte Blood Tests and Emerging Approaches: The evolution of high-throughput sequencing and bioinformatics has enabled integration of multiple biomarker classes. Assays combining ctDNA mutations, methylation, fragmentomics, and protein biomarkers have shown high accuracy in detecting multiple cancers, including CRC [34]. Multi-cancer early detection (MCED) platforms such as Galleri® utilize cfDNA methylation profiling and are being evaluated in large population-based trials [35]. While promising, cost, scalability, and need for real-world validation remain barriers to routine clinical application.

Advantages and Limitations

Blood-based biomarkers are minimally invasive, acceptable to patients, and suitable for serial monitoring. They provide complementary value to stool-based tests and colonoscopy, especially for MRD detection and surveillance. However, their sensitivity for adenomas and early-stage CRC remains suboptimal, costs are relatively high, and technical variability limits widespread adoption. Large-scale trials and standardization are required before routine implementation in population-level screening programs.

Clinical Utility and Comparative Effectiveness

The translation of stool- and blood-based biomarkers from research to clinical practice hinges on their diagnostic accuracy and ability to complement or substitute colonoscopy. Biomarker tests are increasingly assessed not only by sensitivity and specificity but also by predictive values, patient acceptability, and feasibility for integration into large-scale screening programs.

Sensitivity, Specificity, and Predictive Values versus Colonoscopy: Colonoscopy remains the gold standard for CRC detection, with sensitivities exceeding 95% for invasive cancer and 85–90% for advanced adenomas [36]. However, its invasiveness, cost, and requirement for bowel preparation limit uptake. Stool-based fecal immunochemical testing (FIT) demonstrates sensitivity of 70–80% for CRC and 25–40% for advanced adenomas, with specificity around 90% [37]. Multi-target stool DNA (mt-sDNA) tests improve sensitivity to approximately 92% for CRC and 42% for advanced adenomas, though specificity declines to about 87% [38].

In comparison, blood-based methylated SEPT9 (mSEPT9) testing yields a sensitivity of 60–75% and specificity around 90% [39]. While colonoscopy still outperforms biomarker assays in sensitivity for precancerous lesions, biomarker-based approaches enhance compliance and are valuable for individuals who decline colonoscopy. (Figures 1 and 2)

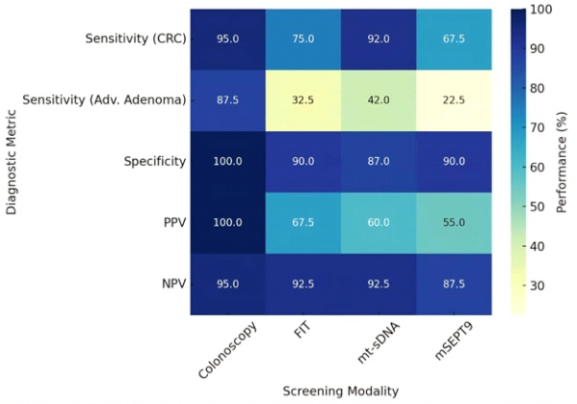

Figure 1: Diagnostic Performance of Colonoscopy and Biomarker -Based Tests for Colorectal Cancer Detection

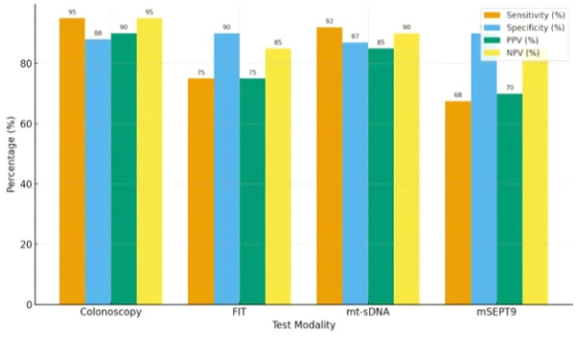

Figure 2: Sensitivity, Specificity, and Predictive Values versus Colonoscopy

Sensitivity and specificity values adapted from recent clinical studies [36-39]. Predictive values (PPV, NPV) approximated assuming 5% CRC prevalence in screening populations. Colonoscopy remains the reference standard, while stool- and blood-based assays improve accessibility and compliance.

Stool-based tests such as FIT and mt-sDNA are particularly suited for population-level CRC screening given their non-invasiveness and relatively high adherence rates [38]. FIT is widely

adopted in national screening programs due to its affordability and logistical feasibility [39]. Blood-based tests, particularly ctDNA, are emerging as tools not only for screening but also for post-treatment surveillance. Detection of ctDNA after surgery is strongly associated with recurrence, with reported lead times of 8–12 months compared to imaging or CEA monitoring [40]. This capacity for minimal residual disease (MRD) detection positions ctDNA as a transformative marker in longitudinal cancer care.

Combination Strategies

Evidence suggests that combining stool and blood biomarkers can improve diagnostic performance. For example, pairing mt-sDNA with blood-based methylation panels or protein biomarkers may offset limitations of single-test strategies [41]. Hybrid approaches integrating stool DNA, FIT, and ctDNA are under evaluation in prospective trials, with preliminary data indicating higher sensitivity without substantial loss in specificity [42]. Such multimodal biomarker strategies are expected to be particularly beneficial in personalized screening algorithms and risk-adapted surveillance.

Future Perspectives:

The field of colorectal cancer (CRC) biomarker research continues to evolve, with stool- and blood-based assays showing increasing promise as complementary or alternative tools to colonoscopy. As evidence accumulates, several trends and opportunities are shaping the future of CRC screening, surveillance, and personalized management.

Integration into Risk-Stratified Screening Programs: Biomarker-based tests are likely to be incorporated into stratified screening strategies tailored to individual risk profiles. Combining stool DNA, FIT, and ctDNA assays with clinical risk factors and family history may enhance early detection while optimizing resource allocation [43].

Technological Advances and Multi-Omics Approaches: Emerging technologies such as next-generation sequencing (NGS), digital PCR, and machine learning–assisted biomarker discovery are refining diagnostic accuracy [44]. Multi-omics integration—combining genomics, epigenomics, transcriptomics, and proteomics—offers the potential for highly sensitive, non-invasive assays that capture the full molecular heterogeneity of CRC[45].

Liquid Biopsy and MRD Monitoring: ctDNA assays are moving beyond screening to play a pivotal role in minimal residual disease (MRD) detection and longitudinal monitoring. Several ongoing clinical trials are investigating ctDNA-guided adjuvant therapy decisions, which could reduce overtreatment and improve patient outcomes [46].

Global and Resource-Sensitive Adoption: In high-income countries, novel biomarker assays are increasingly available; however, their implementation in low- and middle-income countries (LMICs) remains limited by cost and infrastructure. Adaptation of low-cost stool-based tests like FIT, with incremental introduction of blood biomarkers, could provide an equitable path forward[47]

CONCLUSION

Stool- and blood-based biomarkers have emerged as important innovations in colorectal cancer detection and management. While colonoscopy remains the gold standard, biomarkers provide non-invasive, acceptable, and scalable alternatives that improve screening uptake, enable post-treatment surveillance, and open avenues for personalized oncology. Stool-based tests such as FIT and multitarget stool DNA assays show high sensitivity for CRC, whereas blood-based assays, including ctDNA and methylated SEPT9, hold promise for MRD monitoring and early recurrence detection. Challenges remain in assay standardization, cost-effectiveness, and equitable access across populations. Nevertheless, the integration of these biomarkers into multimodal strategies, supported by technological advances and global collaboration, will likely transform CRC prevention and care in the coming decade.

RECOMMENDATIONS

Risk-Stratified Screening: Incorporate stool- and blood-based biomarkers such as mt-sDNA, FIT, and mSEPT9 into national screening programs as

adjuncts to colonoscopy, especially for individuals unable or unwilling to undergo colonoscopy.

Post-Treatment Surveillance & MRD: Use circulating tumor DNA (ctDNA) testing to detect minimal residual disease and monitor recurrence, offering greater prognostic accuracy than traditional markers like CEA or imaging.

Cost-Effectiveness in LMICs: Prioritize affordable and scalable tools like FIT in low- and middle-income countries, with phased adoption of advanced biomarkers based on local cost-effectiveness and infrastructure capacity.

Standardization & Regulation: Establish harmonized testing protocols, biomarker thresholds, and global guidelines; streamline regulatory approvals to accelerate clinical integration.

Multimodal Approaches: Combine stool, blood, and clinical risk data into integrated diagnostic algorithms to enhance sensitivity and specificity while minimizing false positives.

Research & Multi-Omics: Promote large, multicenter validation studies and develop multi-omics biomarker panels (genomic, epigenomic, transcriptomic, proteomic) to better address tumor heterogeneity.

Equity & Collaboration: Foster global equity in CRC screening through public–private partnerships, capacity building, and technology transfer to reduce disparities in detection and outcomes.

Conflict of interest

There are no conflicts of interest.

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