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Advances and Ongoing Challenges in Colorectal Cancer

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Rezumat

Progrese și provocări actuale în cancerul colorectal

Cancerul colorectal (CRC) rămâne o problemă majoră de sănătate publică la nivel global, cu o incidență în creştere în rândul adulților tineri şi o mortalitate persistent ridicată în stadiile avansate, în pofida progreselor ştiințifice şi tehnologice semnificative. Etiologia sa este multifactorială, implicând factori de stil de viață, susceptibilitate genetică, inflamație cronică şi disbioză a microbiomului intestinal. Progresele recente în screening, profilare moleculară, chirurgie şi terapii sistemice au remodelat semnificativ managementul cancerului colorectal. Acest review narativ a fost realizat printr-o căutare extensivă a literaturii în bazele de date PubMed/MEDLINE, Scopus şi Web of Science, acoperind publicații apărute în perioada ianuarie 2015 - iunie 2025. Au fost selectate articole evaluate ştiințific riguros care abordează epidemiologia CRC, mecanismele moleculare, strategiile de screening şi diagnostic, managementul chirurgical, terapiile sistemice şi modalitățile terapeutice emergente. Datele au fost sintetizate calitativ şi organizate în domenii tematice relevante clinic. Progresele recente în screeningul CRC, incluzând tehnici endoscopice avansate, testarea ADN-ului fecal şi biomarkerii serici, au îmbunătățit detectarea precoce, deşi implementarea acestora rămâne inegală. Caracterizarea moleculară, precum statusul MSI-H/dMMR, mutațiile RAS/RAF, amplificarea HER2 şi subtipurile moleculare de consens, ghidează evaluarea prognostică şi terapiile personalizate. Chirurgia rămâne piatra de temelie a tratamentului cu intenție curativă, tehnicile minim invazive şi robotice reducând morbiditatea, cu menținerea siguranței oncologice. Proceduri precum excizia mezocolică completă şi excizia totală a mezorectului, alături de strategiile multimodale pentru boala avansată, au extins opțiunile terapeutice. În ciuda acestor progrese, persistă provocări importante, incluzând rezistența terapeutică, heterogenitatea tumorală, eficacitatea limitată a imunoterapiei în tumorile cu stabilitate microsatelitară şi creşterea incidenței CRC cu debut precoce. Progresele viitoare se bazează pe medicina de precizie, monitorizarea ghidată de ctDNA, strategiile țintite asupra microbiomului şi optimizarea selecției chirurgicale.

Cuvinte cheie: cancer colorectal, mecanisme moleculare, screening şi diagnostic, chirurgia colorectala, terapii țintite

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Abstract

Colorectal cancer (CRC) remains a major global health concern, with a rising incidence among younger adults and persistently high mortality in advanced stages, despite significant scientific and technological progress. Its etiology is multifactorial, involving lifestyle factors, genetic susceptibility, chronic inflammation, and gut microbiome dysbiosis. Recent advances in screening, molecular profiling, surgery, and systemic therapies have substantially reshaped CRC management. This narrative review was conducted through a comprehensive literature search of PubMed/MEDLINE, Scopus, and Web of Science databases, covering publications from January 2015 to June 2025. Peer-reviewed articles addressing CRC epidemiology, molecular pathways, screening and diagnostic strategies, surgical management, systemic therapies, and emerging treatment modalities were selected. Evidence was qualitatively synthesized and organized into clinically relevant thematic domains. Recent progress in CRC screening, including advanced endoscopic imaging, fecal DNA testing, and blood-based biomarkers, has improved early detection, although implementation remains uneven. Molecular characterization – such as MSI-H/dMMR status, RAS/RAF mutations, HER2 amplification, and consensus molecular subtypes – guides prognostic assessment and personalized therapy. Surgical resection remains the cornerstone of curative-intent treatment, with minimally invasive and robotic approaches reducing morbidity while maintaining oncologic safety. Techniques such as complete mesocolic excision and total mesorectal excision, along with multimodal strategies for advanced disease, have expanded therapeutic options. Despite these advances, challenges persist, including therapeutic resistance, tumor heterogeneity, limited immunotherapy efficacy in microsatellite-stable disease, and rising early-onset CRC. Future progress relies on precision medicine, ctDNA-guided monitoring, microbiome-targeted strategies, and optimized surgical selection.

Keywords: colorectal cancer, molecular pathways, screening and diagnosis, colorectal surgery, targeted therapie

Introduction

Colorectal cancer is one of the most significant global health challenges, ranking among the leading causes of cancer incidence and mortality worldwide. Recent epidemiological evaluations indicate that CRC remains the third most commonly diagnosed malignancy and the second leading cause of cancer-related death (1). Of growing concern is the rising incidence of early-onset CRC, particularly among individuals under 50 years, a trend with multifactorial origins that remain incompletely understood (2). Moreover, CRC continues to impose a major socioeconomic burden on healthcare systems (3).

CRC develops through the interplay of lifestyle factors, genetic predispositions, chronic inflammation, and gut microbiome dysbiosis. Well-established risk factors include diets rich in processed meats, obesity, physical inactivity, alcohol consumption, and smoking, while hereditary syndromes such as Lynch syndrome contribute to a smaller but clinically important subset (4). Microbiome disturbances further accelerate carcinogenesis through inflammatory and metabolic pathways (5).

From a molecular perspective, CRC is a heterogeneous disease arising through several pathways, including the adenoma-carcinoma sequence, serrated pathway, and MSI-driven tumorigenesis. Advances in sequencing technologies have refined our understanding of key molecular alterations (KRAS, NRAS, BRAF, HER2 amplification, MMR deficiency) (4). Increasing evidence highlights the pivotal role of cancer stem cells (CSCs) in tumor initiation, metastasis, recurrence, and therapeutic resistance (6). CD34-positive stromal and progenitor cells may also modulate CSC behavior, angiogenesis, and tumor microenvironment remodeling, suggesting potential relevance in CRC biology despite not being a conventional diagnostic marker (7). The Consensus Molecular Subtypes (CMS) classification further enhances prognostic stratification and guides personalized therapy (8).

Substantial progress in screening and diagnostic technologies has improved early detection. Colonoscopy remains the gold standard, complemented by fecal immunochemical tests (FIT), multitarget stool DNA testing, and emerging liquid biopsy biomarkers (9). Advanced imaging tools such as narrow-band imaging and AI-assisted polyp detection have increased diagnostic accuracy (10). However, disparities in screening uptake across populations remain a critical barrier to timely diagnosis (11).

Therapeutically, CRC management relies on multidisciplinary and individualized approaches. Surgery remains the cornerstone of curative-intent treatment, with standardized techniques such as complete mesocolic excision and total mesorectal

excision improving oncologic outcomes (12). Minimally invasive and robotic approaches demonstrate reduced morbidity with preserved oncologic safety (13). Targeted therapies and immunotherapy have transformed systemic management, particularly in biomarker-selected populations (14). Circulating tumor DNA (ctDNA) is emerging as a valuable tool for detecting minimal residual disease and guiding treatment personalization (15). Despite these advancements, CRC management continues to face challenges, including therapeutic resistance, tumor heterogeneity, limited immunotherapy efficacy in microsatellite-stable tumors, and the rising incidence of early-onset disease (2,14). These unmet needs underscore the necessity for an updated synthesis of current knowledge.

Therefore, the aim of this review is to consolidate recent multidisciplinary progress, identify persisting challenges, and outline future research directions essential for improving outcomes in colorectal cancer.

Material and Methods

This manuscript was designed as a narrative review aiming to synthesize and critically discuss recent advances and persistent challenges in CRC, with a particular focus on epidemiology, molecular pathways, screening and diagnostic strategies, surgical management, systemic therapies, and emerging treatment modalities. Given the broad and multidisciplinary scope of the topic, a narrative review approach was considered the most appropriate to integrate evidence from heterogeneous study designs and rapidly evolving research fields.

A comprehensive literature search was conducted using the electronic databases PubMed/MEDLINE, Scopus, and Web of Science. The search covered publications from January 2015 to June 2025, in order to capture the most recent and clinically relevant developments in colorectal cancer research.

The search strategy combined Medical Subject Headings terms and free-text keywords, including but not limited to: "colorectal cancer", "colorectal carcinoma", "screening", "early detection", "molecular pathways", "Wnt signaling", "Notch", "Hedgehog", "Hippo/YAP", "cancer stem cells", "surgery", "total mesorectal excision", "complete mesocolic excision", "minimally invasive surgery", "robotic surgery", "systemic therapy", "targeted therapy", "immunotherapy", "circulating tumor DNA", and "emerging therapies". Additional articles were identified through manual screening of reference lists from key review articles and landmark studies.

Inclusion and Exclusion Criteria

Articles were included if they met the following criteria:

- Peer-reviewed publications written in English;
- Review articles, randomized controlled trials, observational studies, meta-analyses, and high-impact translational or experimental studies relevant to colorectal cancer;
- Studies addressing at least one of the predefined thematic domains: epidemiology and risk factors, molecular biology, screening and diagnostics, surgical techniques, systemic and targeted therapies, or emerging therapeutic approaches.

Exclusion criteria included:

- Case reports with limited generalizability;
- Conference abstracts without full-text availability;
- Articles not directly related to colorectal cancer or lacking clinical or biological relevance.

The selection of articles was performed by screening titles and abstracts for relevance, followed by full-text evaluation of eligible publications. Due to the narrative nature of the review, no formal quantitative synthesis or meta-analysis was undertaken. Instead, data were qualitatively synthesized and organized into thematic sections reflecting major domains of colorectal cancer research and clinical management.

The included studies were critically analyzed to highlight consensus findings, areas of controversy, and emerging concepts. Priority was given to recent high-quality evidence, international guidelines, and studies with significant clinical or translational impact.

This review does not follow a systematic review or PRISMA-based methodology and therefore does not aim to provide an exhaustive or statistically pooled analysis of the literature. Rather, it offers a structured, expert-driven synthesis intended to contextualize current knowledge, identify persistent challenges, and outline future research directions in colorectal cancer.

Epidemiology and Risk Factors

CRC incidence and mortality show substantial geo-

graphic and socioeconomic variation. Europe, Oceania, and North America consistently report the highest incidence rates, whereas Africa and the Eastern Mediterranean region have the lowest (16,17). These differences reflect disparities in screening implementation, dietary and lifestyle patterns, population aging, and socioeconomic development (18). Countries with very high human development index (HDI) values generally exhibit higher incidence but more stable or declining mortality trends, largely due to earlier detection and improved treatment (19-21). In contrast, many transitioning or middle-HDI countries – such as Brazil, Costa Rica, Colombia, Kuwait, and India – have experienced steady increases in CRC incidence over recent decades, paralleling shifts toward westernized diets and lifestyles (19,22).

Future projections indicate a pronounced rise in the global CRC burden, with new cases expected to increase by more than 60% by 2040. The largest relative increases are predicted for regions that currently have lower incidence, particularly Africa, Asia, and Latin America, where rapid urbanization and lifestyle changes are accelerating exposure to modifiable risk factors. These trends underscore the urgency of strengthening population-level prevention and early detection strategies in resource-limited settings (10,23).

A particularly important epidemiological development is the rising incidence of early-onset CRC (EOCRC). Despite overall stabilization or modest declines in older populations in several high-income countries, CRC rates continue to rise among individuals younger than 50 years. Early-onset cases are more frequently diagnosed at advanced stages and show a predilection for distal colon and rectal locations (23). This growing trend has been documented across both developed and developing countries, suggesting contributions from shared global risk factors, including obesity, metabolic dysfunction, dietary patterns, and microbiome alterations (23,24).

These evolving epidemiological patterns highlight widening disparities in CRC burden and emphasize the need for targeted prevention strategies, especially in younger populations and regions undergoing rapid socioeconomic transition.

CRC develops through a complex interplay between modifiable lifestyle factors and non-modifiable biological determinants (16). Among the modifiable risk factors, alcohol consumption, tobacco smoking, obesity, sedentary behavior, and unhealthy dietary patterns consistently show strong associations with increased CRC risk (25-29). High alcohol intake, particularly heavy drinking, contributes to carcinogenesis partly through DNA methylation changes. Smoking exposes colonic epithelial cells to multiple carcinogens such as nitrosamines and polycyclic aromatic hydrocarbons, promoting genetic instability. Obesity contributes to CRC through chronic inflammation, insulin resistance, elevated growth factors, and increased bile acids (30). Low physical activity further amplifies CRC risk by promoting metabolic dysfunction and slowing intestinal transit. Diets rich in red and processed meats, cooked at high temperatures or preserved through curing or smoking, expose the colorectal mucosa to carcinogenic compounds, while excessive dietary fat may also contribute to risk. Psychological stress has been proposed as an emerging risk factor, potentially through chronic activation of stress pathways affecting immune function and tumor biology, although evidence remains inconsistent (23,31,32).

Non-modifiable risk factors play an equally important role in defining high-risk individuals and guiding screening strategies. Age remains the strongest predictor, with the majority of CRC cases occurring in individuals over 50 years, though early-onset CRC is rising. Men consistently have higher incidence rates than women. Genetic predispositions such as familial adenomatous polyposis (APC mutations) and Lynch syndrome (mismatch repair gene mutations) substantially increase lifetime CRC risk, though these syndromes account for a small percentage of overall cases but a higher proportion of early-onset CRC. A positive family history of CRC or advanced adenomas further doubles or quadruples risk, warranting earlier or more intensive screening (33). Exposure to abdominal or pelvic radiation – especially for previous malignancies – is another relevant risk factor (16).

Several medical conditions also increase CRC susceptibility. Chronic inflammatory bowel diseases, including ulcerative colitis and Crohn's disease, substantially elevate long-term CRC risk due to persistent mucosal inflammation. Additional conditions linked to increased risk include cystic fibrosis, diabetes mellitus, insulin resistance, renal transplantation, cholecystectomy, certain cardiovascular diseases, and chronic bacterial or viral infections such as Helicobacter pylori or human papillomavirus. Increasing evidence also underscores the importance of gut microbiota composition. Dysbiosis, reduced microbial diversity, and the predominance of specific bacterial species have

been associated with CRC development through effects on bile acid metabolism, inflammation, and production of carcinogenic metabolites. Emerging studies highlight the potential for microbiome modulation as a preventive or therapeutic strategy, though further research is needed (34,35).

Molecular Pathways and Tumor Biology

The tumor biology of CRC is driven by an intricate network of molecular pathways that regulate cell proliferation, differentiation, metabolism, and interactions with the surrounding microenvironment. These pathways, which are essential for normal intestinal homeostasis, become dysregulated during malignant transformation, resulting in uncontrolled growth, tumor heterogeneity, and the emergence of aggressive cellular subpopulations. Among the most influential molecular systems implicated in CRC pathogenesis are the Wnt/ß-catenin, Notch, Hedgehog (Hh), and Hippo/YAP-TAZ pathways. Their functional interdependence contributes substantially to tumor initiation, progression, and metastatic dissemination (4,36, 37)(*Table 1*).

Wnt/β-catenin Pathway

The Wnt/ß-catenin pathway represents the central regulatory axis of intestinal stem cell maintenance and is one of the earliest and most frequently altered pathways in colorectal carcinogenesis. Under normal conditions, ß-catenin is continuously degraded through a destruction complex composed of APC, AXIN, CK1, and GSK3. Mutations affecting the components of this complex – especially truncating mutations of APC – lead to ß-catenin stabilization and accumulation in the nucleus. There, ß-catenin partners with TCF/LEF transcription factors to activate genes associated with proliferation, stemness, metabolic reprogramming, and resistance to apoptosis (38-40).

Persistent activation of Wnt signaling enhances epithelial-mesenchymal transition, invasive behavior, and expansion of undifferentiated tumor-initiating cells. Crosstalk with stromal and inflammatory mediators such as HGF, TNF-α, or IL-6 further amplifies Wnt-driven transcriptional programs. As a result, Wnt signaling not only initiates colorectal tumor formation but also sustains a dynamic pool of cells capable of adapting to therapeutic and environmental pressures (38-40).

Notch Signaling Pathway

The Notch pathway regulates cell fate decisions, lineage specification, and maintenance of intestinal progenitor compartments. In CRC, aberrant Notch activation leads to impaired differentiation and prolonged survival of proliferative cell populations. The pathway is initiated through ligand-receptor interactions between neighboring cells, resulting in release of the Notch intracellular domain (NICD), which translocates to the nucleus and activates transcriptional programs that suppress differentiation (41,42).

Upregulation of Notch activity promotes retention of an immature phenotype, contributing to intratumoral heterogeneity and reinforcing stem-like traits. Notch signaling enhances survival at the tumor invasive front and supports cellular plasticity, allowing cells to shift between proliferative and migratory states. Interactions with other pathways, particularly Wnt and Hedgehog, further consolidate a transcriptional landscape that favors continuous renewal and adaptive growth (41,42).

Hedgehog Signaling Pathway

The Hedgehog pathway plays an essential role in orchestrating epithelial-stromal communication and regulating cell differentiation. Although normally involved in limiting crypt proliferation, aberrant activation of Hedgehog signaling contributes to colorectal tumorigenesis by enhancing survival and clonogenic potential. Activation occurs when Hedgehog ligands bind to PTCH1, releasing suppression of SMO and activating GLI transcription factors (43,44).

In CRC, activation of the Hh-GLI axis promotes

Table 1. Key molecular pathways implicated in colorectal cancer (49).

Molecular Pathway	Physiological Role	Alterations in CRC	Therapeutic Implications
Wnt/β-catenin	Intestinal stem cell renewal	APC mutations; β-catenin nuclear accumulation	Wnt inhibitors, CSC-targeted therapies
Notch	Cell fate determination	Overactivation → dedifferentiated phenotype	γ-secretase inhibitors, combination approaches
Hedgehog (Hh)	Epithelial–stromal signaling	GLI activation → proliferation, resistance	SMO/GLI inhibitors, stroma-targeting strategies
Hippo/YAP–TAZ	Growth regulation, tissue architecture	YAP nuclear localization → invasion, metastasis	YAP/TEAD inhibition, ECM-modifying therapies

expression of genes involved in cell cycle progression, anti-apoptotic responses, and maintenance of an undifferentiated state. Hedgehog signaling also cooperates with Notch and Wnt pathways, amplifying proliferative signals and supporting hierarchical organization within the tumor. Furthermore, increased Hedgehog activity has been associated with metabolic alterations and increased resistance to cellular stress, both of which facilitate tumor expansion and persistence (43,44).

Hippo/YAP–TAZ Pathway

The Hippo pathway regulates cell proliferation, tissue architecture, and organ size through modulation of the transcriptional co-activators YAP and TAZ. When Hippo signaling is inactive, YAP/TAZ translocate to the nucleus and stimulate expression of genes promoting growth, dedifferentiation, survival, and mechanical adaptation. In colorectal cancer, upregulated YAP activity is frequently observed and correlates with enhanced invasiveness, metastatic potential, and poor clinical outcomes (45,46).

YAP/TAZ activation is influenced by extracellular matrix stiffness, cytoskeletal organization, and mechanical stress within the tumor microenvironment. These biomechanical cues create a positive feedback loop that reinforces YAP-driven transcription. Importantly, YAP interacts with ß-catenin and TEAD transcription factors, integrating mechanical signals with core oncogenic pathways and enabling dynamic switches between proliferative and invasive phenotypes. This integration underscores the role of Hippo signaling as a major regulator of tumor plasticity (45,46).

Tumor Biology and Microenvironmental Influence

The tumor microenvironment critically shapes signaling dynamics and contributes to the complexity of colorectal cancer biology. Fibroblasts, immune cells, endothelial cells, and extracellular matrix components release numerous soluble factors that stimulate oncogenic pathways. Cytokines such as IL-6, TGF-ß, and HGF activate intracellular cascades including STAT3, Wnt, and ERK, promoting proliferation, invasion, and cellular adaptability. Hypoxic regions within tumors stabilize HIF transcription factors, driving metabolic shifts and increasing resistance to apoptosis (47,48).

Immune components – such as tumor-associated macrophages, regulatory T cells, and myeloid-derived suppressor cells – create an immunosuppressive milieu that facilitates tumor progression and shields malignant cells from immune-mediated elimination. These microenvironmental interactions reinforce the activity of Wnt, Notch, Hedgehog, and Hippo pathways, fostering a highly adaptable and resilient tumor ecosystem (47-49).

Advances in Screening and Early Detection Diagnostic and Staging Tools

Early detection and accurate staging of CRC are fundamental pillars in reducing disease-related mortality and improving long-term outcomes. Rapid progress in screening technologies, non-invasive biomarkers, endoscopic imaging, and artificial intelligence has reshaped current strategies for population-level prevention and clinical diagnosis. Traditional modalities such as colonoscopy and fecal-based tests remain essential, yet their performance is increasingly complemented by molecular assays, radiologic advances, and risk-stratified approaches. At the same time, innovations in diagnostic imaging and staging tools provide enhanced precision in identifying tumor extent, nodal involvement, and metastatic spread. Integrating these approaches into clinical practice is crucial for optimizing patient selection, guiding therapy, and enabling personalized management across the CRC continuum.

Advances in Screening and Early Detection

Colonoscopy remains the gold standard for CRC screening due to its unique ability to both detect and remove precancerous lesions during the same procedure. High-definition white-light colonoscopy has significantly improved the detection of subtle mucosal abnormalities, while enhanced imaging techniques reduce the variability associated with operator experience. Evidence shows that colonoscopy offers the highest sensitivity for identifying advanced adenomas and serrated lesions, substantially lowering interval cancer rates when performed in high-quality programs Flexible sigmoidoscopy, while limited to the distal colon, continues to demonstrate utility in population-based screening, particularly in regions with restricted access to full colonoscopy (50).

Fecal immunochemical testing (FIT) remains a cornerstone of non-invasive screening worldwide. Its advantages include simplicity, affordability, and higher specificity compared to traditional guaiac-based tests. Large cohort studies confirm that annual or biennial FIT reduces CRC mortality by enabling early colonoscopic evaluation in

individuals with occult bleeding. Meanwhile, multi-target stool DNA tests (mt-sDNA), incorporating methylated DNA markers such as NDRG4, BMP3, and mutant KRAS, provide enhanced sensitivity for both early-stage CRC and advanced adenomas, making them valuable alternatives for individuals who decline colonoscopy or prefer non-invasive testing (9).

Traditional stool and endoscopic tests are increasingly supplemented by biomarker-driven strategies. Blood-based assays have gained considerable attention due to their accessibility and potential to identify biologically aggressive lesions. Methylated SEPT9 DNA testing represents one of the most widely studied blood biomarkers, demonstrating promising sensitivity in population-level studies. Newer multi-marker panels integrating methylated DNA fragments, protein markers, and circulating microRNAs provide improved diagnostic accuracy and may enhance overall uptake of screening programs (51). Emerging modalities include metabolomic profiling, volatile organic compound (VOC) analysis, and microbiome-derived biomarkers. Gut microbiota signatures – particularly the enrichment of Fusobacterium nucleatum or depletion of protective species – have shown diagnostic potential for identifying high-risk individuals. Such approaches could eventually complement stool or plasma testing and support risk-adapted screening strategies (52).

Radiologic techniques are assuming a greater role in CRC early detection for individuals unable or unwilling to undergo colonoscopy. CT colonography (virtual colonoscopy) provides high-resolution visualization of the colonic lumen with excellent sensitivity for advanced lesions. Its minimal invasiveness, lack of sedation, and rapid acquisition time make it suitable for large-scale screening settings. MRI colonography, though less widely available, offers comparable accuracy without ionizing radiation and is beneficial in patients with contraindications to CT exposure. Capsule endoscopy has emerged as an alternative for complete mucosal visualization, especially when colonoscopy is incomplete. Technological improvements – including dual-camera systems, wider angles of view, and enhanced battery life – combined with AI-driven interpretation tools allow for more accurate detection of colonic polyps in a minimally invasive format (53).

Artificial intelligence is transforming CRC screening at multiple levels. AI-assisted colonoscopy improves adenoma detection rates through real-time computer-aided polyp detection (CADe) and computer-aided diagnosis (CADx). These systems reduce dependence on operator skill and significantly lower miss rates for flat and diminutive lesions. Meta-analyses show that AI can increase adenoma detection by 20-30%, translating into improved long-term prevention outcomes. Machine learning models integrating clinical, genetic, and lifestyle data are now being used to predict individual CRC risk and determine personalized screening intervals. Remote screening strategies using smartphone-based diagnostics, tele-endoscopy, and home-based sample collection kits are emerging as promising solutions to overcome geographic and socioeconomic disparities in access to screening services (53-55). Despite these promising results, several limitations currently restrict the widespread implementation of AI-assisted screening technologies. Most AI systems have been validated primarily in controlled or high-volume expert centers, and their generalizability across diverse populations and real-world clinical settings remains uncertain. Variability in image acquisition, bowel preparation quality, and endoscopy platforms may influence performance outside trial conditions. In addition, regulatory approval pathways, cost-effectiveness considerations, and integration into existing screening workflows represent important barriers to routine clinical adoption. At present, AI-assisted tools should be considered adjunctive technologies that complement established screening strategies rather than replacements in population-based CRC screening programs (53) (*Table 2*).

Diagnostic and Staging Tools in Colorectal Cancer

Endoscopy remains the primary diagnostic tool for CRC, but major innovations have expanded its precision. High-definition endoscopes with improved contrast and resolution facilitate detection of flat lesions, sessile serrated lesions, and early mucosal abnormalities. Narrow-band imaging (NBI), autofluorescence imaging, linked color imaging (LCI), and dye-based chromoendoscopy enhance visualization of vascular and mucosal patterns, enabling more accurate differentiation between benign and neoplastic tissue . Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) allow en bloc removal of superficial neoplasms, offering curative options for early-stage CRC. These techniques reduce the need for surgery and yield high-quality tissue specimens for detailed histopathological evaluation. Endoscopic full-thickness resection (EFTR) has emerged for

Table 2. Current CRC screening methods (56).

Screening Method	Sensitivity for CRC	Advantages	Limitations
Colonoscopy	95–99%	Gold standard; diagnostic + therapeutic	Invasive; requires bowel prep, sedation
Fecal Immunochemical Test (FIT)	70–80%	Inexpensive; non-invasive; easy uptake	Lower sensitivity for advanced adenomas
Multitarget Stool DNA	90–92%	High sensitivity; detects MSI	Costly; false positives possible
Methylated SEPT9 Blood Test	60–75%	Very easy to administer	Lower overall accuracy
CT Colonography	85–90%	Minimally invasive; no sedation	Radiation exposure; bowel prep required
AI-Assisted Colonoscopy	+20–30% ADR increase	Reduces miss rate of subtle lesions	Requires advanced equipment and expertise

challenging lesions located in difficult anatomical areas (57).

Cross-sectional imaging plays a pivotal role in diagnostic confirmation and preoperative staging. CT scanning remains the standard tool for assessing distant metastases, particularly hepatic and pulmonary involvement. Multiphasic liver CT and MRI provide detailed information on metastasis count, vascular relationships, and resectability, which are essential for treatment planning (58,59).

MRI is central for local staging in rectal cancer, offering unparalleled accuracy in evaluating mesorectal fascia involvement, extramural vascular invasion (EMVI), and tumor depth. These parameters influence decisions regarding neoadjuvant chemoradiotherapy, surgical approach, and potential for sphincter-preserving procedures (60). PET-CT serves as a problem-solving modality in cases with equivocal findings or suspected occult metastases and contributes to treatment stratification in advanced disease (61). Radiomics – quantitative extraction of imaging features – represents an emerging frontier in staging. By correlating texture, shape, and intensity features with tumor biology, radiomics may predict treatment response, aggressiveness, and patient outcomes (62).

Surgical Management of Colorectal Cancer

Surgical management remains the central and most definitive component of curative-intent therapy for colorectal cancer, forming the foundation upon which multimodal treatment strategies are built. Over recent years, significant advances in surgical anatomy, operative technology, and perioperative care have reshaped contemporary approaches to both colon and rectal cancer. A key principle emphasized in modern practice is meticulous respect for embryological planes, as this has proven critical for maximizing tumor clearance and optimizing long-term oncologic outcomes. For colon cancer, CME with central vascular ligation has emerged as an oncologic gold standard. This technique preserves the mesocolic fascial envelope and allows extensive lymphadenectomy with intact nodal basins. The emphasis on sharp dissection, high vascular ligation, and removal of the entire mesocolon results in specimens with superior integrity, reduced local recurrence risk, and improved disease-free survival, as demonstrated in high-quality surgical oncology cohorts (10,63,64).

In rectal cancer, TME remains one of the most transformative innovations in the history of colorectal surgery. By removing the entire mesorectum enclosed within its fascial sheath, TME minimizes the risk of leaving behind microscopic tumor deposits, particularly near the circumferential resection margin, a critical determinant of pelvic recurrence and overall survival. The introduction of TME into standard practice has led to a sharp decline in local recurrence rates and has enabled more precise risk stratification when integrating neoadjuvant therapy. As highlighted in the JNMS review, meticulous dissection within the avascular presacral plane and careful preservation of autonomic nerves are essential elements of high-quality TME that directly impact both oncological control and postoperative functional outcomes (65,66).

Minimally invasive techniques have significantly accelerated the evolution of CRC surgery. Laparoscopic colectomy and rectal resection have proven equivalent to open surgery in oncological terms, while offering substantial benefits such as reduced postoperative pain, decreased wound complications, shorter physiological stress response, and earlier return to normal activities (67,68). Multiple randomized and observational studies confirm that laparoscopy maintains lymph node yield, margin quality, and long-term cancer-specific survival, making it appropriate for the majority of colon and upper rectal cancer cases (10, 68,69). However, pelvic anatomy presents unique challenges for rectal cancer, particularly in male

patients, those with obesity, and in low tumors. In such settings, robotic-assisted surgery provides improved articulation, enhanced visualization, and greater precision in deep pelvic dissections (69-71). According to existing data, robotic TME demonstrates lower conversion rates, better preservation of autonomic nerves, and potentially improved CRM and sphincter-preservation outcomes in selected patients with mid to low rectal cancer. The robotic platform also appears to reduce technical variability between surgeons, though financial and logistical factors limit universal adoption (13,69, 72,73).

Beyond minimally invasive radical resections, organ-preserving strategies are gaining traction in early rectal cancer and in patients achieving excellent responses to neoadjuvant therapy. Local excision techniques such as transanal endoscopic microsurgery and transanal minimally invasive surgery allow full-thickness removal of early T1 tumors with favorable histology (74,75). These methods help avoid the morbidity and functional impact of radical rectal resection, though their success depends on strict selection criteria and precise preoperative staging. Additionally, non-operative "watch-and-wait" management is increasingly considered for patients achieving complete clinical response after chemoradiotherapy. Such approaches require highly regimented, long-term surveillance, as the risk of local regrowth remains clinically relevant. Nevertheless, in well-selected patients, these strategies offer promising organ-preservation potential with excellent colorectal function and quality of life outcomes (76,77).

Surgical management of metastatic CRC continues to evolve. Resection of liver and lung metastases is associated with substantial survival benefit when complete removal is achievable. Hepatic metastasectomy can yield long-term survival exceeding 50% in selected oligometastatic cases (78). Success depends on tumor distribution, remnant liver volume, bilobar involvement, and biological responsiveness to systemic therapy. Current data emphasize the importance of multidisciplinary review, advanced imaging, and precise intraoperative assessment in determining resectability (79). Similarly, pulmonary metastasectomy may be appropriate for isolated lung lesions in controlled systemic disease, especially in patients with good functional reserve. For both liver and lung interventions, perioperative chemotherapy often plays a critical role in downsizing disease to achieve negative-margin resection and in selecting patients with favorable tumor biology (80).

Locally advanced primary tumors, particularly T4 cancers invading adjacent organs, require en bloc multivisceral resection. Piecemeal excision or dissection between involved structures must be avoided to prevent tumor spillage and incomplete clearance. When performed in specialized centers, multivisceral resections can achieve oncologic outcomes comparable to standard resections in earlier disease stages, provided that R0 margins are obtained. Another essential aspect of contemporary colorectal surgery involves perioperative optimization (10). ERAS protocols have radically changed postoperative trajectories by reducing stress response, shortening hospitalization, and improving return to baseline function. ERAS elements include carbohydrate loading, avoidance of routine drains or nasogastric tubes, early mobilization, and multimodal analgesia aimed at minimizing opioid use (81,82).

Functional outcomes and quality of life considerations have become central to the evaluation of surgical success. Low rectal resections can result in challenging postoperative syndromes, including low anterior resection syndrome (LARS), characterized by urgency, clustering, fecal incontinence, and altered bowel habits. Nerve damage may lead to urinary or sexual dysfunction. High-quality TME with meticulous nerve preservation mitigates these risks, but functional impact remains an important determinant of patient satisfaction and long-term well-being (31). Intraoperative fluorescence imaging, particularly indocyanine green (ICG) angiography, is increasingly used to assess real-time perfusion at anastomotic sites to reduce the risk of anastomotic leakage, one of the most feared postoperative complications (83,84).

Looking to the future, surgical management of CRC is becoming increasingly guided by tumor biology, technological innovation, and personalized decision-making. Robotic platforms continue to evolve with augmented reality, improved haptics, and integrated imaging. ctDNA may soon guide not only systemic therapy but also surgical timing and selection of candidates for organ preservation or intensified resections. Precision navigation, enhanced visualization, and biologically informed strategies are likely to further refine surgical indications, improve outcomes, and minimize morbidity (85) (*Table 3*).

Systemic Therapy and Targeted Approaches

Systemic therapy for CRC has undergone major

Table 3. Current Surgical Techniques in CRC (85, 86).

Surgical Technique	Main Indications	Advantages	Limitations
Complete Mesocolic Excision (CME)	Colon cancer	Extensive lymphadenectomy, improved oncologic margins	Technically demanding
Total Mesorectal Excision (TME)	Rectal cancer	Reduced local recurrence	Risk of urinary/sexual dysfunction
Laparoscopic Resection	Colon and upper rectum	Less pain, shorter recovery	Challenging in bulky tumors
Robotic TME	Narrow pelvis, obese patients	Superior visualization, lower conversion	High cost
Local Excision (TEM/TAMIS)	Early rectal cancers	Organ preservation	Requires strict selection and precise staging

transformation in recent years, moving from traditional cytotoxic chemotherapy toward biomarker-driven, targeted, and immunomodulatory approaches. Despite the persistence of tumor heterogeneity and complex resistance mechanisms, a deeper understanding of CRC biology – particularly molecular subtypes, pathway dysregulation, and the tumor microenvironment – has enabled increasingly personalized treatment strategies. Conventional chemotherapy remains foundational, but its limitations in efficacy and toxicity have accelerated the integration of precision oncology, targeted agents, and immunotherapy into modern treatment paradigms (*Table 4*).

Cytotoxic chemotherapy regimens such as FOLFOX and FOLFIRI continue to serve as the backbone of treatment for advanced CRC, offering proven survival benefits but frequently constrained by resistance and cumulative toxicity (87, 88). Escalated regimens like FOLFOXIRI can yield superior outcomes in selected patients, although toxicity remains a major concern. Innovative combination approaches are being explored to enhance chemosensitivity; for example, the integration of the oncolytic virus CVB3 PD-H with FOLFOXIRI has shown synergistic cytotoxicity and immune-stimulatory potential in preclinical models, suggesting a pathway to dose reduction and improved tolerability (87).

Targeted therapies have become increasingly central in metastatic CRC (mCRC) management, guided by molecular profiling. EGFR inhibitors (cetuximab, panitumumab) demonstrate significant benefit in RAS wild-type tumors, whereas activating mutations in KRAS, NRAS, or BRAF predict poor response and drive resistance via downstream pathway activation (89). For BRAF-mutated CRC, monotherapy with EGFR inhibitors is ineffective, but combination regimens incorporating BRAF inhibitors have shown improved outcomes in later treatment lines (89). Anti-angiogenic therapy, particularly VEGF/VEGFR inhibition (e.g., bevacizumab), remains a cornerstone of systemic treatment and continues to be refined due to its relevance in metastatic dissemination and tumor vascular remodeling (87).

Immunotherapy represents the most transformative development in CRC therapy, particularly for MSI-H/dMMR tumors, which exhibit high mutational burden and enhanced neoantigenicity. Checkpoint inhibitors such as pembrolizumab and nivolumab have demonstrated durable responses and are recommended as first-line therapy in this subgroup. However, the majority of CRCs are microsatellite stable (MSS) and do not respond to current immunotherapies, creating an urgent need for strategies to overcome resistance. Ongoing research explores combination regimens involving targeted agents, chemotherapy, and immune

Table 4. Systemic Therapies in CRC and Corresponding Biomarker Requirements

Therapy Class	Representative Agents	Required Biomarker	Key Clinical Benefit
Cytotoxic Chemotherapy	FOLFOX, FOLFIRI	None	Backbone of systemic treatment
Anti-EGFR Therapy	Cetuximab, Panitumumab	RAS wild-type	Improved OS and PFS in mCRC
Anti-VEGF Therapy	Bevacizumab	None	Angiogenesis inhibition, synergistic with chemo
BRAF-Targeted Therapy	Encorafenib + anti-EGFR	BRAF V600E mutation	Improved outcomes in refractory cases
Immunotherapy	Pembrolizumab, Nivolumab	MSI-H/dMMR	Durable deep responses
Nanomedicine Platforms	L1CAM-targeted nanoparticles	Mesenchymal/stem-like phenotype	Enhanced delivery & reduced systemic toxicity

modulators to enhance immunogenicity and reverse immune exclusion (87).

Emerging systemic modalities reflect rapid progress in molecular oncology. Liquid biopsy is becoming a powerful tool for tracking tumor evolution, detecting resistance mutations, and guiding adaptive therapy. CtDNA is increasingly used to monitor minimal residual disease, assess treatment response, and personalize systemic decisions in real time. Precision-medicine-driven approaches also include next-generation sequencing (NGS), single-cell transcriptomics, and CRISPR-based technologies, which are expanding the catalog of actionable alterations and enabling more tailored therapeutic interventions (87,90).

Novel nanotechnology-based delivery systems represent another frontier in systemic therapy. Advanced nanoplatforms capable of selectively targeting metastatic subpopulations – such as L1CAM-positive cells – have been shown to inhibit mesenchymal traits, reduce tumor growth, and improve intratumoral drug distribution in vivo, illustrating the potential of nanomedicine to enhance efficacy and reduce systemic toxicity. These innovations align with a growing emphasis on overcoming chemoresistance, modulating the tumor microenvironment, and addressing the biological diversity underlying treatment failure (87).

Emerging Therapeutic Modalities in Colorectal Cancer

The therapeutic landscape of CRC is undergoing a profound shift, driven by rapid advances in molecular oncology, immunology, and targeted drug delivery systems. As traditional cytotoxic and targeted agents reach the limits of their efficacy in many patient subgroups, a new generation of emerging therapeutic modalities is poised to expand treatment opportunities, overcome resistance mechanisms, and personalize care with unprecedented precision. These innovative strategies draw upon a deeper understanding of tumor heterogeneity, microenvironmental dynamics, and metastatic biology – factors increasingly recognized as central barriers to durable response with existing therapies.

Among the most promising developments is the refinement of liquid biopsy technologies, particularly ctDNA, which has begun to redefine disease monitoring and therapeutic decision-making. ctDNA shows exceptional sensitivity for detecting minimal residual disease (MRD), enabling much earlier identification of recurrence compared with conventional imaging (91). The integration of ctDNA into adjuvant therapy algorithms may allow escalation of treatment for molecularly "positive" patients and de-escalation for those with no detectable disease, minimizing toxicity without compromising oncologic outcomes. As ctDNA also captures tumor evolution in real time, it holds significant potential for guiding adaptive therapy and intercepting emerging resistance mutations before clinical progression becomes evident (92). Despite its considerable clinical potential, several limitations currently restrict the routine implementation of ctDNA analysis. There is substantial heterogeneity among available assay platforms, with differences in sensitivity, specificity, and analytical thresholds. The lack of standardized timing for ctDNA assessment and absence of consensus-driven algorithms to guide therapeutic decisions further limit its clinical applicability. In addition, most evidence supporting ctDNA-guided management derives from observational studies and ongoing clinical trials, with limited prospective validation in routine practice. At present, ctDNA should be considered primarily a risk-stratification and research tool, with broader clinical implementation dependent on further validation and guideline integration (93,94).

Parallel to molecular monitoring, next-generation immunotherapy strategies are gaining momentum. While immune checkpoint inhibitors have transformed outcomes in MSI-H/dMMR CRC, the vast majority of patients with microsatellite-stable (MSS) tumors remain refractory. New approaches aim to overcome this barrier by altering the immunologic contexture of the tumor microenvironment. These include combination regimens pairing checkpoint blockade with VEGF inhibitors, MEK inhibitors, or radiotherapy, all designed to increase tumor immunogenicity and enhance T-cell infiltration (95). Other modalities being explored include bispecific antibodies that redirect cytotoxic T cells toward CRC antigens, as well as engineered cytokines that selectively stimulate intratumoral immune activity. Preclinical studies have also shown considerable interest in oncolytic virotherapy, which not only induces direct tumor lysis but also produces strong in situ vaccination effects, priming cytotoxic immune responses that can synergize with systemic immunotherapy (96).

Another rapidly advancing field is nanomedicine, which offers novel solutions to long-standing challenges in drug delivery. Nanoparticle-based platforms can encapsulate chemotherapy, RNA therapeutics, or targeted agents and deliver them

selectively to tumor sites, thereby improving intratumoral drug concentration while reducing systemic toxicity. Emerging nanocarriers are being engineered to target metastatic subclones – particularly those exhibiting stem-cell-like or mesenchymal characteristics – by exploiting surface markers such as L1CAM, EPCAM, or integrins. These platforms also show promise in sensitizing resistant tumors to chemotherapy by modulating drug efflux pumps, reprogramming the tumor microenvironment, or enabling controlled, sustained drug release (97).

Innovative gene-editing and gene-regulation strategies represent another frontier. CRISPR-based systems are being developed to silence oncogenic drivers, correct pathogenic mutations, or modulate immune-regulatory pathways. Although still in early phases of research, these approaches demonstrate potential to precisely interrupt molecular circuits driving CRC progression and resistance. Single-cell transcriptomics and spatial genomics are simultaneously refining the understanding of tumor evolution, providing the blueprint for next-generation gene-targeted therapies (98).

Radiation oncology is likewise evolving through the integration of high-precision radiation techniques and synergistic systemic combinations. Stereotactic body radiotherapy (SBRT), when paired with immunotherapy or DNA-repair inhibitors, is being investigated as a means of inducing immunogenic cell death and amplifying systemic anti-tumor responses. This strategy is particularly relevant for oligometastatic disease, where ablative therapies may complement systemic regimens to achieve long-term control (99,100).

Together, these emerging therapeutic modalities mark a decisive shift toward biology-driven, highly individualized treatment frameworks. While many remain in early clinical testing, their integration holds tremendous promise for improving outcomes in both early-stage and metastatic CRC, particularly in patient populations underserved by current systemic options. Continued refinement of these approaches – supported by biomarker-guided selection, real-time molecular monitoring, and advances in tumor profiling – will be essential to translating scientific innovation into meaningful clinical benefit.

Strengths and Limitations of This Review

One of the principal strengths of this review is its comprehensive and multidisciplinary scope, which integrates current evidence spanning epidemiology, molecular and tumor biology, screening and diagnostic strategies, surgical management, systemic therapies, and emerging treatment modalities in colorectal cancer. By addressing these interconnected domains within a single framework, the review offers a broad yet clinically oriented synthesis of the evolving CRC landscape. Particular emphasis is placed on contemporary developments such as molecular stratification, precision oncology, minimally invasive and robotic surgical techniques, organ-preserving strategies, and circulating tumor DNA–guided monitoring, all of which are increasingly relevant to modern clinical practice.

Another strength lies in the focus on recent, high-impact literature, allowing the review to reflect current standards of care while highlighting ongoing transitions in CRC management. The thematic organization facilitates critical interpretation rather than simple listing of studies, enabling the identification of consensus areas, unresolved controversies, and emerging directions with potential translational impact. This approach aims to bridge the gap between rapidly advancing molecular research and practical surgical and oncologic decision-making.

Several limitations should also be acknowledged. This manuscript was designed as a narrative review and does not adhere to a systematic or PRISMA-based methodology. Consequently, the literature selection is not exhaustive and may be influenced by thematic prioritization and clinical relevance. No formal quantitative synthesis or meta-analysis was performed, and conclusions are derived from qualitative interpretation of the available evidence. Additionally, given the fast-paced evolution of colorectal cancer research, some areas discussed may require frequent updating as new data emerge. Despite these limitations, this narrative review seeks to contextualize current knowledge, underscore persistent challenges, and provide a balanced perspective that may inform both clinical practice and future research.

Cinical Implications

The advances discussed in this review have direct implications for clinical practice across the entire colorectal cancer care continuum. Improved risk stratification through molecular profiling enables more precise selection of systemic therapies, surgical strategies, and surveillance

intensity, supporting a more personalized approach to patient management. Refinements in minimally invasive and robotic surgery contribute to reduced perioperative morbidity, improved functional outcomes, and faster postoperative recovery, while maintaining oncological safety.

Enhanced screening strategies and emerging biomarkers facilitate earlier detection of disease and more tailored surveillance protocols, particularly in high-risk and younger populations. The increasing availability of tools such as ctDNA analysis offers additional opportunities for postoperative risk assessment and treatment adaptation, although their integration into routine practice requires careful clinical validation. Collectively, these developments underscore the importance of multidisciplinary decision-making and coordinated care pathways, integrating surgical, oncological, molecular, and diagnostic expertise to optimize long-term outcomes and quality of life for patients with colorectal cancer.

Over the last five years, clinical practice in colorectal cancer has changed substantially, driven by the integration of molecular profiling into routine therapeutic decision-making, the broader adoption of minimally invasive and robotic surgical approaches, and the increasing use of multimodal and organ-preserving strategies in selected patients. Screening paradigms have expanded beyond conventional methods through the incorporation of advanced endoscopic imaging, multitarget stool DNA testing, and emerging blood-based biomarkers, while artificial intelligence has begun to enhance detection rates and procedural quality. In parallel, systemic treatment algorithms have evolved toward biomarker-guided selection, and ctDNA has emerged as a promising adjunct for postoperative risk stratification and disease monitoring. Together, these changes reflect a shift toward more personalized, adaptive, and multidisciplinary care pathways in contemporary colorectal cancer management.

Current Controversies in Colorectal Cancer Management

Despite significant advances in colorectal cancer management, several key areas remain subject to ongoing debate, reflecting the rapid evolution of technology and the heterogeneity of clinical practice. The optimal integration of artificial intelligence into screening programs continues to raise important questions regarding external validation, cost-effectiveness, and real-world applicability across diverse healthcare systems. Although AI-assisted tools have demonstrated improved detection rates in controlled settings, uncertainty persists regarding their performance in population-based screening programs, integration into existing workflows, and impact on clinical outcomes.

Similarly, while ctDNA has emerged as a promising biomarker for minimal residual disease detection and postoperative surveillance, its clinical implementation remains challenging. Limitations include the absence of standardized analytical thresholds, variability among assay platforms, and a lack of consensus on how ctDNA results should guide therapeutic decisions. Consequently, the role of ctDNA in directing adjuvant therapy and modifying surveillance strategies remains an area of active investigation.

In rectal cancer, non-operative "watch-and-wait" strategies following complete clinical response remain controversial, particularly with respect to long-term oncologic safety, optimal patient selection, and surveillance intensity. While this approach offers potential functional benefits, concerns persist regarding the risk of local regrowth and the need for highly specialized follow-up protocols. Furthermore, despite the success of immunotherapy in microsatellite instability-high tumors, effective strategies to overcome primary and acquired resistance in microsatellite-stable colorectal cancer remain elusive. Addressing these current controversies will require prospective clinical validation, standardized treatment algorithms, and equitable access to emerging technologies across healthcare systems.

Future Directions and Conclusions

Colorectal cancer remains a complex global health challenge, characterized by multifactorial etiology, marked molecular heterogeneity, and persistent disparities in early detection and access to optimal care. Despite substantial advances in screening technologies, minimally invasive and robotic surgery, systemic therapies, and precision-oncology strategies, CRC continues to cause significant morbidity and mortality, particularly among younger populations and in regions undergoing rapid socioeconomic transition.

Progress in molecular profiling has improved prognostic stratification and biomarker-driven treatment selection, while innovations such as circulating tumor DNA analysis offer promising

tools for early detection of recurrence and real-time monitoring of therapeutic response. Surgical management has also evolved through anatomy-based techniques, organ-preserving strategies, and optimized perioperative pathways, leading to improved oncologic and functional outcomes.

Nevertheless, major challenges persist, including therapeutic resistance, limited efficacy of immunotherapy in microsatellite-stable tumors, tumor microenvironment-driven heterogeneity, and the rising incidence of early-onset CRC. Future progress will depend on the integration of high-resolution molecular characterization, liquid biopsy-guided adaptive therapy, and advanced targeted delivery systems, within a multidisciplinary, patient-centered framework. Continued research and equitable implementation of evidence-based practices are essential to translate scientific advances into meaningful clinical benefit.

Conflict of Interest

All authors declare that they have no conflict of interest.

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