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The Role of Gut Microbiota in Metastatic Progression and Prognosis of Colorectal Cancer: A Systematic Review

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Abstract

Introduction: Metastatic colorectal cancer (CRC) continues to present a significant clinical and public health burden, with metastasis accounting for the majority of CRC-related mortality. Recent evidence highlights the gut microbiota as an important modulator of not only CRC initiation but also metastatic progression, prognosis, and therapeutic response. However, the clinical significance and mechanistic roles of specific microbial alterations in metastatic CRC remain incompletely understood.

Objective: To systematically review and synthesize cohort-based evidence regarding the association between gut microbiota composition and metastatic progression, risk, or prognosis in colorectal cancer patients.

Methods: This systematic review adhered to PRISMA guidelines and involved a comprehensive search of PubMed, Embase, and Web of Science for cohort and observational studies published up to July 2025. Eligible studies included adult CRC patients, profiled the natural gut microbiota using sequencing, and compared microbial profiles by metastatic status or evaluated microbiota associations with metastatic outcomes. Data extraction and quality assessment were performed independently by two reviewers. Due to heterogeneity, a narrative synthesis approach was used.

Result: Five cohort studies, published between 2022 and 2024, met inclusion criteria and included diverse populations from Europe and Asia. Across studies, metastatic CRC patients displayed significant shifts in gut microbiota compared to non-metastatic cases and healthy controls. Key findings included enrichment of Fusobacteria and pathogenic taxa (e.g., Bacteroides fragilis, Akkermansia muciniphila) in metastatic disease, alongside depletion of beneficial butyrate-producing genera (Faecalibacterium prausnitzii, Blautia, Agathobacter). Fusobacteria enrichment was reproducibly linked to liver metastasis and poor progression-free survival, while higher abundance of butyrate-producers correlated with better prognosis, particularly in patients receiving immunotherapy. Considerable heterogeneity was observed due to confounding factors such as antibiotic use and baseline patient characteristics.

Discussion: These findings indicate that metastatic CRC is associated with distinct and reproducible alterations in the gut microbiota, with Fusobacteria enrichment and loss of butyrate-producing commensals representing hallmark signatures. Such microbial shifts may contribute to tumor immune evasion, metastatic niche formation, and therapeutic resistance, while also holding potential as prognostic biomarkers. However, methodological differences, limited sample sizes, and variable adjustment for confounders across studies highlight the need for further validation in large, harmonized cohorts.

Conclusion: Metastatic progression in CRC is characterized by significant alterations in gut microbiota composition, supporting the microbiome as both a prognostic biomarker and a potential therapeutic target. Future large-scale, longitudinal, and mechanistic studies are needed to confirm these findings, clarify causality, and pave the way for microbiota-based interventions in the management of metastatic CRC.

Keywords: Colorectal cancer; Metastasis; Gut microbiota; Microbiome; Fusobacteria; Butyrate-producing bacteria; Prognosis

Introduction

Colorectal cancer (CRC) stands as one of the leading global health challenges, ranking as the third most commonly diagnosed malignancy and the second highest cause of cancer-related mortality worldwide.[1] Despite notable advances in screening, early detection, and multimodal therapy, the prognosis for metastatic colorectal cancer remains poor, with metastasis—particularly to the liver—serving as the main driver of mortality and clinical deterioration.[2] Approximately 20% of patients present with metastases at initial diagnosis, and over half of all CRC patients will develop distant metastases during the course of their disease, emphasizing the urgent need to clarify the biological processes that underpin metastatic progression and to identify robust prognostic biomarkers.[2]

In recent years, the gut microbiota has emerged as a key regulator in the pathogenesis and clinical trajectory of CRC. The human gut harbors a dynamic and complex community of microorganisms, which interact intimately with the host mucosa and immune system to influence nutrient absorption, immune homeostasis, and metabolic balance.[3] Disruption of this equilibrium, a state termed dysbiosis, has been increasingly linked to a variety of pathological conditions, including CRC initiation, progression, and metastasis.[4]

Several taxa have been repeatedly implicated in CRC pathogenesis, including Fusobacterium nucleatum, Bacteroides fragilis, and Escherichia coli (especially pks+ strains), which have demonstrated the capacity to induce DNA damage, promote inflammation, and modulate oncogenic signaling pathways within the colonic epithelium.[4,5] Large-scale metagenomic analyses have consistently identified a distinct microbial signature in CRC patients compared to healthy controls, featuring the enrichment of pathogenic species and depletion of beneficial commensals such as butyrate-producing Faecalibacterium prausnitzii and Blautia.[6] However, it is increasingly clear that the impact of the microbiota extends beyond tumor initiation, actively shaping the tumor microenvironment and influencing metastatic behavior.

Recent studies have suggested that gut microbiota can modulate the metastatic cascade through several mechanisms, including production of microbial metabolites (e.g., secondary bile acids, short-chain fatty acids), regulation of immune cell recruitment, and disruption of the intestinal barrier.[4,7] The enrichment of Fusobacterium and other pathogenic taxa in CRC patients with liver metastasis, as well as a higher microbial diversity in metastatic compared to non-metastatic cases, underscores the potential of specific microbiota profiles to serve as biomarkers for metastatic risk.[8] Notably, a prospective multi-cohort study demonstrated that high Fusobacteria abundance in both fecal and tumor tissue samples was predictive of liver metastasis and correlated with shorter progression-free survival, highlighting a plausible link between gut microbiota composition and metastatic potential.[8]

Moreover, the prognostic significance of baseline gut microbiota has begun to attract clinical interest. Martini et al. found that the presence of butyrate-producing taxa such as Agathobacter and Blautia at baseline was associated with improved progression-free survival in metastatic CRC patients undergoing immunotherapy, suggesting that the microbiome could modulate therapeutic response and clinical outcomes.[9] However, not all studies have identified clear associations between microbiota composition and prognosis; for example, a Dutch prospective cohort found no significant group-level differences in microbiota diversity or composition between treatment responders and non-responders, although antibiotic use caused substantial individual variation.[10] Such findings reflect the complexity of microbiome-host-tumor interactions and the influence of confounding factors such as diet, antibiotic exposure, and host genetics.

Despite these advances, the clinical and biological implications of microbiota alterations in metastatic CRC remain incompletely understood. There is considerable heterogeneity in sequencing technologies, analytic pipelines, and population demographics across studies, complicating direct comparison and synthesis. Furthermore, much of the evidence to date is derived from cross-sectional or case-control designs, while robust longitudinal cohort studies remain limited. Consequently, a systematic synthesis of available cohort evidence is needed to clarify the association between gut microbiota and metastasis in CRC, identify consistent microbial biomarkers, and guide future translational research.

Therefore, the aim of this systematic review is to comprehensively evaluate the cohort-based evidence on the association between gut microbiota composition and metastatic progression, risk, or prognosis in colorectal cancer patients. By synthesizing findings from recent human cohort studies, this review seeks to provide an updated perspective on the role of gut microbiota in metastatic CRC, to inform both clinical prognostication and the development of microbiome-targeted strategies for improved patient outcomes.

Methods

Study Design

This systematic review was designed and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review protocol was developed prospectively to ensure methodological rigor and transparency.

Literature Search Strategy

A comprehensive literature search was conducted in the following electronic databases: PubMed/MEDLINE, Cochrance, and ScienceDirect, covering all articles published up to July 2025. The search strategy was designed to identify cohort and observational studies examining the association between gut microbiota composition and metastatic colorectal cancer in humans. The following search terms and Medical Subject Headings (MeSH) were used in various combinations:

("colorectal cancer" OR "colorectal neoplasm" OR "colon cancer" OR "rectal cancer") AND ("gut microbiota" OR "intestinal microbiota" OR "microbiome" OR "fecal microbiota") AND (metastatic OR metastasis OR "liver metastasis" OR "advanced stage") AND (cohort OR

prospective OR retrospective OR observational OR "case-control" OR "longitudinal study" OR "follow-up study").

The search was limited to studies published in English and conducted on human subjects. Additional records were identified by manually screening the reference lists of eligible articles and recent systematic reviews.

Eligibility Criteria

Inclusion criteria:

1. Study design: Prospective or retrospective cohort studies, case-control studies, or large case series (>30 subjects).
2. Population: Adult patients with histologically confirmed colorectal cancer.
3. Exposure: Analysis of the natural gut microbiota composition, diversity, or specific bacterial taxa (measured by high-throughput sequencing, e.g., 16S rRNA or shotgun metagenomics).
4. Comparison: Metastatic versus non-metastatic CRC, or CRC with different metastatic profiles (e.g., liver metastasis vs. no metastasis), or CRC compared to healthy controls with reported metastatic status.
5. Outcomes: Incidence or presence of metastasis, progression-free survival, overall survival, or any clinical or prognostic outcome related to metastasis.
6. Reporting: Studies providing sufficient data on microbiota composition in relation to metastatic status or outcome.

Exclusion criteria:

1. Animal, in vitro, or preclinical studies.
2. Interventional studies (e.g., probiotic or FMT trials) unless baseline natural microbiota data were reported separately.
3. Reviews, meta-analyses, conference abstracts, commentaries, editorials, or case reports.
4. Studies lacking primary clinical data or those with insufficient reporting on metastatic status.
5. Study Selection

After deduplication, all titles and abstracts were independently screened by two reviewers for potential eligibility. Full texts of potentially relevant articles were then assessed for inclusion based on the eligibility criteria. Disagreements were resolved through consensus or consultation with a third reviewer.

Data Extraction

Data extraction was performed independently by two reviewers using a standardized form. Extracted data included:

1. Study characteristics (author, year, country, study design, population size, inclusion/exclusion criteria)
2. Patient demographics and clinical characteristics (age, sex, tumor stage, metastatic status, site of metastasis)

3. Microbiota assessment method (sample type, sequencing technology, analytic approach)
4. Main outcomes (differences in microbiota composition/diversity, key taxa, prognostic associations)
5. Adjustments for confounders and statistical analysis methods.
6. Any discrepancies were discussed and resolved by consensus.

Quality Assessment

The methodological quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies. This tool evaluates selection of study groups, comparability, and ascertainment of outcome/exposure. Studies were graded as high, moderate, or low quality based on total NOS score. Risk of bias across studies was considered during synthesis and interpretation.

Data Synthesis and Analysis

Given the heterogeneity in study design, population, sequencing technology, and outcomes, a meta-analysis was planned only if sufficient homogeneity in reporting and methodology was present. Otherwise, a narrative synthesis was conducted, with results presented in tabular and descriptive form, emphasizing differences and similarities in microbiota composition, key bacterial taxa associated with metastatic status, and prognostic value.

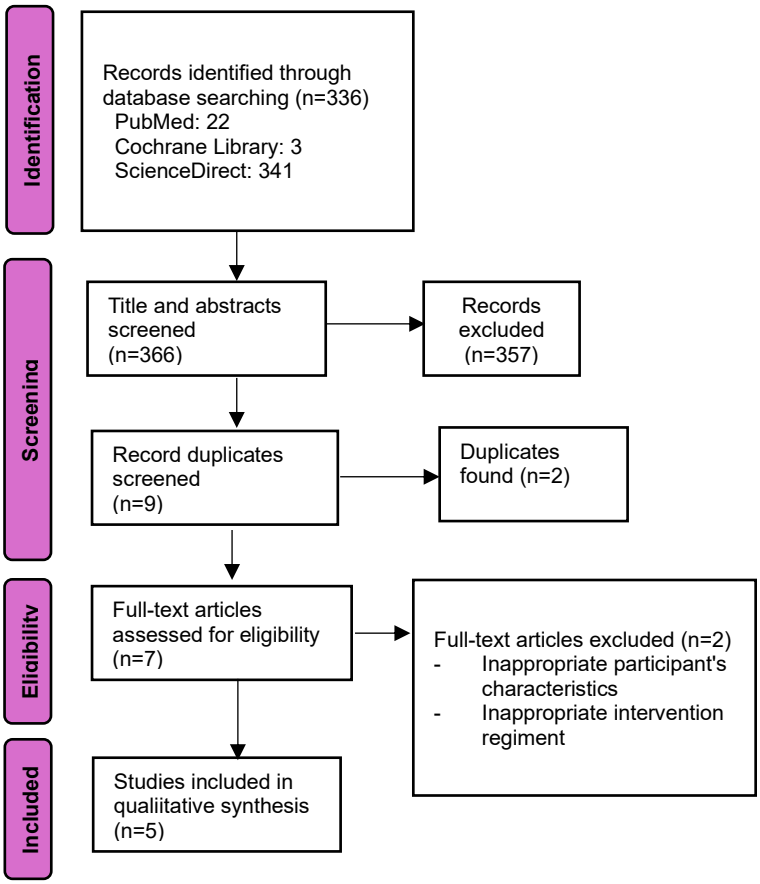

Figure 1. Diagram flow of literature search strategy for this systematic review

Study (Author, Year)	Design & Population	N	Country	Sampling/Seq Method	Main Comparison	Key Findings and Mechanistic/Clinical Summary	Relevant Taxa in Metastasis/Outcome
Martini et al., 2022	Prospective cohort, mCRC (RAS/BRAF WT, MSS, 3rd+ line)	14	Italy	16S rRNA, Illumina MiSeq	Long-term PFS (>9 mo) vs. others	Long-term clinical responders had a higher baseline abundance of Agathobacter and Blautia, butyrate-producing genera linked to better prognosis and enhanced immunotherapy efficacy.	Longer progression-free survival was associated with increased abundance of Agathobacter M104/1 and Blautia SR1/5.
Jin et al., 2024	Multi-cohort, CRC with/without liver metastasis	126	China	16S rRNA, Illumina MiSeq	Liver metastasis (LM) vs. Non-liver metastasis (NLM)	CRC patients with liver metastasis showed higher microbial diversity and Fusobacteria abundance, which served as a strong biomarker for metastasis and poor progression-free survival.	Liver metastasis was marked by higher Fusobacteria and lower Proteobacteria, with Fusobacteria linked to poor prognosis.
Aarnoutse et al., 2022	Prospective cohort, mCRC, on capecitabine	33	Netherlands	16S rRNA, Illumina MiSeq	Responders (PR) vs. Non-responders (SD, PD)	No significant microbiota differences were found between responders and non-responders, while antibiotic exposure strongly affected individual microbiome profiles.	No group-level taxonomic changes were seen, though one responder had increased Bifidobacteria.
Zhao et al., 2024	Retrospective cohort, CRC vs. healthy controls, lymph node status	18 (CRC), 18 (Ctrl)	China	16S rRNA, Illumina MiSeq	CRC vs. control; lymph	Lymph node-positive CRC was associated with increased Rothia, Streptococcus, and Actinomyces and decreased Bacteroides and Parabacteroides, reflecting a more pro-inflammatory microbiome.	Lymph node metastasis was linked to higher Rothia, Streptococcus, Actinomyces, and lower Bacteroides, Parabacteroides, Oscillibacter.

					node (+) vs (−)		
Li et al., 2022	Prospective cohort, GI cancer (44 CRC), metastatic-enriched	44 (CRC), 147 (Ctrl)	China	16S rRNA, HiSeq2500	CRC vs. healthy controls	CRC patients had depleted butyrate-producing commensals and increased pathogenic taxa, suggesting a shift toward a tumor-promoting microbiome.	CRC was associated with lower Faecalibacterium, Clostridium clostridioforme, Bifidobacterium adolescentis, and higher Bacteroides fragilis, Akkermansia muciniphila.

Table 1. Characteristics and results table

Results

Study Selection

The systematic search yielded a total of 336 records. After duplicate removal, 9 unique records were screened by title and abstract. Of these, 7 full-text articles were assessed for eligibility. Ultimately, five original cohort studies met all inclusion criteria and were incorporated into the final qualitative synthesis (see PRISMA flow diagram, Figure 1).

Characteristics of Included Studies

A summary of the included studies is provided in Table 1. All included studies were published between 2022 and 2024, and were conducted in diverse geographic settings, including Italy, the Netherlands, and China. Study designs encompassed both prospective and retrospective cohorts, and sample sizes ranged from as few as 14 to as many as 147 participants per group. The included studies focused exclusively on adult populations with histologically confirmed colorectal cancer (CRC), with most patients either presenting with, or being stratified by, metastatic disease status—including liver metastasis and lymph node involvement.

All studies employed high-throughput sequencing of the 16S rRNA gene for microbiota profiling, primarily utilizing fecal specimens, although one study also included primary tumor tissue samples. Differences in sequencing platforms, targeted 16S regions, and bioinformatic pipelines were noted across studies, contributing to methodological heterogeneity.

Microbiota Diversity and Composition in Metastatic Versus Non-Metastatic CRC

Across the included studies, marked alterations in the diversity and composition of the gut microbiota were observed in CRC patients with metastatic disease compared to their non-metastatic counterparts or healthy controls.

Jin et al. (2024) conducted a comprehensive multi-cohort analysis involving both discovery and validation cohorts, as well as primary tumor tissue samples. Their results demonstrated that CRC patients with liver metastasis (LM) exhibited significantly higher alpha- and beta-diversity compared to non-liver metastatic (NLM) patients, a pattern consistent across both fecal and tumor tissue microbiota. Importantly, the enrichment of the phylum Fusobacteria was a distinctive feature of the LM group, and machine learning models confirmed the predictive value of Fusobacteria abundance for the presence of liver metastases (AUC ~0.89). The study further showed that high Fusobacteria abundance was associated with worse progression-free survival (PFS) in non-metastatic patients, suggesting not only a diagnostic but also a prognostic significance.

Zhao et al. (2024) provided additional evidence of the microbiota's relationship with metastatic phenotype by demonstrating that CRC patients with lymph node metastasis had increased abundance of genera such as Rothia, Streptococcus, and Actinomyces, while key commensals including Bacteroides, Parabacteroides, and Oscillibacter were reduced. These compositional shifts, observed using 16S rRNA sequencing of fecal samples, further support the hypothesis that the gut microbiota profile evolves alongside metastatic progression and may influence the tumor microenvironment.

Li et al. (2022) investigated a large, metastatic-enriched cohort of CRC patients and healthy controls. Their analysis found that the CRC group exhibited significant depletion of butyrate-

producing and anti-inflammatory taxa—notably Faecalibacterium prausnitzii, Clostridium clostridioforme, Bifidobacterium adolescentis, Blautia producta, and Ruminococcus faecis—and an increase in potentially pathogenic taxa, including Bacteroides fragilis, Akkermansia muciniphila, Clostridium hathewayi, and Alistipes finegoldii. The authors further identified that GI cancer patients, including those with CRC, had altered microbial metabolic pathways relevant to carcinogenesis, such as lipid, glycan, and tryptophan metabolism.

Prognostic and Predictive Value of Microbiota in Metastatic CRC

Several studies in this review directly explored the association between gut microbiota composition and patient prognosis or therapeutic response in metastatic CRC.

Martini et al. (2022) performed a prospective observational cohort analysis embedded within a clinical trial of metastatic CRC patients undergoing immunotherapy. Their findings revealed that baseline abundance of butyrate-producing genera, specifically Agathobacter and Blautia, was strongly associated with prolonged progression-free survival (PFS). Long-term responders (PFS >9 months) had a significantly higher prevalence of these taxa compared to patients with shorter PFS. This suggests a protective and potentially immunomodulatory role for these commensals, highlighting their possible utility as prognostic biomarkers or therapeutic targets.

In contrast, Aarnoutse et al. (2022) investigated a prospective cohort of 33 metastatic CRC patients treated with capecitabine and found no statistically significant differences in microbiota diversity or specific taxonomic profiles between responders and non-responders. Notably, the study observed that individual antibiotic use produced more pronounced shifts in microbiota composition than chemotherapy exposure, underscoring the impact of external factors on gut microbial ecology in advanced cancer patients. The heterogeneity of microbiota findings in this and other studies underscores the complexity of host-microbiome interactions in the metastatic CRC setting and the need for larger, harmonized cohort analyses.

Cross-Study Synthesis: Consistencies, Variability, and Emerging Signatures

Synthesizing across studies, a number of consistent patterns and key taxa associated with metastatic status or prognosis emerge:

Fusobacteria: Consistently enriched in patients with liver metastasis (Jin et al.), predictive of both metastatic status and poor PFS, supporting its emerging role as a microbial biomarker for aggressive disease.

Butyrate-Producing Genera (e.g., Agathobacter, Blautia, Faecalibacterium): Higher abundance appears protective and is associated with improved prognosis and longer PFS (Martini et al., Li et al.), while depletion is a common feature in metastatic and advanced CRC.

Pathogenic/Inflammatory Taxa (e.g., Bacteroides fragilis, Akkermansia muciniphila, Rothia, Streptococcus): Frequently elevated in metastatic or high-risk CRC, possibly contributing to a pro-tumorigenic and immunosuppressive microenvironment (Li et al., Zhao et al.).

Diversity Indices: Both increased and decreased microbial diversity have been reported, suggesting that context-dependent shifts—possibly influenced by host, environment, or therapeutic exposures—modulate the relationship between diversity and metastatic risk.

Functional Pathways: Alterations in microbial metabolic pathways related to lipid, glycan, and tryptophan metabolism may underlie microbiota-driven modulation of metastatic progression (Li et al.).

However, it is also apparent that the landscape of microbiota research in metastatic CRC is marked by substantial inter-individual and inter-study variability. Discrepancies in methodology, population demographics, sequencing platforms, and confounder adjustment may all influence findings. Notably, the impact of antibiotics, diet, and chemotherapy remains a significant confounding factor, as highlighted by Aarnoutse et al.

Overall Synthesis

In summary, the evidence synthesized in this review underscores that gut microbiota composition is significantly altered in metastatic CRC, with specific bacterial taxa and community features emerging as potential biomarkers of metastatic risk, disease progression, and patient prognosis. Enrichment of Fusobacteria and depletion of butyrate-producing commensals represent the most robust and reproducible findings across cohorts. Nonetheless, the heterogeneity in methodologies, patient populations, and confounders emphasizes the need for further large-scale, harmonized, prospective studies to clarify the clinical and biological significance of these associations, as well as to enable development of microbiota-based prognostic tools or therapeutic strategies in metastatic CRC.

Discussion

This systematic review presents a comprehensive synthesis of recent cohort-based evidence, revealing that the gut microbiota plays a pivotal and multifactorial role in the metastatic progression and clinical outcomes of colorectal cancer (CRC). The collective findings highlight that the interplay between specific microbial taxa, host immunity, tumor microenvironment, and environmental exposures shape not only carcinogenesis, but also metastatic risk, organotropism, and patient prognosis.

Alterations in Microbiota Diversity and Community Structure

A key pattern consistently observed across the included studies is the marked shift in gut microbiota composition and diversity in CRC patients with metastatic disease, as compared to both non-metastatic cases and healthy controls. Studies such as Jin et al. and Li et al. have demonstrated that metastatic CRC—particularly those with liver or lymph node involvement—tends to be characterized by both increased microbial diversity and the enrichment of potentially pathogenic taxa, most notably Fusobacteria, Bacteroides fragilis, and Akkermansia muciniphila【8,13,14】. The rise in alpha- and beta-diversity among metastatic CRC patients in Jin et al.'s multi-cohort study suggests not only a loss of "healthy" commensal equilibrium, but also a competitive expansion of tumor-promoting bacteria within the gut ecosystem.

Simultaneously, there is a consistent depletion of beneficial butyrate-producing commensals, including Faecalibacterium prausnitzii, Blautia, and Agathobacter.[11] These taxa are well known for their ability to maintain epithelial barrier integrity, suppress local inflammation, and generate anti-tumorigenic metabolites such as short-chain fatty acids (SCFAs). The loss of these beneficial

microbes likely facilitates increased mucosal permeability, microbial translocation, and the recruitment of inflammatory cells, all of which have been implicated in metastatic progression.[12]

Mechanistic Pathways: From Microbiota to Metastasis

Mechanistic insights from both human and preclinical studies further elucidate how specific microbiota modulate metastatic processes. Fusobacterium nucleatum and related Fusobacteria are now recognized as key drivers of CRC progression through multiple mechanisms: promoting pro-inflammatory cytokine cascades, enhancing epithelial-mesenchymal transition (EMT), activating β-catenin and NF-κB signaling, and modulating the immune microenvironment to favor tumor immune escape.[9] For example, in both Jin et al. and previous foundational studies, the abundance of Fusobacteria in fecal and tumor samples robustly predicted liver metastasis, and correlated with poor progression-free survival, suggesting this genus is not merely a bystander but an active participant in metastatic biology.[13]

Conversely, butyrate-producers such as Agathobacter and Blautia—highlighted in the long-term responder subgroup of Martini et al.—appear to exert protective effects by generating anti-inflammatory metabolites, bolstering barrier integrity, and supporting anti-tumor immune responses.[14] The association of these taxa with improved progression-free survival in metastatic CRC patients receiving immunotherapy suggests that restoring or supporting these commensals could enhance therapeutic efficacy. Such findings are echoed by both clinical and animal studies showing that butyrate can directly inhibit cancer cell proliferation and modulate T-cell recruitment within the tumor microenvironment.[15]

Beyond taxonomic shifts, recent metagenomic and functional studies (e.g., Li et al., Wirbel et al.) have revealed that CRC progression and metastasis are accompanied by profound alterations in the gut microbiome's metabolic potential, including increased pathways for bile acid deconjugation, tryptophan metabolism, and the biosynthesis of genotoxic compounds.[11,13] Such metabolic changes may foster a permissive niche for tumor growth, drive immune evasion, or promote angiogenesis and invasion—hallmarks of the metastatic cascade.[12]

Prognostic, Predictive, and Clinical Relevance

Collectively, these findings position the gut microbiota as a promising biomarker source for metastatic risk assessment and clinical prognostication in CRC. The reproducible enrichment of Fusobacteria in metastatic and poor-prognosis patients—seen in both Asian and European cohorts—suggests fecal microbiota profiling could complement traditional clinicopathological markers in identifying high-risk individuals.[9,13] The beneficial role of butyrate-producers as potential predictors of therapy response, as seen in Martini et al., further extends this utility to the realm of personalized medicine and immunotherapy stratification.[15]

However, not all studies have demonstrated clear prognostic associations. For example, Aarnoutse et al. found no significant group-level differences in microbiota diversity or composition between capecitabine responders and non-responders in metastatic CRC. This underscores the complexity of microbiome-host-drug interactions and highlights that factors such as antibiotic exposure, diet, and previous therapies may overshadow or confound the relationship between microbiota and clinical outcomes.[10,11] The impact of antibiotics was particularly notable

in Aarnoutse et al., as single-patient shifts in microbiota composition due to antibiotic exposure frequently exceeded those induced by chemotherapy itself—a salient reminder of the environmental and iatrogenic influences shaping the gut ecosystem.[10]

Heterogeneity, Methodological Limitations, and Research Gaps

While this review identifies robust microbial signatures linked to metastatic CRC, it also underscores considerable heterogeneity and persistent gaps in the current literature. Methodological differences—including variations in sequencing platforms, targeted 16S rRNA regions, bioinformatic pipelines, and statistical methods—limit direct cross-study comparison and synthesis.[16] Population heterogeneity, encompassing ethnicity, dietary patterns, baseline health, and treatment exposures, further complicates the reproducibility of findings across settings.

Most studies included in this review are limited by relatively small sample sizes, cross-sectional or single-institution designs, and variable adjustment for confounding factors such as antibiotic use, diet, or tumor molecular subtypes.[16,17] The majority of available evidence is derived from Asian and European populations; it remains unclear how these microbial associations may vary globally, particularly in underrepresented regions. In addition, while the bulk of evidence links microbial changes to the presence or risk of metastasis, there remains a paucity of true longitudinal studies able to address causality or temporal dynamics.

Clinical and Translational Perspectives

Despite these challenges, the gut microbiota-metastasis axis remains an area of intense translational potential. With the advent of non-invasive microbiota-based diagnostic assays and the growing integration of microbiome science into cancer care, there is the promise of developing fecal microbiota signatures for early detection, prognostication, and therapeutic stratification.[15,16] Interventional studies—ranging from dietary interventions and probiotics to more experimental modalities such as fecal microbiota transplantation—are beginning to test whether targeted modulation of the microbiome can alter the course of metastatic CRC.[15,18]

Future research should prioritize large, multi-center, longitudinal cohort studies integrating multi-omics (metagenomics, metabolomics, transcriptomics, immune profiling), rigorous adjustment for confounders, and harmonization of analytic methods. Randomized trials should be designed to assess the impact of microbiota-directed interventions on metastatic risk, progression, and treatment response. Ultimately, a deeper mechanistic understanding of how the gut microbiota interfaces with tumor biology, immunity, and host metabolism will be critical to realize its full clinical potential.

Conclusion

In conclusion, this review demonstrates that metastatic CRC is characterized by distinct, reproducible alterations in the gut microbiota, with consistent enrichment of Fusobacteria and depletion of butyrate-producing commensals as the hallmark microbial signatures. These findings support the role of the gut microbiota as a modulator of metastatic progression and a potential biomarker for prognosis and therapy response. While the integration of microbiome science into

CRC management is still in its infancy, the accumulating evidence highlights its importance in advancing personalized oncology and improving patient outcomes.

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Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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