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EARLY DETECTION OF COLORECTAL CANCER: THE ROLE OF MOLECULAR AND BIOCHEMICAL BIOMARKERS

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Abstract

Early detection of colorectal cancer includes identifying asymptomatic malignancy and precancerous lesions. This short narrative review examines the clinical role and limitations of biochemical and molecular biomarkers. Fecal hemoglobin is an established screening marker, whereas conventional serum tumor markers have limited diagnostic value in asymptomatic populations. Stool DNA and RNA assays can improve sensitivity by combining molecular signals with hemoglobin testing. Blood-based cell-free DNA tests provide another screening option but detect relatively few advanced precancerous lesions. Biomarker testing should therefore be integrated with appropriate patient selection and timely colonoscopy after a positive result.

Keywords: Colorectal cancer; early detection; biomarkers; fecal immunochemical test; stool DNA; cell-free DNA.

Clinical background

Colorectal cancer screening aims to identify early malignancy and lesions that can be removed before invasive cancer develops. Colonoscopy permits direct examination and tissue sampling, but preparation requirements and invasiveness can discourage participation. Noninvasive biomarkers offer alternative initial tests. Their value depends not only on detecting existing cancer but also on identifying precancerous lesions and ensuring completion of further investigation [1].

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Biochemical biomarkers

The fecal immunochemical test (FIT) detects human hemoglobin in stool using antibodies. It can be performed at home without bowel preparation or dietary restrictions. However, it measures bleeding rather than a cancer-specific alteration, and a negative result does not exclude colorectal neoplasia. Repeated testing at recommended intervals is essential [1].

Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are unsuitable as stand-alone screening tests. Their limited sensitivity for early disease and elevations unrelated to cancer reduce their usefulness in asymptomatic individuals. CEA is more relevant to monitoring established colorectal cancer than to population screening. A study of asymptomatic adults confirmed the poor screening performance of both serum markers [2].

Molecular biomarkers in stool

Multitarget stool DNA assays combine tumor-associated DNA markers, including abnormal methylation patterns, with fecal hemoglobin testing. In the BLUE-C study of 20,176 participants, a next-generation assay detected 93.9% of colorectal cancers and 43.4% of advanced precancerous lesions. The corresponding sensitivities for FIT were 67.3% and 23.3%. However, specificity among participants without advanced neoplasia was lower for the DNA assay than for FIT: 90.6% versus 94.8%. Thus, improved detection came with more false-positive results [3,4].

RNA-based stool testing provides another approach. In the CRC-PREVENT trial, an assay combining eight RNA transcripts, FIT, and smoking status achieved 94% sensitivity for colorectal cancer and 46% for advanced adenomas; specificity was 88% among participants with no lesions on colonoscopy [5]. These results should not be directly ranked against other trials because populations and lesion definitions differ.

Blood-based biomarkers and clinical implications

Cell-free DNA assays identify cancer-associated changes in circulating DNA, such as abnormal methylation and fragmentation patterns [3]. In the ECLIPSE study, involving 7,861 evaluable participants, a blood-based assay achieved 83.1% sensitivity for colorectal cancer and 89.6% specificity among those without advanced neoplasia. However, sensitivity for advanced

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precancerous lesions was only 13.2% [6]. The overall cancer sensitivity should not be interpreted as sensitivity for stage I cancer alone.

The 2026 American Cancer Society guideline includes stool DNA and RNA tests among preferred screening options, while reserving blood-based tests for individuals who decline or do not complete preferred methods. A positive stool or blood test requires follow-up colonoscopy. For newer molecular assays, single-round diagnostic accuracy does not itself establish long-term reductions in mortality; repeated-round performance, adherence, affordability, and access to colonoscopy remain important [3].

Conclusion

Molecular biomarkers have expanded noninvasive colorectal cancer screening, particularly through combined stool DNA or RNA and hemoglobin testing. FIT remains an established option, whereas conventional serum tumor markers are not recommended for screening. Blood-based assays offer an alternative for selected individuals, but their limited detection of precancerous lesions must be clearly recognized [1,2,3].

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