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**Molecular profiling-directed individualized adjuvant therapy in colorectal cancer:
Bridging consensus guidelines to clinical disparities**

Cheng XF. Molecular profiling in CRC adjuvant therapy

Abstract

Colorectal cancer (CRC) adjuvant therapy is evolving from tumor-node-metastasis stage-based strategies toward molecular-profiling-guided precision medicine. This minireview, based on a comprehensive literature search in PubMed and Web of Science using keywords related to CRC biomarkers and adjuvant therapy (from 2010 to 2025), examines how key biomarkers, including mismatch repair (MMR) status, rat sarcoma viral oncogene homolog/rapidly accelerated fibrosarcoma mutations, consensus molecular subtypes, and circulating tumor DNA, refine risk stratification and treatment selection. Despite consensus guidelines advocating individualized therapy, significant disparities persist in real-world implementation due to technical variability in testing, limited or evolving evidence for specific scenarios (*e.g.*, adjuvant immunotherapy for MMR-deficient/microsatellite instability-high patients, wherein phase 3 trials such as ATOMIC have yet to report mature overall survival data), and health economic barriers. The minireview analyzes gaps across testing, decision-making, and dynamic monitoring phases, and proposes integrated solutions involving technological innovation (*e.g.*, artificial intelligence-integrated multiomics, circulating tumor DNA monitoring), optimized clinical pathways, and supportive health policies. Bridging these gaps requires multidisciplinary collaboration to translate molecular insights into equitable, personalized adjuvant care for CRC patients.

Key Words: Colorectal cancer; Adjuvant therapy; Molecular subtyping; Consensus molecular subtypes; Circulating tumor DNA; Precision medicine

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Core Tip: Molecular profiling, including mismatch repair deficiency/microsatellite instability, circulating tumor DNA (ctDNA), and consensus molecular subtypes, refines

risk stratification and guides personalized adjuvant therapy in colorectal cancer. Persistent gaps between guidelines and practice stem from technical variability, limited evidence for novel strategies (*e.g.*, ctDNA-guided escalation), and health economic disparities. Bridging these requires integrated artificial intelligence-multiomics decision tools, dynamic ctDNA monitoring, and health policy reforms supporting equitable implementation.

INTRODUCTION

Colorectal cancer (CRC), ranking among the most common malignancies globally, continues to pose a significant public health challenge. For patients with operable, locally advanced (stage II/III) disease, postoperative adjuvant therapy is a critical component of the curative strategy, aiming to eradicate minimal residual disease (MRD), thereby reducing the risk of recurrence and metastasis and improving long-term survival[1]. Traditionally, adjuvant chemotherapy decisions have long relied on tumor-node-metastasis (TNM) pathological staging, establishing a relatively standardized paradigm. Combination chemotherapy is recommended for stage III patients, while observation or single-agent chemotherapy may be considered for low-risk stage II patients[2]. However, clinical practice has revealed significant limitations in this anatomy-based one-size-fits-all approach, as substantial heterogeneity exists in the intrinsic biological behavior, treatment response, and long-term outcomes among patients with the same stage of cancer[3]. Some stage II patients experience early recurrence despite undergoing surgery, whereas some stage III patients achieve long-term survival even without chemotherapy[4]. This underscores the urgent need for prognostic and predictive biomarkers that can transcend TNM staging to more accurately reflect the biological essence of the tumor, thereby identifying individuals who truly benefit from chemotherapy and sparing others from ineffective treatment and its associated toxicities.

Since the turn of the 21st century, the wave of precision medicine has profoundly reshaped the CRC management paradigm. Its core lies in shifting decision-making from being guided by macroscopic clinicopathological features towards a model driven by

microscopic molecular biomarkers. Molecular subtyping deconstructs CRC into a series of distinct molecular subtypes characterized by unique genetic mutations, expression profiles, and pathway activities[5]. Landmark events emblematic of this shift include the following. The identification of mismatch repair (MMR) proficiency/deficiency and microsatellite instability (MSI) status, which not only correlates with genetic background but also serves as a powerful biomarker predicting response to immune checkpoint inhibitors, ushering in a new era of immunotherapy for MMR deficiency (dMMR)/MSI high (MSI-H) patients[6]. The identification of rat sarcoma viral oncogene homolog (RAS)/rapidly accelerated fibrosarcoma (RAF) mutation status, which forms the basis of anti-epidermal growth factor receptor (EGFR) therapy resistance in metastatic disease, is also being included as a prognostic factor in adjuvant therapy risk assessment[7]. Systems like consensus molecular subtypes (CMSs), which reveal the biological characteristics of different subtypes from a multiomics perspective, provide a theoretical framework for understanding treatment sensitivity[8]. The maturation of circulating tumor DNA (ctDNA) liquid biopsy enables ultrasensitive monitoring of MRD, making dynamic risk assessment and personalized adjustment of adjuvant therapy intensity possible, marking a leap from static to dynamic management of treatment decisions[9]. Based on robust evidence, international authoritative guidelines, such as those ² from the National Comprehensive Cancer Network and European Society for Medical Oncology, have systematically incorporated testing for key molecular biomarkers into their recommendations, striving to build a framework for individualized adjuvant therapy[10]. Nevertheless, a significant gap persists between guideline consensus and clinical practice. Firstly, technical accessibility and standardization are uneven; healthcare institutions of different levels and across regions exhibit vast disparities in testing platforms, quality control, and bioinformatic interpretation capabilities[11]. Even when testing is feasible, challenges such as variability in next-generation sequencing (NGS) panels, choice of biopsy platforms, and reporting standards remain. Secondly, ambiguities exist in evidence interpretation and clinical decision-making[12]. For instance, high-level evidence is still lacking regarding the optimal timing of adjuvant

immunotherapy for stage III dMMR cancer or the optimal intensification strategy for ctDNA-positive cancer, leading to varied approaches in practice[13]. Finally, health economic challenges cannot be overlooked. The high costs of advanced testing and targeted/immunotherapeutic agents, against a backdrop of uneven resource distribution, exacerbate disparities in healthcare access and hinder the equitable realization of precision medicine.

To ensure a comprehensive and reproducible evidence synthesis, the literature search for this minireview was conducted using PubMed and Web of Science. The search strategy used key terms related to “colorectal cancer”, “adjuvant therapy”, “molecular biomarkers” (e.g., “dMMR”, “MSI”, “ctDNA”, “CMS”), and “precision medicine”. The search was limited to articles published between January 2010 and August 2025 to capture the most relevant advances in the field. Inclusion criteria prioritized clinical trials, meta-analyses, and consensus guidelines published in English, while exclusion criteria removed editorials, case reports, and studies lacking primary data. This structured approach aimed to balance breadth with specificity, providing a robust foundation for analyzing gaps between guidelines and real-world practice.

This minireview aims to systematically examine the current landscape of molecular subtype-driven personalized adjuvant therapy for CRC, with a focus on analyzing the roots of the discordance between guidelines and real-world practice and potential solutions. The following sections will first elaborate on the recent advances in key molecular subtyping tools, then provide an in-depth analysis of specific discrepancies in the testing, decision-making, and monitoring phases. Finally, we propose integrated pathways to bridge these gaps from technological, clinical, and policy dimensions, hoping to provide a reference for advancing precision oncology practice from consensus to widespread and equitable implementation.

CORNERSTONE OF MOLECULAR SUBTYPING FOR ADJUVANT THERAPY DECISION-MAKING IN CRC: FROM STATIC MARKERS TO A DYNAMIC ATLAS

The precision of adjuvant therapy for CRC is built upon an increasingly sophisticated molecular subtyping system. This system has evolved from relying on single, static biomarkers to integrating genomic, transcriptomic, and liquid biopsy data into a dynamic, multidimensional atlas, providing an unprecedented scientific basis for individualized decision-making.

Clinical significance and evolution of key biomarkers

Current clinical practice still centrally revolves around a set of validated key biomarkers. dMMR/MSI-H stands as the most prominent example[14]. dMMR/MSI-H status serves not only as a screening indicator for Lynch syndrome but has also revolutionized the treatment landscape for these patients (accounting for 5%-15% of locally advanced CRC) due to its predictive value for exceptional response to immunotherapy[15]. The definitive role of immune checkpoint inhibitors in the adjuvant setting is currently under investigation in phase 3 trials (*e.g.*, the ATOMIC study). The primary endpoint of disease-free survival in ATOMIC is pending final analysis and publication; thus, mature overall survival data are not yet available. However, the remarkable efficacy established in the metastatic setting and the high pathological response rates observed in the neoadjuvant setting foreshadow their significant potential, driving their evaluation in perioperative therapy[16]. Secondly, the value of *RAS* and *BRAF* gene mutations lies primarily in prognostic estimation and treatment exclusion. *RAS* mutations are a marker of primary resistance to anti-EGFR therapy in metastatic CRC[17]. In the adjuvant context, similar to *BRAFV600E* mutation, they are primarily prognostic indicators of poor outcomes[18]. However, aside from exploratory potential benefit of more intensive chemotherapy regimens (*e.g.*, FOLFOXIRI: Folinic acid, 5-fluorouracil, oxaliplatin, and irinotecan) for patients with *BRAFV600E* mutation, effective adjuvant targeted strategies specifically for these mutations are currently lacking, highlighting an unmet need in this area[19]. While emerging actionable targets (such as human epidermal growth factor receptor 2 amplification, neurotrophic tyrosine receptor kinase fusions, and *KRASG12C* mutation) have corresponding approved targeted drugs in the metastatic setting, their application

in adjuvant therapy lacks high-level evidence[20,21]. Although these rare mutations account for a low percentage in the population, they are highly significant for carriers and represent a precise direction for future clinical research.

Molecular subtyping systems: From consensus to functional insights

Going beyond individual gene mutations, molecular subtyping based on gene expression profiles provides a higher-dimensional biological perspective. The CMS classification categorizes CRC into four subtypes: CMS1 (immune-activated), CMS2 (canonical), CMS3 (metabolic), and CMS4 (mesenchymal)[5]. These subtypes exhibit significant differences in prognosis, tumor microenvironment characteristics, and potential treatment sensitivity[5,22]. For instance, the CMS4 subtype is stroma-rich and associated with high invasiveness and poor prognosis, whereas CMS1 is linked to MSI-H and immune cell infiltration[5,23]. Although CMS classification offers profound biological insights, its direct clinical translation faces challenges, primarily due to intratumoral heterogeneity and the practical difficulty of obtaining stable classification from formalin-fixed paraffin-embedded tissues[24,25]. As a complementary model, the CRC intrinsic subtype (CRIS) classification has been proposed. Derived from patient-derived xenograft model data, CRIS focuses more on the intrinsic properties of cancer cells themselves, stripped of the influence of the tumor microenvironment, and shows promise in predicting responses to targeted therapies (*e.g.*, anti-EGFR therapy)[26,27]. Integrating CMS with classification systems such as CRIS holds potential for building more comprehensive and robust predictive models, representing an important direction for future research.

CtDNA: Ushering in a new era of dynamic risk-adapted therapy

CtDNA technology represents one of the most disruptive advances in the adjuvant therapy field in recent years. By detecting tumor-derived DNA in the blood, it enables ultrasensitive monitoring of MRD[28]. Accumulating evidence from pivotal studies (*e.g.*, DYNAMIC-II and CIRCULATE) continues to confirm the core value of ctDNA for postoperative risk stratification in stage II/III CRC. For example, the DYNAMIC study

of stage II disease demonstrated that ctDNA-guided management was noninferior to standard management for 2-year recurrence-free survival (hazard ratio not provided) while reducing the proportion of patients receiving adjuvant chemotherapy. The CIRCULATE-Japan GALAXY subgroup analysis showed a significant survival benefit for ctDNA-positive patients with resected colorectal liver metastases who received adjuvant chemotherapy based on positive ctDNA (3-year recurrence-free survival 86.4% vs 30.4%; hazard ratio = 0.11, 95% confidence interval: 0.03-0.36)[29-31]. This is shifting the adjuvant therapy paradigm from a fixed stage-guided approach to a dynamic risk-adapted strategy. Both treatment de-escalation strategies based on negative ctDNA results (as successfully demonstrated in stage II disease by the DYNAMIC study) and treatment intensification strategies (exploring more effective regimens for ctDNA-positive patients) are now central focuses of clinical research[30,32]. However, this paradigm shift brings new challenges. Despite significant clinical need, most current guidelines still recommend ctDNA-MRD testing within clinical trial frameworks, and key issues such as its standardization, optimal timing of testing, and the best intervention for positive patients remain to be resolved.

The cutting edge: The microcosm revealed by single-cell and spatial omics

Single-cell sequencing and spatial omics technologies represent the next frontier[33]. They overcome the limitations of traditional bulk sequencing by resolving intratumoral heterogeneity at single-cell resolution, identifying rare resistant clones, and precisely mapping the complex geographical relationships and interactions between cancer cells and components of the tumor microenvironment, such as immune cells and fibroblasts[34]. These technologies are profoundly refining our understanding of tumor biology; for example, they have revealed heterogeneity among cancer-associated fibroblasts in the CMS4 subtype and specific immunosuppressive niches[35,36]. Nevertheless, the greatest current challenge lies in translating these high-dimensional, complex data into clinically applicable, simple biomarkers. This requires innovation in bioinformatic methods and rigorous correlation with clinical endpoints. Although the

path ahead is long, these technologies will undoubtedly lay the groundwork for developing more precise prognostic models and identifying novel therapeutic targets, ultimately pushing personalized therapy to a deeper level.

FROM CONSENSUS TO PRACTICE: AN IN-DEPTH ANALYSIS OF CORE DISCREPANCY AREAS

Although international guidelines have established a theoretical framework for molecular subtype-driven decision-making, its translation into real-world clinical practice remains challenging. Figure 1 preliminarily outlines an idealized decision pathway integrating molecular subtyping and ctDNA dynamic monitoring; however, significant gaps exist between guideline recommendations and bedside decision-making at each step of this pathway (testing, treatment decision, dynamic monitoring). The following sections provide an in-depth analysis of these core areas of discrepancy.

Discrepancies at the testing level: The dilemma of technical standardization and accessibility

Precise testing is the prerequisite for precision therapy, yet the testing process itself is a starting point for discrepancies. Firstly, technical standardization and quality control are major hurdles. Although NGS has become mainstream, significant variations exist among different commercial kits in terms of gene coverage, sequencing depth, and sensitivity, leading to results that may not be directly comparable[37,38]. For instance, the concordance of results for MSI status among immunohistochemistry, polymerase chain reaction, and NGS methodologies is not 100% [39]. Furthermore, there is a lack of clear consensus on the optimal scenarios and timing for tissue biopsy *vs* liquid biopsy (postoperative baseline *vs* monitoring during surveillance)[40,41]. The interpretation of test reports also highly depends on the bioinformatics analytical capabilities and standards of the laboratory, leading to frequent occurrences of “one report, multiple interpretations”.

Secondly, issues of accessibility and health economics exacerbate healthcare disparities. The high costs of advanced molecular profiling and the unequal distribution of technological resources create significant barriers for many institutions and regions, limiting the universal application of guideline recommendations[42,43]. In summary, the dilemmas of standardization and accessibility at the testing level ultimately manifest directly as substantial clinical variations in the interpretation and application of key biomarkers. As summarized in Table 1, from established markers like dMMR to emerging ones like ctDNA, the clinical application of nearly all molecular biomarkers in the adjuvant setting faces significant discrepancies between consensus recommendations and practical operation, the roots of which profoundly reflect multilevel challenges in technology, evidence, and healthcare systems. These post-testing discrepancies, in turn, lead to greater dilemmas at the treatment decision level.

Discrepancies at the treatment decision level: Evidence gaps and individualized trade-offs

Even with accurate molecular information, clinical decision-making often resides in a gray zone of insufficient evidence. Taking dMMR/MSI-H tumors as an example, despite their remarkable response to immunotherapy in the neoadjuvant/metastatic settings, mature data from large phase 3 trials, specifically in the adjuvant setting, are not yet fully available[44,45]. For stage III dMMR tumors, choosing between traditional chemotherapy and seeking novel strategies, primarily within the context of clinical trials investigating adjuvant immunotherapy[46], such as the ATOMIC trial, whose definitive efficacy results remain pending. Key unanswered questions include the optimal sequence (neoadjuvant *vs* adjuvant) and integration strategies with chemotherapy[47,48].

For the majority of patients with microsatellite stability (MSS)/proficient MMR tumors, the core therapeutic challenge is the ineffectiveness of immunotherapy. However, new strategies are emerging to break this impasse. The latest research indicates that combination therapies aimed at remodeling the tumor immune microenvironment are a key exploratory direction for turning “cold” tumors “hot”[49,50]. For instance, the

CAPability-01 study led by Sun Yat-sen University Cancer Center demonstrated that the programmed cell death protein 1 inhibitor pembrolizumab, combined with the histone deacetylase inhibitor chidamide and antiangiogenic therapy, achieved a 44% objective response rate in refractory metastatic MSS CRC, revealing the potential of epigenetic immunomodulation[51]. Concurrently, research from Tianjin Medical University Cancer Institute and Hospital showed that the antiangiogenic agent regorafenib can synergize with programmed cell death protein 1 inhibitors by modulating immune cell infiltration in the tumor microenvironment to reverse immunosuppression[52].

Although encouraging, the efficacy and safety of such combination strategies in the adjuvant setting remain entirely unknown and highly controversial. Treatment decisions for patients with rare mutations (*e.g.*, human epidermal growth factor receptor 2-positive, neurotrophic tyrosine receptor kinase fusions) rely more heavily on extrapolation from metastatic setting data, lacking direct high-level evidence, forcing both clinicians and patients to weigh benefits and risks amidst uncertainty[53,54].

Treatment decisions for stage III CRC typically reflect the complexity of integrating clinical and molecular information. The IDEA study introduced clinical risk stratification, but how to combine this with molecular features like *BRAF* mutation status or CMS classification to more precisely identify patient subgroups needing 3 *vs* 6 months of adjuvant chemotherapy remains an unresolved question[55]. This highlights the limitations of relying solely on TNM staging and underscores both the great potential of molecular risk factors in refining traditional staging for more precise stratification and the current lag in their application.

Discrepancies in dynamic monitoring and resistance management: Countering tumor evolution

Tumors are not static entities; their clonal evolution is a core reason for treatment failure, posing an ultimate challenge to the static subtyping model based on a single biopsy[56]. Tumor heterogeneity means that primary tumors, metastatic lesions, and even different regions within the same lesion can possess distinct molecular characteristics[57]. The

molecular profile obtained from the initial surgical specimen may not fully represent the genomic landscape of the tumor at recurrence, challenging the “one-test-fits-all” model. This underscores the critical need for dynamic monitoring strategies, for which ctDNA technology serves as a cornerstone.

Consequently, managing resistance mechanisms is a severe impending challenge in the era of adjuvant targeted and immunotherapy[58]. Although the current use of adjuvant targeted therapy is limited, as research progresses, more patients may receive such treatments in this setting. However, unlike in metastatic disease, strategies for monitoring the emergence of resistant clones (*e.g., via* ctDNA monitoring for specific mutations), understanding the patterns of molecular evolution after resistance, and determining subsequent intervention strategies (which regimen to switch to) in the adjuvant setting are almost completely unexplored[59-61], although trials like DYNAMIC and CIRCULATE are pioneering this approach, their long-term outcomes on resistance management are still maturing. This challenge is compounded by a lack of technical standardization across ctDNA-MRD assay platforms, including variability in technology selection, timing for testing, and thresholds for defining positivity, which can lead to results that are not directly comparable between different laboratories and studies. As summarized in Table 2, key parameters such as assay technology (tumor-informed *vs* tumor-agnostic), optimal timing windows (*e.g.,* post-operative baseline at 4-6 weeks), and positivity thresholds (varying by variant allele frequency or fragment count) remain ununiformed. This variability poses a significant barrier to the broad clinical adoption and interpretation of ctDNA results, underscoring the urgent need for industry-wide technical standards.

BRIDGING THE GAP: A MULTIDIMENSIONAL INTEGRATED PATHWAY TOWARDS THE FUTURE

Bridging the chasm between consensus guidelines and clinical practice necessitates a multidimensional, systemic transformation encompassing technological innovation, clinical practice, and healthcare system reform. This requires focusing not only on

cutting-edge technology but also on building a compatible clinical application ecosystem and a supportive policy framework. In the following analysis, we explicitly distinguish between fundamental evidence gaps (lack of knowledge requiring new research) and practical implementation barriers (known solutions facing adoption hurdles) to clarify the nature of each challenge.

Technological innovation pathway: Building the next-generation decision support engine

Future technological innovation aims to translate high-dimensional, complex biological data into actionable clinical insights. The core objective is to propel decision-support tools from scientific discovery to clinically usable in a substantive leap[62]. Building on foundational advances in single-cell and spatial omics, the first priority is the evolution in the depth and utility of multiomics integration. Genomics alone is insufficient to fully characterize a tumor. A significant evidence gap persists in proving that complex multiomics models outperform single biomarkers in predicting adjuvant therapy outcomes within prospective trials[63-65]. A landmark study published in August 2024, presenting the largest global multiomics atlas of CRC (involving 1063 samples), exemplifies this path[66]. This study not only systematically revealed novel driver events but, more importantly, developed a clinically applicable molecular subtyping tool named CRC prognostic subtype using deep learning algorithms and has made it open source. This marks a transition where multiomics analysis is moving from basic research providing biological insights to a decision-support engine capable of generating stable, interpretable clinical subtypes[66]. For instance, combining such novel molecular subtypes with specific pathway activation status may more accurately identify subgroups sensitive to specific chemotherapies or targeted therapies compared to traditional methods[67]. Second is the deep application and platform-based implementation of artificial intelligence (AI) and machine learning. AI serves as the core engine for synthesizing multiomics data into real-time clinical guidance, such as optimizing chemotherapy duration or estimating the probability of benefit from

immunotherapy[68-70]. AI has shown potential in automatically identifying tumor regions from pathological images and predicting MSI status or gene mutations, offering a potential low-cost precision screening tool to improve testing accessibility[71,72]. This integration has moved beyond proof-of-concept into tangible clinical platforms. Initiatives like the CancerX project in the United States, aimed at accelerating AI-powered cancer technologies, clearly demonstrates systematic efforts to integrate AI and multiomics for optimizing cancer prevention, diagnosis, and treatment[73,74]. Even at the diagnostic front end, innovations like novel oral contrast agents (*e.g.*, methylene blue enteric-coated sustained-release tablets), which increase the adenoma detection rate during colonoscopy, exemplify how technological innovation aids precision medicine from the very source[75,76]. Finally, functional precision medicine, represented by organoid models, offers a novel approach. A critical evidence gap is the lack of data correlating *ex vivo* drug sensitivity in organoids with actual patient response in the adjuvant setting[77,78]. This integrated technological ecosystem - spanning multiomics, AI, and functional models - collectively bridges the gap between complex data and clinically actionable insights.

Clinical practice pathway optimization: Forging a new closed-loop management model

Technological innovation must benefit patients through optimized clinical pathways. The transition to new models is hampered by both unanswered questions (evidence gaps) and systemic inertia (implementation barriers). The primary task is establishing clear, integrated clinical decision algorithms. These algorithms should start at diagnosis, systematically guiding clinicians through molecular test selection (*e.g.*, first-line core biomarker testing *vs* timing of subsequent NGS); risk stratification based on integrated staging (clinical + molecular); selection of corresponding treatment strategies (including standard therapy and clinical trial options); and ctDNA-based dynamic monitoring and intervention pathways[79,80]. This will significantly reduce practice variation due to ambiguous guideline interpretation. Secondly, the traditional multidisciplinary team (MDT) model must be upgraded to MDT 2.0. The conventional MDT (surgery, medical

oncology, radiation oncology, radiology, and pathology) needs to incorporate molecular pathologists, bioinformaticians, and genetic counselors[81,82]. The molecular pathologist ensures test quality and accurate interpretation; the bioinformatician aids in understanding complex NGS reports and subtyping results; and the genetic counselor assesses hereditary risk and facilitates family management[83,84]. Only through such deep integration can molecular information be efficiently translated into clinical decisions. Taking a stage III dMMR CRC patient as an example, the MDT 2.0 discussion would no longer be confined to 3 vs 6 months of chemotherapy. Instead, it would comprehensively evaluate: Feasibility and local accessibility of neoadjuvant immunotherapy (where evidence is more established); if proceeding directly to surgery, whether to choose standard adjuvant chemotherapy or actively seek clinical trials for adjuvant immunotherapy (where evidence is maturing); and how to formulate a personalized surveillance plan including imaging and ctDNA. This process perfectly illustrates the shift from a traditional model to a precision-integrated paradigm.

Health policy and system building pathway: Constructing a sustainable support environment

Without supportive policies and systems, even proven technologies fail. Policy challenges also split into validating value (evidence gaps) and enabling adoption (implementation barriers). The first priority is promoting the standardization and regulation of testing. Health regulatory agencies, in collaboration with professional societies, must develop and promote technical guidelines, laboratory accreditation standards, and quality control systems for molecular testing to ensure the accuracy and comparability of results across different institutions[85]. This is the cornerstone of all precision medicine practice. Second, exploring value-based healthcare payment models is crucial. Reimbursement policies should incentivize, not hinder, precision testing. Necessary tests with proven cost-effectiveness (*e.g.*, dMMR/MSI, RAS/BRAF) should be covered. Simultaneously, value-based agreements could be explored, for instance, providing incentives for care pathways that successfully achieve treatment de-escalation

based on ctDNA results (saving subsequent treatment costs), thereby steering resources to the most efficient areas. Third, there must be a strong emphasis on building real-world data (RWD) platforms. Randomized controlled trials have limited generalizability in complex, heterogeneous real-world settings[86]. Establishing national or regional CRC multiomics clinical databases that collect treatment, testing, follow-up, and outcome data can generate living evidence that is more relevant to clinical practice[87]. This RWD can not only supplement randomized controlled trial evidence and validate the real-world effectiveness of innovative therapies but also help discover new biomarkers and provide localized evidence for health technology assessment, ultimately creating a virtuous cycle from evidence generation to practice optimization[88,89]. Through the coordinated drive of technology, clinical practice, and policy - the “three horses drawing the chariot” - we can systematically bridge the gap, transforming molecular subtype-guided personalized adjuvant therapy from an aspirational vision into an accessible reality for every CRC patient. In summary, the realization of future precision adjuvant therapy depends on the deep integration of technology, clinical practice, and policy systems, ultimately building a closed-loop management ecosystem spanning from diagnosis to dynamic monitoring. This integrated framework is designed for adaptability (Figure 2). It begins with comprehensive baseline analysis (which can range from full multiomics profiling to a core set of essential tests based on resource availability), formulates personalized plans through an AI and MDT2.0-powered intelligent decision center (where the MDT 2.0 model can be scaled to include available local expertise), and implements dynamic monitoring and adaptive intervention based on ctDNA (with monitoring cadence adaptable to local capacities). The entire process is empowered by a sustainable support system, which includes the tiered policy and economic levers necessary for implementation across diverse resource settings. This closed-loop paradigm signifies the transition of CRC adjuvant therapy from static standardization to dynamic personalized management.

Finally, a critical and often overlooked dimension is ensuring the transferability of precision medicine strategies to resource-constrained settings, which is essential for

global health equity. This requires the development of tiered, pragmatic implementation levers. Firstly, health insurance coverage should prioritize universally reimbursing a core set of essential biomarker tests (*e.g.*, dMMR/MSI, RAS/BRAF), which have the strongest evidence base and cost-effectiveness, before expanding to more comprehensive NGS panels[90]. Secondly, when advanced molecular subtyping (*e.g.*, CMS and CRIS) is unavailable, clinical decision-making must revert to robust, validated clinical risk stratification algorithms (*e.g.*, integrating TNM stage, lymphovascular invasion, and tumor grade) derived from studies like IDEA, ensuring that risk-adapted therapy remains feasible[91]. Thirdly, for dynamic monitoring, the frequency of ctDNA testing can be adapted to local capacities; for instance, a reduced cadence (*e.g.*, postoperative baseline and annual surveillance) may be adopted where more frequent monitoring is not sustainable, while still capturing major recurrence events[92]. Aligning the precision medicine framework (Figure 2) with these practical tiers ensures that the core principles of molecular-guided care can be implemented effectively across diverse economic environments, from high-resource centers performing full multiomics integration to clinics relying on core immunohistochemistry and basic clinical parameters.

CONCLUSION

Molecular subtyping has irreversibly propelled CRC adjuvant therapy from a population-statistics-based one-size-fits-all model into a new era of personalized decision-making centered on tumor biology[24,93]. This minireview has systematically examined how key molecular tools - from dMMR/MSI and RAS/RAF to ctDNA and multiomics classifications - have progressively formed the cornerstone of precision therapy, while providing a critical analysis of the real-world challenges encountered during their clinical translation, spanning testing standardization, treatment decision-making, and dynamic monitoring. These challenges are not isolated issues but rather the inevitable result of intertwined technological limitations, clinical evidence gaps, and disparities in healthcare systems. Looking ahead, the evolutionary trajectory for CRC adjuvant therapy is clear: A shift from the current reliance on static subtyping from a

single biopsy towards a dynamic intervention loop that spans the entire patient journey. The realization of this paradigm depends on synergistic progress in three key areas: Technologically, the deep integration of AI with multiomics data will give rise to more powerful predictive models, while organoid and liquid biopsy technologies provide critical support for enabling real-time guided, dynamically adjusted treatment strategies. Clinically, decision-making processes must be reconfigured to prioritize dynamic indicators like ctDNA monitoring as the core basis for adjusting treatment intensity, supported by an upgraded MDT model that ensures molecular information is accurately interpreted and applied. Systemically, there is a need to establish payment policies that incentivize precision testing and value-based care, coupled with strengthened RWD platforms to generate evidence more relevant to complex clinical scenarios.

To accelerate the translation of molecular insights into tangible patient benefit, we propose the following immediate, actionable recommendations derived from our analysis. (1) Clinical practice: Implement universal reflex testing for dMMR/MSI and RAS/BRAF status at diagnosis, and integrate ctDNA-based MRD assessment at 4-6 weeks postoperatively as a standard component of risk stratification for stage II/III CRC. MDT discussions should explicitly formulate contingency plans based on ctDNA results (escalation for positive, de-escalation for negative); (2) Research prioritization: Prioritize prospective clinical trials evaluating adjuvant immunotherapy for stage III dMMR patients and novel combination strategies (such as histone deacetylase inhibitors with immunotherapy) for MSS/proficient MMR tumors. Concurrently, validate AI-based tools for MSI prediction from histology slides to improve testing accessibility; and (3) Policy and system development: Health institutions should establish accredited molecular tumor boards with mandated inclusion of molecular pathologists and genetic counselors. Payers should develop reimbursement pathways for value-based care, such as bundled payments for ctDNA-guided management cycles, to incentivize high-value practices.

To definitively bridge the evidence gaps identified in this minireview, future research must prioritize prospective validation studies for two critical innovation pillars:

Integrated AI-omics decision support tools that synthesize multidimensional data into actionable outputs; and ctDNA-guided intervention strategies that dynamically adjust therapy based on MRD monitoring. The ongoing analysis of trials like ATOMIC (for adjuvant immunotherapy) and the long-term follow-up of DYNAMIC/CIRCULATE (for ctDNA-guided therapy) will be pivotal in providing the missing high-level evidence with robust effect sizes. Ultimately, fulfilling the promise of molecular subtyping for every patient cannot be achieved by a single technological breakthrough or guideline update alone. It requires a shared commitment and a systematic, engineering-style effort from clinicians, researchers, policymakers, and payers. By constructing an ecosystem that balances technological innovation, clinical practicality, and sustainable policy support, we can genuinely bridge the chasm between consensus and bedside practice, ushering in the ultimate transition of CRC adjuvant therapy from standardization to true personalization.

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