

PERSPECTIVE ARTICLE

The molecular revolution in colorectal cancer screening: Towards earlier, smarter, and noninvasive detection

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Abstract

Colorectal cancer (CRC) remains a leading cause of cancer-related morbidity and mortality worldwide, with many cases still diagnosed at advanced stages despite being largely preventable through early screening. Conventional screening approaches, such as colonoscopy and fecal occult blood testing, are effective but limited by invasiveness, low compliance, and suboptimal sensitivity for early-stage disease, underscoring the need for more precise and acceptable alternatives. Recent advances in molecular diagnostics have enabled the detection of cancer-associated genetic and epigenetic alterations, including mutations in APC, KRAS, BRAF, and TP53, as well as microsatellite instability and aberrant DNA methylation, which may be detectable years before clinical manifestation of disease. Emerging technologies such as liquid biopsy and multitarget stool DNA testing are transforming CRC screening by providing minimally invasive approaches with improved diagnostic performance. These advances are further supported by next-generation sequencing, multiplex polymerase chain reaction, artificial intelligence, and machine learning, which enable the identification of complex biomarker patterns that were previously inaccessible. Several molecular assays have already received regulatory approval and show strong clinical utility, particularly in populations less likely to undergo invasive procedures. However, important challenges persist, including false-positive and false-negative results, high cost, lack of standardization, and ethical concerns related to data privacy, particularly in resource-limited settings. As the field advances toward precision prevention, integrating individualized risk profiling with molecular screening strategies may improve diagnostic accuracy and patient outcomes. Ultimately, the success of molecular CRC screening will depend not only on technological innovation but also on ensuring equitable access, affordability, and patient trust. In this perspective, we highlight the molecular revolution in CRC screening, emphasizing how modern technologies have enhanced the speed, accuracy, and uptake of screening strategies. While traditional methods are hindered by limited patient compliance and diagnostic performance, the integration of advanced molecular diagnostics (including liquid biopsies and multitarget DNA testing) is reshaping early detection. Nevertheless, the full potential of this “molecular revolution” will only be realized by addressing barriers related to cost, standardization, and global health equity.

Keywords: Colorectal cancer; Molecular diagnostics; Liquid biopsy; Stool DNA testing; Early cancer detection; Epigenetic biomarkers; Precision screening

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1. Introduction: The imperative for better detection

Colorectal cancer (CRC) remains one of the leading causes of cancer-related morbidity and mortality worldwide. Despite being largely preventable through early detection, many cases are still diagnosed at advanced stages. Traditional screening methods such as colonoscopy and fecal occult blood testing have proven valuable; however, their limitations—such as invasiveness, low compliance, and reduced sensitivity for early lesions—highlight the urgent need for more precise, accessible, and patient-friendly tools. In this context, molecular detection technologies are redefining the future of CRC screening by identifying cancer-associated genetic and epigenetic signatures long before clinical symptoms appear.¹ The emergence of molecular detection technologies is particularly encouraging, as it addresses long-standing barriers associated with conventional screening approaches that are often avoided due to discomfort or inconvenience, thereby contributing to delayed diagnosis and missed opportunities for early intervention. The idea that a simple blood or stool test could reveal the earliest signs of cancer, quietly, accurately, and without discomfort, is a major step forward not only for medicine but for patients everywhere. It is also a reminder that progress in healthcare is not just about science; it is about dignity, choice, and giving people better ways to protect their lives. This perspective highlights the molecular revolution in colorectal cancer

screening, focusing on how modern technologies have enhanced speed, accuracy, and uptake.

2. The molecular basis of colorectal cancer detection

At the molecular level, CRC is a heterogeneous disease driven by a series of well-characterized genetic and epigenetic alterations. Mutations in *APC*, *KRAS*, *BRAF*, and *TP53*, along with microsatellite instability and aberrant DNA methylation, serve as critical biomarkers of tumorigenesis^{2,3} (Table 1). These molecular footprints are detectable in stool, blood, and other body fluids, forming the foundation for modern molecular diagnostics. The concept is straightforward yet transformative: instead of waiting for morphological changes, clinicians can now detect CRC by identifying its molecular traces, sometimes years before tumors become visible through imaging or colonoscopy⁴ (Table 2). This advancement underscores how far scientific understanding has progressed in decoding the body’s biological signals. Each mutation, each epigenetic change, indicates (at the molecular level) how cells lose their balance and begin to behave abnormally. Molecular signals associated with disease progression were previously undetectable, hidden within complex biological systems. Advances in molecular diagnostics enable their detection, often long before clinical disease becomes apparent. This shift highlights a fundamental transformation in early detection strategies, from reliance on visual inspection

Table 1. Mutations in key genes that serve as biomarkers for tumorigenesis

Mutation	Key findings and codons	Role in progression	Relation to other mutations
<i>TP53</i>	Mostly in “hot spot” codons; transitions in cytosine–phosphate–guanine dinucleotides.	Central role in progression; frequency increases with Dukes’ stage.	Often inversely correlated with <i>KRAS</i> .
<i>KRAS</i>	High percentage at codon 12; low at codon 13 or 61.	Does not appear to be related to tumor stage/progression.	Inversely related to <i>BRAF</i> mutation and <i>TP53</i> alteration.
<i>BRAF</i>	Very low frequency in sporadic cases.	Potential alternative pathway for cell transformation.	Associated with microsatellite instability; it rarely co-exists with <i>KRAS</i> or <i>TP53</i> .
<i>APC</i>	Conceptualized as a central “gatekeeper.”	Involved in the initial adenoma-to-cancer transition.	Part of the fundamental triad with <i>KRAS</i> and <i>TP53</i> .

Note: The table was generated using data published by Calistri et al.⁵

Table 2. Comparison between conventional and molecular methodologies in colorectal cancer screening

Feature	Conventional (colonoscopy/fecal occult blood testing)	Molecular (liquid biopsy/stool DNA testing)
Invasiveness	High (colonoscopy)	Low (minimally invasive)
Compliance	Lower due to discomfort	Higher (patient-friendly)
Sensitivity	Varies (can miss early lesions)	High for genetic/epigenetic markers
Key targets	Visible lesions/occult blood	<i>APC</i> , <i>KRAS</i> , <i>BRAF</i> mutations; DNA methylation

via endoscopy to molecular interrogation of minimally invasive samples such as blood or stool. Collectively, this shift represents hope, hope that knowledge at the molecular level can truly save lives through earlier and more compassionate intervention.

3. Emerging technologies in molecular detection

Recent years have witnessed remarkable innovations in noninvasive CRC detection technologies. Liquid biopsy, which analyzes circulating tumor DNA and circulating tumor cells in blood, is revolutionizing early cancer diagnostics by providing real-time, minimally invasive insights into tumor biology and evolution.⁶ Similarly, stool DNA testing has gained prominence through multitarget assays such as Cologuard, which combine mutation and methylation markers to improve sensitivity compared with standard fecal occult blood testing.^{7,8}

Beyond genetic alterations, epigenetic biomarkers are showing considerable diagnostic promise. Methylated genes such as *SEPT9*, *NDRG4*, and *BMP3* have demonstrated clinical utility, with methylated *SEPT9* already incorporated into Food and Drug Administration-approved blood-based assays.⁹ In parallel, advances in next-generation sequencing and multiplex polymerase chain reaction technologies have enabled simultaneous detection of multiple biomarkers, thereby improving both sensitivity and specificity.¹⁰ When integrated with artificial intelligence and machine learning (Figure 1), these platforms are increasingly capable of identifying complex molecular patterns that were previously undetectable using conventional bioinformatics approaches.¹¹ Reading about the published new technologies in CRC detection fills scientists with both awe and optimism. The idea that a simple blood test could pick up tiny fragments of tumor DNA, or that stool tests can now detect multiple cancer signals at once, feels almost like science fiction—but it is real and happening today. These innovations are not just technical achievements; they can change how people experience screening. Patients no longer need to fear or be uncomfortable about getting tested. These tools are a reminder that progress in medicine is deeply personal: it can transform anxiety into empowerment, giving people an early chance to fight a disease that has taken too many lives for too long. However, several impediments can hinder the successful implementation of these newer diagnostic technologies. First, many rural health facilities lack the infrastructure to perform advanced molecular testing regularly, resulting in continued reliance on traditional diagnostic methods with lower sensitivity and delayed detection. Second, the effective deployment of these

technologies requires adequately trained personnel, and shortages of skilled staff may further constrain adoption. Strengthening workforce capacity through equitable training and deployment strategies could help address this challenge. Third, cost remains a significant barrier, particularly in low-income and resource-limited settings, where out-of-pocket expenses may deter individuals from participating in routine screening. Without appropriate cost-reduction strategies or reimbursement mechanisms, equitable access to molecular diagnostics may be compromised.

4. Clinical translation and screening impact

Molecular tests are gradually transitioning from research settings to clinical practice. Several have gained regulatory approval and are being incorporated into national screening programs.¹² Compared to colonoscopy, molecular assays offer a noninvasive, more acceptable alternative, especially for populations with low adherence to invasive procedures. Studies have shown that multitarget stool DNA testing achieves sensitivities of over 90% for CRC detection, surpassing traditional fecal immunochemical tests.⁸ Moreover, the adaptability of liquid biopsy allows for longitudinal disease monitoring, recurrence detection, and even evaluation of treatment response—bridging diagnostics with precision oncology.¹³ One of the most important aspects of the clinical impact of these molecular tests is how they bring science directly to the people who need it. Knowing that a simple, noninvasive test can catch colorectal cancer early—and that it is becoming part of actual screening programs—feels incredibly empowering. It is no longer just about detecting cancer in a lab; it is about giving individuals real, actionable knowledge about their health. Collectively, this raises our hope that more lives can be saved, especially in communities where traditional screening is difficult or intimidating. It is a reminder that medical innovation is not just about technology—it is about accessibility, trust, and improving patient experiences.

5. Challenges and unresolved questions

Despite these achievements, key challenges remain. False-positive and false-negative results continue to pose clinical dilemmas, partly due to tumor heterogeneity and technical variability. Standardization of assays across laboratories remains limited, complicating cross-study comparisons.¹⁴ Additionally, the cost and infrastructure requirements of advanced molecular diagnostics limit their scalability, particularly in low- and middle-income countries where CRC incidence is rising.¹⁵ Ethical concerns around genomic data privacy and patient consent also warrant ongoing attention as molecular screening becomes more widespread.¹⁶ While the promise of molecular testing

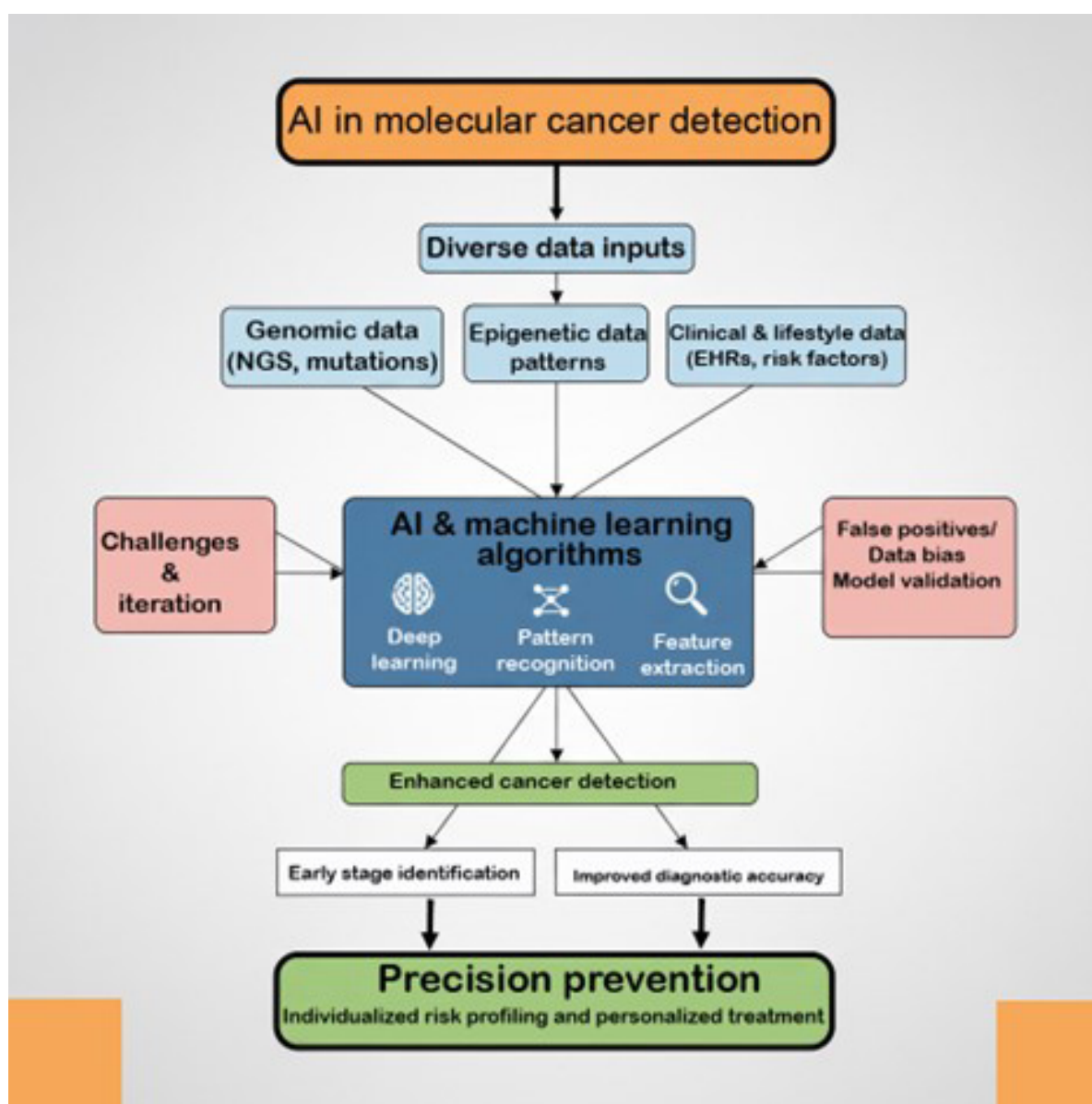


Figure 1. Integration of AI in molecular detection of colorectal cancer. Image created by the authors.

Abbreviations: AI: Artificial intelligence; EHRs: Electronic health records; NGS: Next-generation sequencing.

is exciting, it is important to pause and reflect on the challenges that come with it. False positives or negatives, high costs, and limited access in certain regions are a reminder that innovation alone is not enough. There is a human side to these obstacles, including patients who might be anxious, confused, or unable to afford these tests. This highlights the need for medical progress to advance in parallel with equity, education, and careful implementation. For scientists, acknowledging these challenges is not discouraging; it is a call to action to ensure that breakthroughs benefit everyone, not just those with resources or proximity to advanced healthcare centers.

6. The road ahead: Precision prevention and early detection

The next frontier in CRC detection lies in precision prevention, premised on tailoring screening intervals and methods based on individual molecular risk profiles. Integration of molecular biomarkers with artificial intelligence-driven predictive models could allow truly personalized screening strategies, optimizing resource allocation and patient outcomes. Continued interdisciplinary collaboration among molecular biologists, clinicians, and data scientists will be essential to translate these advances into equitable public health benefits.

Looking ahead, there is a genuine sense of hope about what precision prevention could mean for CRC. The idea that screening could be tailored to an individual's molecular profile feels deeply empowering, i.e., it is not just science for science's sake, but science that respects each person's unique risk. It is inspiring to imagine a world where people no longer have to endure a one-size-fits-all approach, but instead benefit from screening that is smarter, faster, and more predictive. It is a reminder to the scientific community that the true impact of innovation lies in its ability to improve lives in meaningful, personalized ways.

The molecular revolution in CRC screening represents more than a technological breakthrough. It is a paradigm shift in preventive oncology. Molecular assays are not replacing traditional methods but complementing them, offering earlier, smarter, and more patient-centered detection. As the world moves towards an era of precision medicine, the ultimate success of molecular screening will depend not only on scientific innovation but also on ensuring accessibility, affordability, and trust in these transformative technologies.

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Conflict of interest

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References

1. Qi G, Zhao R, Gao C, *et al.* Recent advances and challenges in colorectal cancer: From molecular research to treatment. *World J Gastroenterol.* 2025;31(21):106964.
doi: 10.3748/wjg.v31.i21.106964
2. Takeda M, Yoshida S, Inoue T, *et al.* The role of KRAS mutations in colorectal cancer: Biological insights, clinical implications, and future therapeutic perspectives. *Cancers.* 2025;17(3):428.
doi: 10.3390/cancers17030428
3. Malapelle U, Angerilli V, Intini R, *et al.* Detecting BRAF mutations in colorectal cancer in clinical practice: An Italian experts' position paper. *Crit Rev Oncol Hematol.* 2025;206(2025):104574.
doi: 10.1016/j.critrevonc.2024.104574
4. Dang Q, Zuo L, Hu X, *et al.* Molecular subtypes of colorectal cancer in the era of precision oncology: Current inspirations and future challenges. *Cancer Med.* 2024;13(14):e70041.
doi: 10.1002/cam4.70041
5. Calistri D, Rengucci C, Seymour I, Lattuneddu A, Polifemo AM, Monti F, Saragoni L, Amadori D. Mutation analysis of p53, K-ras, and BRAF genes in colorectal cancer progression. *J Cell Physiol.* 2005;204(2):484-488.
doi: 10.1002/jcp.20310
6. Cohen J. D, Li L, Wang Y, *et al.* Detection and localization of surgically resectable cancers with a multi-analyte blood test. *Science.* 2018;359(6378):926-930.
doi: 10.1126/science.aar3247
7. Imperiale T. F, Ransohoff D. F, Itzkowitz S. H, *et al.* Multitarget stool DNA testing for colorectal-cancer screening. *New Engl J Med.* 2014;370(14):1287-1297.
doi: 10.1056/NEJMoa1311194
8. Rex D. K, Boland C. R, Dominitz J. A, *et al.* Colorectal cancer screening: Recommendations for physicians and patients from the U.S. Multi-Society Task Force on Colorectal Cancer. *Am J Gastroenterol.* 2017;112(7):1016-1030.
doi: 10.1038/ajg.2017.189
9. Song L, Jia J, Peng X, *et al.* The performance of the SEPT9 gene methylation assay and a comparison with other CRC screening tests: A meta-analysis. *Sci Rep.* 2017;7(1):3032.
doi: 10.1038/s41598-017-03321-8
10. Afolabi H.A, Salleh S.M, Zakaria Z, *et al.* Molecular characterization of Colorectal cancer (CRC) using next generation sequencing (NGS) in bridging the gap between research and clinical practice: from biomarker discovery to clinical implementation. *Discov Oncol.* 2025;16,268.
doi: 10.1007/s12672-025-01960-2

11. Zheng R, Su R, Fan Y, *et al.* Machine learning-based integrated multiomics characterization of colorectal cancer reveals distinctive metabolic signatures. *Anal Chem.* 2024;96(21):8772-8781.
doi: 10.1021/acs.analchem.4c01171
12. Tufail M, Jiang CH, & Li N. Wnt signaling in cancer: from biomarkers to targeted therapies and clinical translation. *Mol Cancer.* 2025;24:107.
doi: 10.1186/s12943-025-02306-w
13. Wan J. C. M, Massie C, Garcia-Corbacho J, *et al.* Liquid biopsies come of age: Towards implementation of circulating tumour DNA. *Nat Rev Cancer.* 2017;17(4):223-238.
doi: 10.1038/nrc.2017.7
14. Stecko H, Tsilimigras T.I, Iyer S, *et al.* Comprehensive assessment of genomic heterogeneity, coalterations, and outcomes of patients with colorectal cancer: An AACR GENIE Project analysis. *Surgery.* 2025;185:109475.
doi: 10.1016/j.surg.2025.109475
15. Elbarazi I, Ahmed LA. Alleviating the global burden of cancer through prevention and early detection. *Cancer Control.* 2025;32.
doi: 10.1177/10732748251378666
16. Ghoreyshi N, Heidari R, Farhadi A, *et al.* Next-generation sequencing in cancer diagnosis and treatment: clinical applications and future directions. *Discov Oncol.* 2025;16:578.
doi: 10.1007/s12672-025-01816-9