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Tumor Discovery

MINI-REVIEW

Precision and targeted therapies in curative and metastatic colorectal cancer: Current guidelines and emerging therapies

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Abstract

As the global incidence of colorectal cancer (CRC) continues to rise, particularly among young adults, the integration of precision medicine into clinical management represents an evolving priority. However, the clinical maturity and evidence base of precision oncology differ substantially between metastatic and curative-intent settings. In metastatic CRC, actionable biomarkers frequently direct therapy selection and sequencing, with several matched regimens now incorporated into routine practice. In contrast, curative-intent precision strategies must meet a higher evidentiary bar because many patients are cured by surgery and conventional adjuvant therapy alone. Consequently, any therapeutic escalation requires a clear survival benefit without imposing unnecessary toxicity. This mini review focuses on clinical positioning: what is guideline-positioned today, what is supported by emerging prospective evidence, and what remains investigational. In curative-intent disease, we highlight postoperative circulating tumor DNA (ctDNA) as a powerful prognostic tool for molecular residual disease risk stratification, while emphasizing that routine ctDNA-guided treatment or surveillance modifications remain unproven outside of prospective interventional trials. We also summarize emerging, trial-defined approaches evaluating neoadjuvant and adjuvant immunotherapy in biologically selected early-stage subsets. In metastatic CRC, we review the major actionable subgroups and their matched therapies and discuss practical implementation barriers that affect real-world delivery, including tissue adequacy, turnaround time, acquired resistance, and equitable access. Overall, precision oncology is most practice-defining in metastatic CRC, whereas broader adoption in curative-intent disease still depends on prospective validation showing that biomarker-guided decisions improve disease-free and overall survival.

Keywords: Colorectal cancer; Precision medicine; Adjuvant therapy; Circulating tumor DNA; Molecular residual disease; Immunotherapy; Targeted therapy; Metastatic colorectal cancer

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1. Introduction

Colorectal cancer (CRC) remains a leading cause of cancer-related mortality, and its clinical heterogeneity is increasingly recognized as a major determinant of outcome and treatment benefit.[1–3] CRC also remains a major global health burden; in 2020, it was the third most commonly diagnosed cancer and the second leading cause of cancer-related death worldwide, and in the United States, an estimated 158,850 new colon and rectal cancer cases and 55,230 deaths are projected in 2026.[1,4] Its epidemiology reflects both modifiable and non-modifiable risk factors, including smoking, alcohol use, obesity, sedentary lifestyle, diets high in red and processed meat, age, family history, hereditary cancer syndromes, and inflammatory bowel disease.[4] A subset of cancers of unknown primary may exhibit colorectal-like molecular features and can be managed according to CRC-oriented treatment paradigms.[5,6] However, whether the recognition of these cases has any measurable effect on population-level CRC incidence trends remains uncertain.

Over the last decade, CRC care has evolved from predominantly stage-based pathways to approaches that incorporate molecular subtypes and matched therapies, most clearly in metastatic disease, where actionable biomarkers can define immunotherapy eligibility and guide targeted treatment selection.[7–9] At the same time, the implementation of biomarker-directed care remains uneven in routine practice, as tissue adequacy, assay selection, turnaround time, access to genomic profiling, biologic heterogeneity, and acquired resistance can all influence how consistently these strategies are applied.[8,9] These challenges are compounded by tumor heterogeneity—such as bypass signaling in *BRAF*-mutant CRC—as well as variability in molecular testing platforms, bioinformatics pipelines, and cost barriers that limit equitable delivery of biomarker-directed care.[10,11] Progress in the curative setting has been slower, constrained by the need to balance escalation with the high cure rates of surgery alone.[8,12] These differences make clinical positioning—distinguishing guideline-positioned care from trial-only strategies—central to an effective narrative review of precision oncology in CRC.[8,9]

Accordingly, we focus on two decision points: (i) curative-intent stage II–III disease, where biomarkers and circulating tumor DNA (ctDNA)/molecular residual disease (MRD) platforms primarily support risk stratification and interventional trial design rather than routine biomarker-matched escalation[8,13–15] and (ii) metastatic CRC, where actionable alterations commonly guide therapy selection and sequencing in routine practice.[8,9,16] We emphasize where evidence is supported by interventional outcomes and where key uncertainties remain, particularly the distinction between prognostic risk assessment and predictive treatment selection.[8,16] Screening and early detection strategies are outside the scope of this review.

2. Methods

Major contemporary guidelines (NCCN and selected international guidance) were reviewed, and PubMed/MEDLINE was searched for prospective trials, pivotal single-arm studies, and high-quality observational evidence relevant to (i) curative-intent stage II–III disease and (ii) metastatic CRC through April 2026. United States Food and Drug Administration approvals and prescribing labels were cross-referenced for CRC indications, and ClinicalTrials.gov was queried to verify trial identifiers (NCT numbers), study status, and key protocol details. Search terms included "colorectal cancer," "epidemiology," "miRNA," "cost," "molecular testing," "adjuvant," "ctDNA," "molecular residual disease," "mismatch repair," "MSI," "POLE," "BRAF," "HER2," "KRAS G12C," "NTRK," and "RET." Evidence was synthesized by clinical decision point (what to test and when, and when matched therapy is appropriate), highlighting the strength of evidence, applicability to routine practice, and key uncertainties.

3. Curative-intent colorectal cancer: adjuvant precision strategies and molecular residual disease-directed trials

Adjuvant therapy in resected stage II–III colon cancer has traditionally been guided by anatomic stage and clinicopathologic risk features, with oxaliplatin-based chemotherapy providing durable benefit in appropriately selected patients.[8,17] Navigating this selection process is particularly challenging in older adults, who represent a clinically heterogeneous subgroup in whom severe postoperative complications and treatment-related toxicity are more common. However, prognosis in older patients is not determined by chronological age alone and is also influenced by stage at presentation, primary tumor site, comorbidity burden, frailty, and treatment intensity. This underscores the importance of comprehensive geriatric assessment rather than strict age-based exclusions when considering precision or standard adjuvant therapies.[18,19] Alongside these clinical challenges, adjuvant precision oncology faces distinct practical hurdles. Any therapeutic escalation must prove a meaningful survival benefit over surgery alone, while minimizing toxicity and withstanding the scrutiny of long-term survival endpoints. Early "broad" targeted approaches in unselected populations did not improve outcomes, as illustrated by PETACC-8, where adding cetuximab to adjuvant FOLFOX did not improve

disease-free survival (DFS) even among resected stage III KRAS exon 2 wild-type tumors.[20] Further critical analysis from the PETACC-8 investigators confirmed that even in the most molecularly favorable "triple-negative" (full *RAS* and *BRAF* wild-type) populations, the addition of cetuximab did not improve DFS, suggesting that activity in established metastatic disease may not translate directly into benefit in the postoperative micrometastatic setting.[21] To better understand this treatment resistance and improve patient selection, researchers are increasingly exploring novel blood-based biomarkers. At a translational level, circulating microRNAs (such as miR-19a or miR-31) have emerged as candidate markers to predict resistance to folinic acid, fluorouracil and oxaliplatin (FOLFOX) or anti-epidermal growth factor receptor (EGFR) strategies; however, these signals remain investigational and have not altered routine adjuvant management.[22] Taken together, these negative studies suggest that adjuvant precision strategies should be anchored less in broad extrapolation from metastatic CRC and more in biologically selected subsets and trial-defined escalation frameworks.[8,21] While targeted therapies failed in broad populations, immune-based strategies are showing promise in specific biological subsets. Specifically, hypermutated biology is the clearest rationale for adjuvant immunotherapy, and phase III programs are testing whether checkpoint inhibition added to standard adjuvant therapy improves cure rates in resected deficient mismatch repair (dMMR)/microsatellite instability-high (MSI-H) or *POLE*-mutated disease (e.g., ATOMIC[23]; POLEM[24]), building on the established efficacy of checkpoint inhibition in metastatic *POLE*/*POLD1*-deficient subsets.[25] Pending the availability of mature interventional data and their subsequent integration into established clinical practice guidelines, adjuvant checkpoint inhibition remains investigational and should ideally be restricted to the clinical trial setting.[8] In parallel, perioperative immunotherapy strategies are being tested in localized dMMR/MSI-H colon cancer, where neoadjuvant therapy is not yet guideline-established, and standard management remains surgery followed by stage-adapted adjuvant chemotherapy.[8,26]

AZUR-2 is an ongoing global phase III trial comparing perioperative dostarlimab (neoadjuvant dosing followed by surgery and adjuvant dosing) versus standard-of-care surgery with physician-selected adjuvant chemotherapy or surveillance, with event-free survival as the primary endpoint.[26] PREMICES similarly evaluates whether short-course neoadjuvant PD-1 blockade can enable a structured non-operative ("watch-and-wait") approach in carefully selected responders while prospectively measuring early strategy success and durability alongside patient-centered outcomes.[27] However, because cure-intent populations include many patients already cured by surgery alone, these approaches require mature recurrence and survival outcomes demonstrating that organ preservation or earlier immune intervention does not compromise long-term cure.[8,27] Beyond immunotherapy, biomarker-linked interventions such as low-dose aspirin in phosphoinositide 3-kinase (PI3K)-altered localized CRC are emerging, but they require individualized risk–benefit discussion and should not be presented as universally indicated.[8,28]

To better stratify patients and help identify those who may harbor microscopic disease warranting such tailored interventions, postoperative ctDNA has emerged as a minimally invasive marker of MRD in curative-intent CRC. As a tumor-derived fraction of cell-free DNA with rapid clearance from the circulation, ctDNA enables dynamic and repeatable postoperative assessment and may reveal persistent molecular disease when conventional imaging or serum biomarkers remain unrevealing.[13–16,29–31] Prospective studies and large observational cohorts consistently show that postoperative ctDNA detection and serial ctDNA dynamics correlate strongly with recurrence risk and can precede radiologic relapse, which explains why ctDNA has become a leading platform for postoperative risk stratification and interventional trial design.[13–15,29,31] At the same time, strong prognostic performance should not be conflated with established clinical utility, and current guidance remains insufficient to support routine treatment escalation, de-escalation, or major surveillance changes based on ctDNA outside clinical trials.[8,16] Longitudinal assessment is also likely to be more informative than a single postoperative landmark time point, because a proportion of patients with initially negative ctDNA results ultimately recur, underscoring the importance of serial follow-up in both clinical studies and adaptive trial platforms.[14–16,.29]

Interpretation of ctDNA results is further shaped by assay methodology. Tumor-informed approaches require baseline tumor sequencing to identify patient-specific variants and generally offer higher sensitivity and specificity for recurrence prediction, but they depend on tissue availability, incur higher cost, and usually involve longer turnaround times.[29,31,32] Tumor-agnostic (tumor-naïve) approaches are operationally attractive because they avoid prior tissue sequencing and may facilitate broader implementation, but in current CRC datasets, they generally show lower sensitivity and may be more vulnerable to false-positive or false-negative results depending on assay design and calling thresholds.[29,31] Additional implementation challenges include pre-analytical variability in blood collection, processing, storage, and extraction; biologic variability in ctDNA shedding; and false-positive signals related to clonal

hematopoiesis, particularly in older patients.[29–31] These differences mean that tumor-informed and tumor-agnostic assays should not be treated as interchangeable, and they complicate cross-trial comparisons of ctDNA positivity, clearance, and persistence.[29,31]

A further unresolved question is whether ctDNA should remain primarily a prognostic marker or whether it can also identify patients more likely to benefit from specific adjuvant interventions.[8,16] In a post-hoc companion analysis of CALGB/SWOG 80702, postoperative ctDNA positivity was strongly prognostic (DFS hazard ratio [HR]: 6.12; overall survival HR: 5.86), and ctDNA-positive patients experienced improved DFS with adjuvant celecoxib versus placebo (adjusted HR: 0.61), whereas ctDNA-negative patients did not show a clear DFS benefit.[33] Because the ctDNA-by-treatment interaction was not statistically significant in the overall cohort, however, and reached significance only in a high-quality-sample subset, these findings are best interpreted as hypothesis-generating rather than practice-changing.[33] Taken together, current evidence supports ctDNA as a powerful marker of postoperative risk and a rational framework for adaptive trial design, but not yet as a stand-alone determinant of routine adjuvant intensification, de-escalation, or surveillance modification.[8,16,29–31,33]

A detailed overview of these ongoing and completed efforts is provided in Table 1, which categorizes the current landscape of curative-intent trials by their molecular targets and primary clinical objectives.

Table 1 highlights that, in curative-intent CRC, most precision approaches remain investigational and are best

Table 1. Precision medicine adjuvant/molecular residual disease trials in colorectal cancer

Biomarker	Trial	Population	Intervention	Primary endpoint	Status
dMMR/MSI-H	ATOMIC (Alliance A021502)[23]	Stage III dMMR	mFOLFOX6 ± atezolizumab	DFS	Investigational (phase III; pending guideline incorporation)
dMMR/MSI-H and/or POLE	POLEM[24]	Stage III dMMR or POLE-mut	Chemo vs. chemo → avelumab	DFS	(Terminated early due to recruitment challenges; focus shifted to other dMMR platforms)
BRAF V600E (pMMR)	SOLARIS (Alliance A022004)[34]	Stage II/III BRAF V600E pMMR	Encorafenib + cetuximab vs. surveillance	DFS	Investigational
ctDNA/MRD (platform)	CIRCULATE-Japan[14]	Resectable CRC	ctDNA-guided adaptive platform	Various	Investigational
ctDNA/MRD	GALAXY Japan[13]	Resected stage II–III	Observational ctDNA monitoring	Prognostic	Investigational
ctDNA/MRD (de-escalation)	VEGA[14]	ctDNA− post-op (high-risk stage II / low-risk stage III)	Surgery alone vs. CAPEOX (3 mo)	Non-inferiority DFS	Investigational
ctDNA/MRD (escalation)	ALTAIR[14]	ctDNA+ post-op	TAS-102 vs. placebo	DFS	Investigational
ctDNA/MRD	CIRCULATE-US (NRG-GI008) (NCT05174169)	Stage II–III	ctDNA−: immediate vs. delayed chemo; ctDNA+: intensified chemo	DFS / time-to-ctDNA+	Investigational
ctDNA-directed platform	CLAUDIA[32]	Colon cancer	ctDNA-directed strategy	Trial-defined	Investigational

Notes: ctDNA+ is defined per each trial's assay and sampling schedule; the first postoperative MRD timepoint is typically assessed ~4–10 weeks after surgery (protocol-specific), with the landmark time point for the GALAXY study specifically emphasizing the 4-week postsurgical window.
Abbreviations: CAPEOX: Capecitabine/oxaliplatin; ctDNA: Circulating tumor DNA; DFS: Disease-free survival; dMMR: Deficient mismatch repair; mo: Months; MRD: Molecular residual disease; MSI-H: Microsatellite instability-high; pMMR: Proficient mismatch repair; TAS-102: Trifluridine/tipiracil.

interpreted through the lens of clinical positioning rather than routine treatment selection.[8,9,13–16] These platform studies are specifically designed to bridge the gap between ctDNA's established prognostic utility (recurrence risk) and its unproven predictive role in guiding safe de-escalation or necessary intensification.[8,13–15] Consequently, the evidentiary threshold for broad adoption remains improvement in disease-free and, ideally, overall survival relative to standard management.[14,15] Until these endpoints mature, ctDNA is most appropriately used to support risk-informed counseling and clinical trial enrollment rather than to mandate chemotherapy escalation or intensified surveillance as routine practice.[8,16]

4. Metastatic colorectal cancer: Actionable targets and matched therapy selection

Metastatic CRC has shifted from a chemotherapy-centric paradigm toward one defined by molecular stratification and biologically matched therapies.[7,9] Major guidelines recommend early characterization of MSI/MMR status and key drivers (*KRAS*/*NRAS*, *BRAF*, and *HER2*), with broader next-generation sequencing when feasible to capture less common actionable alterations and consolidate testing, while accounting for tissue adequacy and turnaround time.[8,9] Screening for mismatch-repair deficiency typically relies on immunohistochemistry for MMR proteins and/or MSI testing; however, technical and biologic heterogeneity can complicate interpretation. Occasional discordance between assays may reflect pre-analytic factors, limited tumor cellularity, or true heterogeneity in MMR protein expression, and in selected cases may also be influenced by secondary somatic events.[35,36] In the metastatic setting, the utility of liquid biopsy shifts from MRD detection to tracking molecular evolution.[16] In current practice, baseline plasma profiling is most valuable when tumor tissue is inadequate or when rapid turnaround times are necessary to guide a near-term treatment decision. However, a negative liquid biopsy result often requires reflex tissue confirmation to avoid missing actionable alterations in low-shedding tumors.[8,16] Beyond initial diagnosis, as the landscape of actionable targets and rechallenge strategies expands, the highest-yield application of plasma profiling is increasingly longitudinal. By serially tracking molecular evolution and identifying acquired resistance mechanisms, liquid biopsy can dictate next-line therapy sequencing rather than simply acting as a substitute for baseline tissue genotyping.[8,16,37]

Microsatellite instability-high/deficient mismatch repair disease defines a foundational immunotherapy-responsive subgroup and is guideline-positioned for first-line checkpoint inhibition, with regimen selection individualized to comorbidity profile and toxicity tradeoffs.[8,38–40] For microsatellite-stable disease, *RAS* and *BRAF* status together with primary tumor sidedness define eligibility for anti-EGFR therapy, which is not recommended in *RAS*-mutated tumors and is most relevant for selected left-sided, *RAS* wild-type metastatic CRC, where it can be incorporated into first-line strategies.[8,9,41] Beyond these core decision nodes, several smaller molecular subsets support matched therapy: *BRAF* V600E-mutated metastatic CRC has guideline-positioned BRAF/EGFR-targeted combinations after prior therapy, while earlier-line intensification remains an evolving area that should be interpreted by line of therapy and aligned with guideline updates.[8,42–44] Given the aggressive nature and rapid clinical deterioration associated with *BRAF*-mutant disease, identifying high-risk subsets for earlier-line intensification remains a top research priority.[45] *HER2* amplification (typically in *RAS* wild-type disease) is an actionable later-line target supported by HER2-directed combinations and antibody–drug conjugates.[8,46–48] *KRAS* G12C metastatic CRC is best approached with combined KRAS inhibition plus EGFR blockade, reflecting pathway feedback mechanisms in CRC and supported by prospective efficacy data and regulatory updates.[8,49–51] Adagrasib, an oral small-molecule inhibitor of KRAS G12C, has demonstrated efficacy in heavily pretreated patients when combined with cetuximab, achieving a median overall survival of 15.9 months in the KRYSTAL-1 study.[52] Finally, rare tumor-agnostic fusions (e.g., *NTRK*, *RET*) are uncommon but clinically meaningful when present, reinforcing the value of broad profiling when feasible.[53–56]

The current landscape of validated and emerging matched therapies for metastatic disease is summarized in Table 2, illustrating the diverse targets and clinical evidence supporting their implementation in various lines of therapy.

Metastatic CRC is the setting where precision oncology is most practice-defining, because multiple biomarkers have matched therapies supported by prospective data and incorporated into major guidelines.[8,9,38,42,46,49,50] The key clinical synthesis is not simply which targets exist, but how to prioritize them: MSI-H/dMMR status should be established early, given first-line immunotherapy benefit, while *RAS*/*BRAF*/*HER2* inform initial sequencing and eligibility for anti-EGFR or targeted combinations.[8,9,38,41,42,46] Broad next-generation sequencing can consolidate testing and identify rare actionable alterations, but negative plasma results may require tissue confirmation in low-shedding tumors and should not be treated as definitive in isolation.[8,16,37] Across targets, acquired resistance and

Table 2. Actionable alterations in metastatic colorectal cancer and matched therapies

Biomarker	Line of therapy	Matched therapy	Status	Key evidence
MSI-H/dMMR	1L	Nivolumab + ipilimumab (preferred) or pembrolizumab	FDA-approved; NCCN Category 1	KEYNOTE-177: mPFS 16.5 vs. 8.2 mo. CheckMate 8HW: Nivolumab + ipilimumab was superior to both SOC (HR: 0.21) and nivolumab monotherapy.
RAS wild-type (left-sided)	1L	Anti-EGFR (cetuximab/panitumumab) + chemotherapy	SOC; NCCN Category 2A	CRYSTAL/OPUS Pooled: Improved OS (HR: 0.81) and ORR in *KRAS* wild-type disease.
BRAF V600E[a]	≥2L	Encorafenib + cetuximab	FDA-approved; NCCN Category 1	BEACON: mOS 9.3 mo (triplet/doublet) vs. 5.9 mo (SOC).
	1L	Encorafenib + cetuximab + mFOLFOX6	FDA-approved; NCCN Category 2A	BREAKWATER (2025): Confirmed ORR 60.9% vs. 40.0% (SOC).
HER2 amplification	≥2L	Tucatinib + trastuzumab	FDA-approved; NCCN Category 2A	MOUNTAINEER: Confirmed ORR 38.1%; mOS 24.1 mo.
	≥2L	Trastuzumab deruxtecan	FDA-approved; NCCN Category 2A	DESTINY-CRC01: ORR 45.3% in HER2 3+ or 2+/*in situ* hybridization-positive.
KRAS G12C	≥2L	Sotorasib + panitumumab	FDA-approved; NCCN Category 2A	CodeBreaK 300 (Phase III): mPFS 5.6 mo vs. 2.0 mo (SOC).
	≥2L	Adagrasib + cetuximab	FDA-approved; NCCN Category 2A	KRYSTAL-1: ORR 34%; mPFS 6.9 mo; mOS 15.9 mo.
NTRK Fusion	Any line	Larotrectinib or entrectinib	FDA-approved; NCCN Category 2A	Tumor-agnostic data: ORR 75% across fusion-positive solid tumors.
RET Fusion	≥2L	Selpercatinib	FDA-approved; NCCN Category 2A	LIBRETTO-001: ORR 44%; median duration of response 24.5 mo.

Notes: [a]For *BRAF* V600E, guideline-positioned use is best established after prior therapy (e.g., BEACON).[8,42] Trials evaluating earlier-line intensification should be interpreted by line of therapy and aligned with guideline updates.[8,43,44]
Abbreviations: 1L: First-line; 2L: Second-line; dMMR: Deficient mismatch repair; EGFR: Epidermal growth factor receptor; FDA: Food and Drug Administration; HR: Hazard ratio; mo: Months; mOS: Median overall survival; mPFS: Median progression-free survival; MSI-H: Microsatellite instability-high; NCCN: National Comprehensive Cancer Network; ORR: Objective response rate; SOC: Standard of care.

clonal evolution increasingly drive treatment failure, supporting reassessment (often with plasma-based profiling) when results are likely to change next-line selection.[16,37] Even when biomarkers are identified, real-world barriers—including tissue adequacy, turnaround time, reimbursement, and access to targeted agents or trials—can materially limit delivery of matched therapy outside specialized centers.[8,11,16]

5. Conclusion

Precision oncology in CRC is most clearly practice-changing in metastatic disease, where early molecular characterization can identify immunotherapy-responsive tumors and actionable targets that expand treatment options and inform sequencing.[7–9,38] In curative-intent CRC, precision strategies are advancing—particularly adjuvant chemo-immunotherapy trials in selected stage III dMMR/MSI-H disease and biomarker-linked interventions such as aspirin in PI3K-altered localized disease.[8,23,28] Postoperative ctDNA provides strong prognostic risk stratification and has accelerated MRD-guided trial design; however, current guidance cautions against routine escalation, de-escalation, or surveillance changes based on ctDNA outside clinical trials, underscoring the need for interventional evidence demonstrating improved disease-free and overall survival before routine adoption.[8] Future progress will depend less

on identifying additional candidate biomarkers alone and more on prospective validation showing that biomarker-guided intensification or de-escalation can improve long-term outcomes without adding unnecessary toxicity, particularly in curative-intent disease.[8,14–16] In parallel, the clinical impact of precision oncology will increasingly be determined by implementation factors—timely access to testing, actionable turnaround times, and equitable access to matched therapies and trials.[8,11,16]

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