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Review

Microbiome-Driven Diagnostic and Therapeutic Strategies in Cancer

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Simple Summary

The current review article explores the association of microbes with cancer and suggests possible ways to diagnose and treat cancer. The synergistic association between microbes and cancer paves the way for early detection and timely treatment. The human microbiome plays a major role in health and disease, with emerging data highlighting its potential role in cancer biology. Continued research to understand the essential relationships between cancer and microbial communities can harness the microbiome's potential in oncology and pave the way for novel therapeutic methods with better patient outcomes.

Abstract

In cancer biology, the microbiome has emerged as a revolutionary field, revealing host–microbe interactions that drive cancer initiation, development, metastasis, and therapeutic response. The microbiome plays a mechanistic role in carcinogenesis by directly regulating host cell proliferation, apoptosis, and genomic stability, and indirectly through immune regulation and chronic inflammation. Depending on the microbial genetic makeup and host environment, microbial genotoxins, metabolites, and signaling molecules can either induce tumor growth or exert beneficial anticancer effects. Infectious agents are estimated to trigger a significant proportion of cancers globally, although the mechanistic pathways of the broader microbiome remain less well quantified. Likewise, it has been shown that microbiomes modulate the toxicity and efficacy of cancer treatments—specifically immunotherapy and chemotherapy—by mediating anti-tumor reactions and altering drug metabolism. Microbiome-based diagnostics, predictive markers, and therapeutic strategies like dietary modifications, probiotics, synthetic microbes, and fecal microbiota transplantation have collectively benefited from these breakthroughs. Despite rapid progress, integrating microbiome research into oncology is hindered by patient variability, methodological hurdles, and the difficulty of identifying definitive causal links. Large-scale clinical trials are essential for verifying the functional impact of microbiome-targeted treatments. The current review evaluates the mechanistic influence of microbiomes on cancer diagnosis and therapeutics.

Keywords: cancer biology; diagnostics; microbiome; synthetic microbes; therapeutics

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1. Introduction

The human microbiome comprises a complex ecosystem of bacteria, viruses, fungi, and protozoa that inhabit various parts of the human body. An estimated 100 trillion microbial cells are hosted by the human body, potentially exceeding the 37–40 trillion human cells, and around 2 million genes are encoded by such microbes, in comparison with the 20,000–22,000 genes of the human genome [1,2]. By promoting immune function, regulating essential nutrients, and maintaining intestinal integrity while also influencing the development of disease, the microbiome plays a pivotal role in sustaining human health [3]. As an emerging field, the oncobiome examines microbial communities and their interactions with cancer biology. According to recent studies, there is a shift from linking microorganisms to cancer to exploring mechanistic insights into how these microbes affect cancer development, progression, and treatment [4]. Although researchers were initially skeptical of this field, it has gained considerable traction as studies have begun to demonstrate microbial roles in tumor initiation and progression, the influence of microbiomes on immune responses, and the potential for therapeutic interventions [5,6]. Nevertheless, the field remains in its infancy, with many investigations reporting associations rather than establishing causal relationships, and methodological challenges such as sample contamination and population variability persist.

The human gut microbiome is remarkably diverse, harboring approximately 3000 bacterial species and trillions of microbial cells [7,8]. The formation of the gut microbiome is highly variable, with most individuals sharing a core microbiota of 50–100 bacterial species, chiefly from the Firmicutes and Bacteroidetes phyla [8,9]. About 70% of the total microbial load consists of microorganisms that dwell in the gastrointestinal tract [1]. Approximately 3.3 million exclusive genes in the gut have been revealed by metagenomic studies, substantially more than the human genome [9]. Conducive to the ecosystem's resilience and the host's physiological homeostasis, microbial diversity is notably rich [10,11], comprising more than 700 species and varying across the disparate sites of the oral microbiome [12]. Several factors, such as host age, ethnicity, lifestyle, and diet, can affect microbial composition, which in turn plays a vital role in both oral and systemic health [13,14]. Likewise, the skin microbiome is highly diverse, exhibiting marked variation across body sites and harboring over 1000 bacterial species [15]. The urogenital microbiome also presents considerable diversity, with gender playing a vital role in its composition [16].

The composition of the microbiome is potentially more influenced by environmental and lifestyle factors than by the host's genetics. A benchmark study found that environmental factors such as diet and medication contribute substantially to microbiome variability, often exceeding the contribution of host genetics in some cohorts [17]. Diet, antibiotics, and lifestyle factors, viz. exercise and cleanliness, can affect microbiome shifts and composition within 24–48 h under dietary or antibiotic perturbations [18–20]; external causes can change 30–40% of the microbiota composition throughout life [21]. The dynamic equilibrium of the human microbiome, in which distinct microbial associations are in stable interaction with the host, is referred to as microbial homeostasis. Conversely, pathological disruption of this balance can give rise to a range of health conditions, including obesity, inflammatory bowel disease, and diabetes, collectively referred to as dysbiosis [22,23]; arising from antibiotics, dietary changes, stress, or genetic factors, dysbiosis attenuates host immune responses and fosters a cancer-permissive environment [24,25]. The microbiome also influences tumor angiogenesis and remodeling of the microenvironment, thereby promoting cancer progression through complex associations [26]. DNA damage, chronic inflammation, alterations in immune responses, and alterations in metabolic pathways are induced by dysbiosis; each of these factors contributes to cancer development [27,28]. *Helicobacter pylori* and

Fusobacterium nucleatum, like specific microbes, are linked to the proliferation of cancer cells [29].

The microbiome has been implicated as an active contributor to tumor dissemination rather than a passive observer in cancer metastasis [30], mechanistically modulating immune surveillance, regulating epithelial–mesenchymal transition, and conditioning premetastatic niches [31]. According to recent studies, breast cancer patients exhibit markedly distinct microbiome profiles characterized by reduced *Methylobacterium* and increased Gram-positive organisms. Lung and urogenital microbiota affect cancer development and the tumor immune response and can serve as diagnostic markers [32–35]. A substantial portion of this research, while compelling, remains in its early phases, with current findings predominantly predictive rather than definitively causal.

The rationale for reviewing microbiome-cancer associations lies in the potential to uncover new opportunities for cancer screening, prevention, diagnosis, and treatment through exploration of microbial dysbiosis. There is a need to establish more robust evidence of the interaction between cancer progression and microbiome shifts by standardizing sampling techniques and collecting prediagnostic specimen studies in future research. The human microbiome plays a major role in health and disease, with data highlighting its potential role in cancer biology. Continued research to understand the essential relationships between cancer and microbial communities can harness the microbiome's potential in oncology and pave the way for novel therapeutic methods with better patient outcomes.

Brief method for selecting data and articles for this review: We have extensively searched the published literature in different national and international scientific journals; we have thoroughly searched Google Scholar, PubMed, and Research Gate. The time frame for the current study is 2012 to 2026. Still, we have included the maximum number of articles from the last five years (2020–2025), and the search terms were cancer, diagnostics, microbiome, therapeutics, and synthetic microbes.

2. Organ-Specific Role of Microbiome in Cancer

2.1. Oral Cavity

The discovery of 13 oral bacterial species is distinctively correlated to head and neck squamous cell carcinoma (HNSCC). The evidence suggests a microbial risk associated with an increased relative risk (reported up to ~50% in some cohorts), further establishing a potential link between oral microbiota dysregulation and cancer development and progression, as hallmarks show the oral microbiome and HNSCC association has a major role in microbial dysbiosis [36,37].

2.2. Stomach

Direct cytotoxic DNA damage, activation of tumorigenic pathways, and proinflammatory signaling mechanisms link gastrointestinal malignancies to the gastric microbiome. There is a direct association between microbes such as Helicobacter pylori, Epstein–Barr virus, Escherichia coli, and malignancies, including gastric and colorectal adenocarcinomas [38,39].

2.3. Lower Gastrointestinal Tract

A complex interaction with colorectal cancer (CRC), characterized by definitive microbial dysbiosis that can both promote and significantly prevent cancer development, is primarily mediated by the gut microbiome [40,41].

3. Microbiome as a Diagnostic and Prognostic Tool

The human microbiome has emerged as a promising source of diagnostic and prognostic biomarkers in cancer, supporting early disease detection, risk stratification, and prediction of therapeutic response (Figure 1) and (Table 1). Alterations in microbial diversity and community composition have been associated with cancer stage and progression, enabling identification of microbiome-derived signatures as early diagnostic biomarkers [42]. Non-invasive biological samples, including stool, urine, and saliva, are increasingly used for microbiome-based cancer screening and early detection strategies [43]. Several studies demonstrate that microbial composition can predict treatment outcomes, particularly responses to chemotherapy and immune checkpoint inhibitors [44]. Advances in next-generation sequencing and metagenomic profiling have enabled high-resolution identification of cancer-associated microbial signatures, strengthening their clinical utility as diagnostic and prognostic tools [45,46].

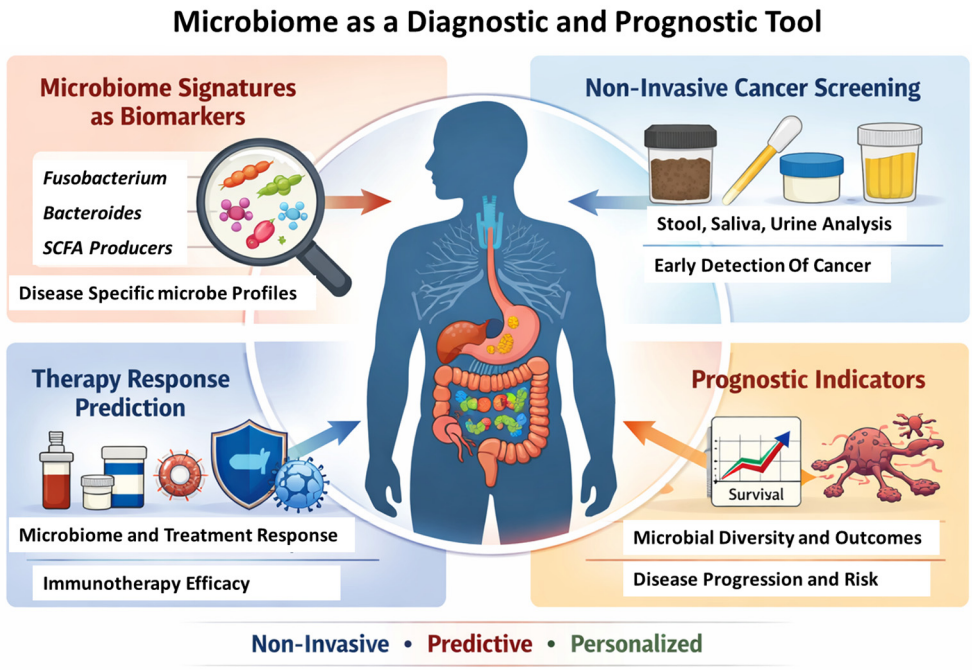


Figure 1. Microbiome as a Diagnostic and Prognostic Tool (Figure was created by the authors using PowerPoint and https://biorender.com/xfjdd0i, accessed on 25 December 2025).

3.1. Microbiome Signatures as Biomarkers

The term microbiome signatures usually refers to disease-associated patterns of microbial taxa, functional genes, or metabolic products that can be continuously detected in affected individuals [47]. *Fusobacterium nucleatum* concentration in tumor tissues and fecal samples has been frequently documented in CRC, where it promotes inflammation, immune evasion, and tumor growth [48,49]. Similarly, altered abundances of Bacteroides fragilis and Escherichia coli, which produce genotoxins, have been linked to CRC development [50]. Changes in the gut microbiota that impact estrogen metabolism—known as the "estrobolome"—have been suggested as possible biomarkers for breast cancer [51]. Functional microbiome signals offer mechanistic insights that go beyond taxonomic markers. Because of compromised epithelial barrier function and immunological dysregulation, reduced populations of short-chain fatty acid (SCFA)-producing bacteria, such as Faecalibacterium prausnitzii, are associated with chronic inflammation and cancer [52]. Therefore, metabolites and pathways originating from microbiomes may serve as useful functional biomarkers that complement conventional molecular diagnostics.

3.2. Non-Invasive Cancer Screening Approaches

The approach of detecting biological samples through non-invasive cancer screening has emerged as a valuable resource, improving patient compliance and facilitating large-scale screening implementation [42]. Regarding conventional Fecal Occult Blood Testing (FOBT) for early-stage detection of CRC, fecal microbiota analysis has demonstrated superior diagnostic sensitivity [49]. Metagenomic studies have already shown that integrating microbial markers enhances detection accuracy, especially when combined with Fecal Immunochemical Testing (FIT). Diagnosis using specific microbial taxa, including *Peptostreptococcus* and *Parvimonas* spp., has been reported to significantly improve CRC diagnostic performance [53]. Beyond CRC, changes in the oral microbiome have been associated with pancreatic cancer and oral squamous cell carcinoma, with increased levels of *Porphyromonas gingivalis* species proposed as potential non-invasive indicators [54]. Similarly, for prostate and bladder cancer, the profiling of the urinary microbiome is being explored as an early diagnostic strategy [55]. The oncology approach is therefore expected to further enhance through the integration of microbiome-derived data into risk stratification and personalized screening frameworks [56]. Risk stratification and customized screening techniques are now possible thanks to further improvements in predictive accuracy achieved by integrating microbiome data with machine learning algorithms [56].

3.3. Predictive Value for Therapy Response and Prognosis

It has been demonstrated that microbiomes affect treatment effectiveness and clinical outcomes, especially in cancer immunotherapy, and play a crucial role in determining host immune responses [57]. A unique gut microbiome enriched in *Akkermansia muciniphila*, *Bifidobacterium longum*, and *Faecalibacterium prausnitzii* was found in melanoma patients responding to immune checkpoint inhibitors (ICIs), according to groundbreaking research [44]. Gut microbiome composition dictates the efficacy and toxicity of immune checkpoint inhibitors, highlighting microbiome-based interventions as promising strategies to personalize and enhance cancer immunotherapy outcomes [58]. These bacteria increase anti-tumor immunity, stimulate cytotoxic T-cell infiltration, and improve antigen presentation. On the other hand, decreased ICI efficacy and worse survival outcomes have been linked to antibiotic-induced changes in gut flora [59]. Microbes can modulate ICI in several ways. The microbes can tune the expression of APCs, dendritic cell activation, and CD8+ T cell expansion, thereby further improving tumor control. The interplay between microbes and immune cells strongly influences the magnitude of the T cell response and their spatial deployment within the tumor. The microbiome–immune interactions ensure that all microenvironments are exposed to cytotoxic effectors once PD-1/PD-L1 signaling is blocked. Microbial metabolites play a pivotal role in elevating ICI response. One microbial metabolite, short-chain fatty acid (SCFA) butyrate, can profoundly influence innate immunity and the mucosal inflammatory response, further supporting the notion that microbial metabolite levels can influence downstream anti-tumor immunity. The microbiome has a bidirectional impact on ICI, as it affects anti-tumor immunity and, conversely, influences epithelial barrier function and systemic inflammation, which are central to immune-related toxicity. The gut microbiota is well known to act on cancer drugs through its translocation, immunomodulation, metabolism, enzymatic degradation, and reduced ecological variation. The microbiota is well known to modulate absorption, excretion, endogenous metabolite production, immune modulation, and the apoptotic pathway for the regulation of cancer drugs. Along with these, the gut microbiota is well known to regulate intestinal permeability by modulating tight junction integrity and the thickness of intestinal mucus layers, which in turn influence the absorption of pharmacological agents. Microbiome composition has predictive importance in addition to determining therapy response. While

pro-inflammatory bacterial enrichment is linked to aggressive tumor characteristics and metastasis, more microbial diversity is typically associated with better progression-free survival and overall survival [60]. The routine clinical use of microbiome-based diagnostics is limited by several issues, despite encouraging data. Finding universal biomarkers is complicated by inter-individual variability driven by host genetics, nutrition, geography, and antibiotic use [61,62]. Another significant obstacle is the absence of standardization in sample collection, sequencing techniques, and data analysis pipelines. Recent advances in multi-omics approaches, including immunogenomics, metabolomics, and microbiomics, are progressively addressing the limitations of microbiome-based diagnostics. With extensive longitudinal studies and well-designed clinical trials, microbiome-derived biomarkers are expected to gain validation for routine clinical application [47]. In oncology, comprehensive microbiome profiling is important for supporting prognostic assessment, guiding individualized therapeutic strategies, and promoting early disease detection. Altogether, the microbiome approach has gained significant importance as a powerful prognostic and diagnostic resource in modern medicine. Disease-specific microbial signatures have the potential to support non-invasive cancer screening, serve as reliable biomarkers for disease identification, and provide valuable prognostic insights into treatment response and patient outcomes (Table 1).

Table 1. Role of the Microbiome as a Diagnostic and Prognostic Tool in Cancer.

Aspect	Microbiome Component	Sample Type	Clinical Application	Key Findings/ Significance	References
Microbiome signatures as biomarkers	*Fusobacterium nucleatum*	Stool, tumor tissue	diagnosis	Enriched in CRC; promotes inflammation and tumor progression	[48,49]
Microbiome signatures as biomarkers	*Bacteroides fragilis*, *E. coli (pks+)*	Stool	CRC risk assessment	Genotoxin-producing strains linked to carcinogenesis	[50]
Non-invasive cancer screening	Gut microbial panels	Stool	CRC screening	Improves sensitivity compared to FOBT/FIT	[49,53]
Prediction of therapy response	*Akkermansia muciniphila*	Stool	Immunotherapy response	Enhances PD-1 inhibitor efficacy in melanoma and non-small cell lung cancer (NSCLC) patients	[59]
Prognostic value	High microbial diversity	Stool	Survival prediction	Associated with improved overall survival in Melanoma and NSCLC cohorts	[60]

4. Microbiome and Cancer Therapeutics

The human body harbors diverse microbes, including bacteria, fungi, viruses, archaea, and protozoa, that live in different organs and on the body's surface. It has been reported that bacteria inhabiting the human microbiome alone outnumber human cells [63]. Most of these microbes are friendly to the human body and exert positive effects on health. The International Agency for Research on Cancer (IARC) has classified only 11 trillion microbes, which are considered carcinogenic to humans, as Group 1 carcinogens. These

carcinogens comprise one bacterial species, three parasitic helminths, and seven viruses. Worldwide, every year, 2.2 million cancer cases are reported, and most of them are linked to the above-described microbes [64]. It is very important to understand how these microbes directly or indirectly influence cancer, as this affects various facets of cancer care, including disease emergence, progression, diagnosis, and therapies.

4.1. Influence of Microbiomes on Chemotherapy Efficacy and Toxicity

The gut microbiota contributes to heterogeneous responses to chemotherapy, as distinct bacterial profiles have been associated with variations in clinical treatment outcomes across multiple observational studies. These findings suggest potential links between gut microbial composition and variability in chemotherapeutic response, efficacy, and toxicity. Several studies have reported associations between specific bacterial species and altered chemotherapy responses in cancer patients [65]. Several bacterial species have been shown to modulate carcinogenic pathways through defined molecular mechanisms. For example, *Fusobacterium nucleatum* activates the Wnt/β-catenin signaling pathway via FadA adhesion, promoting colorectal tumor progression; enterotoxigenic Bacteroides fragilis induces STAT3 and NF-κB signaling through BFT toxin; and pks+ E. coli produces colibactin, which is associated with DNA double-stranded breaks and genomic instability, contributing to tumorigenesis. Despite various advancements, the impact of microbiota on the effectiveness and toxicity of cancer therapies remains poorly understood. The correlation between microbes and the effectiveness of cancer therapies, as reported in several studies, highlights the requirement for additional research in this field [66]. Despite advances in precision treatments such as immunotherapy and targeted therapy, chemotherapy remains widely used due to its broad therapeutic scope, cytotoxic potency, and relatively low cost [65]. The therapeutic effectiveness of chemotherapy is strongly affected by specific microbes that can alter the behavior and action of cancer-fighting agents in the body [66].

Recent experimental and clinical studies have further associated gut microbiota composition with tumor progression, chemotherapy response traits, and treatment-related adverse effects [67]. Chemotherapeutic compounds can transform the profile of gut microbiota, resulting in microbial shifts that may either exacerbate or lessen clinically important side effects. In a review encompassing 22 findings, certain bacterial groups were correlated with improved clinical responses across various malignancies. In pulmonary tumors, enhanced therapeutic outcomes were associated with an increased abundance of Streptococcus mutans, Enterococcus casseliflavus, and Bacteroides species; in contrast, within gastrointestinal cancers, a positive response was linked to higher levels of *Lactobacillaceae*, *Bacteroides fragilis*, and *Roseburia faecis*. As a result, modulating gut microbiota during chemotherapy is emerging as a promising approach to improve therapeutic efficacy and mitigate chemotherapy-induced adverse effects [65].

The microbiota shapes the effects of chemotherapeutic compounds delivered via both oral and parenteral routes, highlighting the core principle of mutual interaction between the host microbiota and tumor therapies (Figure 2).

A pivotal mechanistic basis for this interplay and an important therapeutic target is the microbiota's ability to induce chemoresistance [68]. One such pathway involves the modulation of transmembrane drug transporters, which may influence the movement of cytotoxic drugs into and out of tumor cells, thereby influencing malignant cells' therapeutic response [69]. Additionally, host DNA repair pathways can be altered by the microbiota to improve the efficacy of chemotherapy-induced damage in cancer cells [70]. *Fusobacterium nucleatum* is among the best-characterized chemo-resistant microbes, with a substantial impact on therapeutic response reported [71].

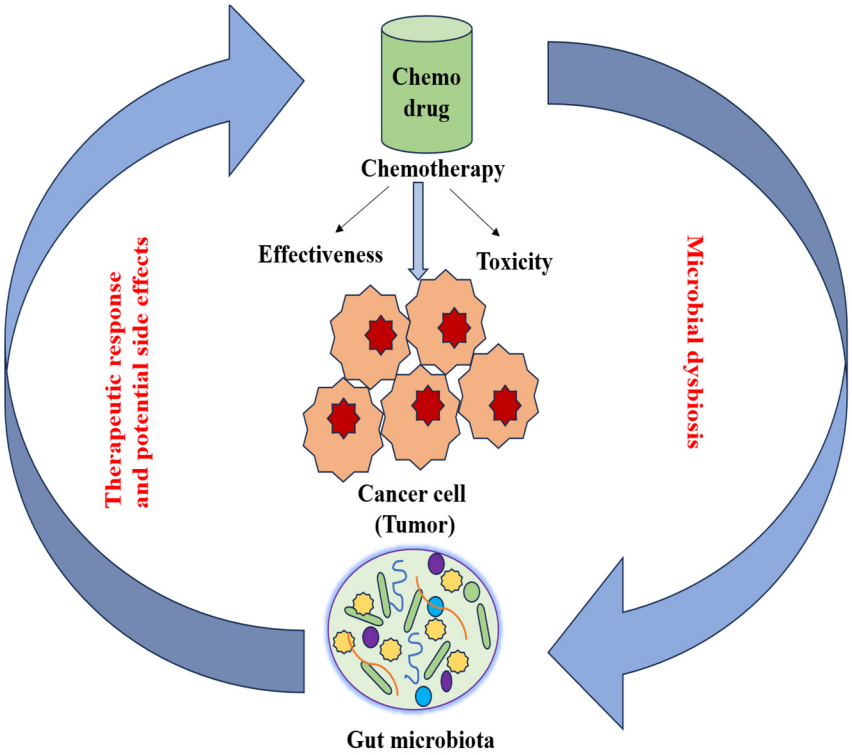


Figure 2. Bidirectional correlation between chemotherapy and microbiota. (Figure was made by authors with the help of PowerPoint.

Major shifts in microbial community profiles are induced by chemotherapeutic regimens, resulting in treatment-associated dysbiosis. A prominent and extensively studied example of microbiota-driven chemotherapy toxicity involves irinotecan (a camptothecin-derived drug used for colorectal cancer, non–small cell lung cancer, and ovarian cancer) [72]; following administration, the drug undergoes modification by host esterases to SN38 (the active, pro-apoptotic form), which targets topoisomerase I, disrupts DNA repair, and promotes cytotoxicity [73]. SN38 is then detoxified in the liver by forming SN38-glucuronide (SN38G), which is excreted in bile and feces. Microbial taxa linked to chemotherapy-induced toxicity included *Prevotella* and *Clostridia* in lung cancer patients, and *Bacteroides* along with *Klebsiella* pneumoniae in patients with gastrointestinal tumors. In summary, microbiota's influence on chemotherapeutic response, efficacy, and toxicity can be attributed to pharmacokinetic and metabolic interactions that alter drug metabolism.

4.2. Role of Immunotherapy Response (Checkpoint Inhibitors)

Immune checkpoint inhibitors (ICIs), including antibodies targeting programmed cell death protein 1 (PD-1), programmed death ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), have significantly improved clinical outcomes across multiple malignancies. However, substantial interpatient variability in response and toxicity remains a major limitation. Emerging evidence suggests that the gut microbiome may influence immunotherapy efficacy, although the strength and nature of this relationship vary across study types. Growing evidence highlights the role of the gut microbiome as an important determinant of immunotherapy outcomes and of immune-related toxicities, including colitis and hepatitis. The gut microbiome interacts synergistically with the host immune system to maintain a balance between tolerance to food-derived antigens and the presence of resident microbes, while safeguarding against pathogens and disturbances induced by drugs and illness [74]. The gut microbiome shapes the immune system through multiple distinct routes. Stimulation of pattern-recognition receptors (PRRs) on intestinal

epithelial cells activates intracellular signaling pathways that promote the secretion of immunomodulatory cytokines. In addition, microbial metabolites, particularly SCFAs, can influence the differentiation of both pro-inflammatory TH1 and TH17 cells and anti-inflammatory regulatory T cells (T-regs) [75]. Immune checkpoints expressed on T cells serve as crucial modulators of the immune system. They safeguard host tissues during responses to pathogens and preserve self-tolerance by attenuating T cell activation, thereby avoiding autoimmune reactions. Cancer cells harness these regulatory pathways to evade immune detection by interacting with checkpoint receptors, thereby downregulating T cell activation and expansion and impairing anti-tumor immune responses. The chief molecular targets of ICIs are programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), both of which are found on T lymphocytes. Malignant cells exploit these receptors to inhibit T-cell-driven immune responses. At present, ICIs are classified into three principal classes: anti-CTLA-4, anti-PD-1, and anti-PD-L1, each designed to block these receptors and restore immune activity against tumor cells [71]. The major characteristics of microbiome studies related specifically to ICIs are highlighted in Table 2.

Table 2. Mechanistic and clinical studies highlighting the interaction between gut microbiome and immune checkpoint inhibitors across various malignancies.

Type of Cancer	Microbiome Evaluation Method	Main Objective	Study
Lung and kidney cancers	Metagenomics at diagnosis	Enrichment of *Akkermansia muciniphila* associated with improved anti-PD-1 response; antibiotic exposure reduced OS (11.5 vs. 20.6 months)	[59]
Metastatic melanoma	16S rRNA, metagenomic shotgun, qPCR	Higher abundance of *Faecalibacterium* associated with improved PFS (9.8 vs. 3.2 months)	[76]
Metastatic melanoma	16S rRNA sequencing, shotgun metagenomics	Microbial diversity correlated with checkpoint inhibitor responsiveness and $CD8^+$ T-cell infiltration	[77]
Metastatic melanoma (n = 6), HCC (n = 2), NSCLC (n = 1), NSCLC/RCC (n = 1)	16S rRNA sequencing, shotgun metagenomics	Association between baseline microbiome and ICI response	[78]
Melanoma and other solid/hematological tumors	16S rRNA with NGS, metagenomic shotgun sequencing	FMT restored anti-PD-1 sensitivity in ~30–40% resistant melanoma patients	[79]
Melanoma, RCC, colorectal cancer, hepatobiliary carcinoma	16S rRNA, metagenomics	Microbiome–immunotherapy crosstalk	[80]
Multiple cancer types	-	Cause-and-effect relationships	[81]
CRC, gastric cancer, esophageal adenocarcinoma	-	Microbiome mechanisms in GI malignancies	[82]
Melanoma, NSCLC, other solid tumors	16S rRNA, metagenomics with ML classifiers	Comprehensive clinical evidence synthesis	[83]
Multiple cancer types	-	Mechanisms and precision therapeutics	[84]

Across multiple cohorts, enrichment of taxa such as *Akkermansia muciniphila*, *Faecalibacterium* spp., and *Bifidobacterium* spp. consistently correlates with improved responsiveness

to checkpoint inhibitors, whereas antibiotic-associated dysbiosis is linked to reduced survival. Several clinical studies have quantitatively demonstrated that gut microbiome composition serves as both a predictive biomarker and therapeutic modulator of immune checkpoint inhibitor (ICI) efficacy across cancers. In a multicenter cohort study involving 249 patients with advanced non-small cell lung cancer and renal cell carcinoma, responders to anti-PD-1 therapy showed significant enrichment of *Akkermansia muciniphila*, and patients receiving antibiotics before immunotherapy exhibited reduced median survival of 11.5 months to 20.6 months [59]. Similarly, in patients with metastatic melanoma (n = 112), increased baseline microbial alpha diversity and enrichment of Faecalibacterium species were associated with prolonged progression-free survival. Another independent melanoma study reported an objective response rate of 40% in microbiome-rich responders compared with 7–8% in non-responders. Furthermore, responders derived fecal microbiota transplantation restored sensitivity to anti-PD-1 therapy in approximately 30–40% of previously resistant melanoma patients. Conversely, enrichment of butyrate-producing genera, including Roseburia and Faecalibacterium, has been linked to improved epithelial barrier integrity and enhanced anti-tumor immune signaling. These microbial signatures therefore represent promising non-invasive diagnostic biomarkers for early disease stratification and prediction of immunotherapy responsiveness in patients. Overall, current evidence supports a contributory role of the gut microbiome in modulating immunotherapy outcomes, but most clinical findings remain associative. Further large-scale, longitudinal, and interventional studies are required to establish causality, improve reproducibility, and enable the development of clinically actionable microbiome-based strategies.

4.3. Microbial Drug Metabolism and Resistance to Anticancer Therapies

The study of microbial drug metabolism is an emerging area of research focused on understanding the complex biochemical interactions between microbes and therapeutic compounds. Microorganisms, including bacteria and fungi, can biotransform anticancer drugs, thereby influencing their efficacy, toxicity, and pharmacokinetic behavior [85,86]. Microbial enzymatic activity can convert inactive prodrugs into active therapeutic metabolites; for example, bacterial β-glucuronides reactivate irinotecan metabolites in the intestine, contributing to both therapeutic effects and gastrointestinal toxicity [87]. Furthermore, gut microbiota can indirectly regulate host drug metabolism by modulating hepatic cytochrome P450 enzyme expression and immune signaling pathways that influence treatment responsiveness [88]. Variations in microbiome composition have been associated with differences in chemotherapy response, with substantial interpatient variability reported during fluoropyrimidine-based therapy, highlighting the role of host–microbiota interactions in determining treatment outcomes. Various strategies in bioinformatics and sequencing have reshaped microbiome research [89]; the incorporation of metagenomic tools has enabled the association of the metabolic capacity of microbial taxa, providing crucial insights into how drug metabolism and patient outcomes are affected by the human microbiota [90]. Computational approaches, such as machine-learning-based prediction of microbiome-mediated drug metabolism, provide valuable insights into host–microbe interactions and complement experimental findings from in vitro, ex vivo, and in vivo cancer models investigating microbiome-driven therapeutic responses [91]. Growing evidence indicates that the gut microbiota plays a vital role in resistance to diverse cancer treatments, including chemotherapy, immunotherapy, radiotherapy, and post-surgical outcomes. These microbial taxa can affect treatment receptivity through various pathways, including modifying drug potency, reducing therapeutic benefit, and contributing to treatment-related toxicities [59]. Numerous studies have indicated the gut microbiome's role in shaping resis-

tance to widely administered chemotherapeutic agents, including irinotecan, oxaliplatin, cyclophosphamide, 5-fluorouracil (5-FU), gemcitabine, and anthracyclines.

4.4. Antibiotic Use and Treatment Outcomes

Antibiotics are often proposed to eliminate harmful microbial communities, yet their effects are imprecise. Their exposure can disrupt the gut microbiota, leading to microbial dysbiosis, which may intensify chemoresistance and result in poor therapeutic outcomes [83,84]. Also, antibiotics given to address chemotherapy-related complications may interfere with the overall effectiveness of treatment [92]. *Lactobacillus murinus* and *Lactobacillus johnsonii* are Gram-positive bacteria that play a key role in modulating the tumor-suppressive efficacy of cyclophosphamide (CTX). Broad-spectrum antibiotics, such as vancomycin and colistin, reduced the therapeutic effects of CTX in mastocytoma- and sarcoma-bearing mice, highlighting the major role of microbes in the CTX response against cancer cells [93]; hence, antibiotics tested against Gram-positive bacteria can negatively affect the effectiveness of cancer therapy [94]. Clinical studies in lung and renal cancer patients have shown that antibiotic exposure before initiation of immune checkpoint inhibitor therapy is associated with significantly reduced progression-free survival and overall survival compared with non-exposed patients [95]. Conversely, in patients with pancreatic cancer, antibiotic use has been associated with improved responses to ICI, likely due to the eradication of tumor-resident bacteria that contribute to an immunosuppressive environment [96,97]. These evaluations reveal that the influence of antibiotics on clinical outcomes depends on the malignancies treated and the therapeutic strategies employed, further emphasizing the importance of the microbiome as a prognostic indicator of therapeutic success. These observations highlight the need for controlled clinical trials evaluating microbiome-targeted interventions, including selective antibiotics, probiotics, and dietary modulation, as adjunct strategies to improve therapeutic outcomes.

5. Targeting Microbiome Dynamics for Disease Management

Immune modulation, disease susceptibility, and host metabolism are all significantly influenced by the human microbiome, especially the gut microbiota. The gut microbiota drives both local and distant oncogenesis by modulating systemic immune tone through molecular mimicry and microbial-associated patterns [98]. Numerous illnesses, including inflammatory bowel disease (IBD), metabolic syndrome, cancer, neurological diseases, and immune-related disorders, have been linked to dysbiosis, an imbalance in microbial makeup and activity [99]. Therapeutic strategies that mainly focus on modulating the gut microbiota have attracted increasing attention as alternatives or complements to conventional treatments, which generally include probiotics, prebiotics, postbiotics, dietary interventions, and fecal microbiota transplantation (FMT) to restore microbial balance (Figure 3). Advances in synthetic biology have also enabled the development of genetically engineered microorganisms, which further expand the potential of microbiome-based therapeutic approaches.

5.1. Probiotics, Prebiotics, and Postbiotics

Probiotics are live microorganisms that are usually associated with health benefits when taken in proper amounts, improving gut health by boosting immunity [100]. Commonly used probiotic genera include *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, and *Enterococcus*. Generally, these microbes produce antimicrobial metabolites that increase epithelial barrier integrity and modulate mucosal immunity by limiting the growth of pathogenic bacteria through competitive exclusion and other protective mechanisms [101]. Probiotic interventions have been extensively studied for gastrointestinal disorders such as

Inflammatory Bowel Disease (IBD) and irritable bowel syndrome (IBS), as well as for antibiotic-associated diarrhea, in which certain strains have been shown to reduce disease duration and severity [102]. The growing body of evidence from meta-analyses also confirms that probiotics may support cancer therapy by improving immune checkpoint inhibitor responses and modulating treatment-related mucositis through gut immune signaling [103]. Probiotic efficacy is highly strain-specific and influenced by host genetics, immune status, and baseline microbiome composition [104]. Accordingly, rigorous clinical validation is important, particularly in immunocompromised patients. The composition and functional activity of the gut microbiota are continuously modulated by prebiotics, thereby promoting the host's health [105]. Common examples of prebiotics include inulin, Fructooligosaccharides (FOS), Galactooligosaccharides (GOS), and resistant starch. The fermentation of prebiotics by gut microorganisms leads to the production of SCFAs, such as acetate, propionate, and butyrate, which play a pivotal role in immune regulation, intestinal homeostasis, and metabolic balance. In this context, butyrate possesses significant anti-inflammatory and anti-carcinogenic properties and serves as the principal energy source for colonocytes [106]. Prebiotic supplementation has been shown to support gut barrier integrity, reduce systemic inflammation, and improve glucose metabolism in therapeutics. Interestingly, when prebiotics are combined with probiotics as synbiotics, prebiotics enhance the survival and colonization of beneficial microbes, resulting in improved therapeutic outcomes [107]. Postbiotics generally enhance the host's gut microbiome health through metabolites, cellular components, and nonviable microbial cells [108]. SCFAs, microbial peptides, enzymes, polysaccharides, lipoteichoic acids, and cell wall fragments are among their components, compared with active probiotics; postbiotics provide several benefits, such as increased stability, safety, and shelf life. They have been shown to improve intestinal barrier function, reduce oxidative stress, and regulate immune responses. For example, butyrate and other microbial metabolites can inhibit the generation of pro-inflammatory cytokines and control the development of T-regulatory cells [109]. Postbiotics have been studied as next-generation microbiome therapies, particularly in pharmaceutical and functional food applications, owing to their well-defined chemical composition and consistent biological activity.

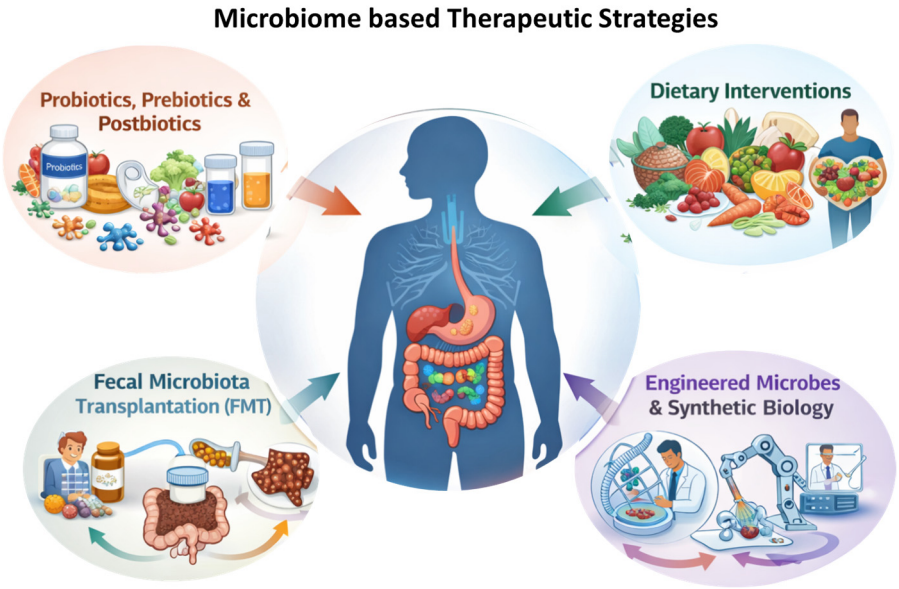


Figure 3. Microbiome-based Therapeutic Strategies. (Figure was created by the authors using PowerPoint and https://biorender.com/xfjdd0i, accessed on 25 December 2025).

5.2. Dietary Interventions

Diet is one of the most important factors influencing gut microbial composition, diversity, and functional activity [110]. The long-term dietary patterns play a vital role in shaping the structure and metabolic output of the gut microbiota. Diets rich in carbohydrates and fats, characteristics of Western dietary habits, are associated with reduced microbial diversity and increased inflammatory responses. In this context, the fiber-rich, plant-based diets enhance the growth of important microbes such as *Faecalibacterium prausnitzii* and *Bifidobacterium* [111]. Bioactive metabolites that affect host physiology are produced by microbial metabolism of food components. The significance of nutritional balance is evident. In contrast, excessive protein fermentation can yield potentially toxic metabolites, such as ammonia and phenolic compounds, whereas fiber fermentation produces beneficial SCFAs [112]. Numerous dietary approaches have shown therapeutic advantages mediated by microbiomes. The Mediterranean diet, rich in unsaturated fats, dietary fiber, and polyphenols, lowers inflammatory indicators and increases microbial diversity [113]. The ketogenic diet has the potential to treat neurological conditions like epilepsy by changing the composition of gut microbes [114]. A low-FODMAPS diet can effectively reduce fermentable carbs and alleviate IBS symptoms; however, long-term impacts on microbial diversity should be carefully considered [115]. To maximize therapeutic outcomes, emerging personalized nutrition techniques aim to tailor dietary therapies to individual microbiome profiles [116].

5.3. Fecal Microbiota Transplantation (FMT)

Transferring fecal material from a healthy donor to a recipient to restore microbial variety and function is known as fecal microbiota transplantation. With cure rates surpassing 90%, FMT has shown impressive efficacy in treating recurrent *Clostridium difficile* infections [117,118]. In addition to *C. difficile*, FMT is being studied for neuropsychiatric conditions, metabolic syndrome, and IBD. However, outcomes have been inconsistent, perhaps because of variations in recipient characteristics, administration methods, and donor microbiota [119]. The creation of standardized screening procedures and the identification of microbial consortia as safer substitutes have been spurred by safety concerns, particularly the possible spread of multidrug-resistant pathogens.

5.4. Engineered Microbes and Synthetic Biology Approaches

Advances in synthetic biology have enabled the creation of engineered microbes capable of detecting, responding to, and treating diseases in situ. Therapeutic compounds, including immune modulators, anti-inflammatory cytokines, and anticancer agents, can be delivered directly to sites of disease using genetically modified strains such as *Escherichia coli* and *Lactococcus lactis* [120]. Engineered microorganisms can also be programmed to recognize disease-associated biomarkers and respond dynamically to pathological signals. For example, engineered *Salmonella typhimurium* strains selectively colonize tumors and have been shown to induce tumor regression in murine models of melanoma and colorectal cancer through localized delivery of cytotoxic proteins. Similarly, modified probiotic platforms have been shown to enhance checkpoint inhibitor efficacy by promoting CD8+ T-cell infiltration in preclinical tumor models [121]. Regulatory, biosafety, and ethical issues remain major obstacles to clinical translation despite the field's potential. Before widespread therapeutic use, long-term safety investigations and robust containment mechanisms were crucial.

In contemporary medicine, microbiome-based treatment approaches represent a rapidly evolving field. Novel approaches to restore microbial balance and treat disease include probiotics, prebiotics, postbiotics, dietary modification, FMT, and engineered microbes. Clinical data are growing, but issues with safety, regulatory approval, and inter-

individual variability persist. It is anticipated that future developments in synthetic biology, systems biology, and personalized medicine will refine microbiome-based treatments and pave the way for more precise and effective interventions (Table 3).

Table 3. Summary of Microbiome-Based Therapeutic Strategies.

Therapeutic Strategy	Definition	Mechanisms	Clinical Applications/Therapeutic Contexts	References
Probiotics	Live microorganisms confer health benefits when administered adequately	Pathogen inhibition, immune modulation, gut barrier enhancement	IBS, IBD, antibiotic-associated diarrhea, adjunct support during cancer therapy	[100,104]
Prebiotics	Beneficial microbes selectively utilize non-digestible substrates	SCFA production, stimulation of beneficial taxa	Metabolic disorders, gut health, and immune regulation	[105,106]
Postbiotics	Non-viable microbial cells or metabolites with health benefits	Anti-inflammatory, antioxidant, and immune signaling modulation	Functional foods, pharmaceuticals, immunomodulation	[108]
Dietary Interventions	Diet-based modulation of gut microbiome composition	Microbial diversity alteration, metabolite production	Metabolic syndrome, IBS, and inflammatory diseases	[121]
Fecal Microbiota Transplantation (FMT)	Transfer of healthy donor microbiota to restore dysbiosis	Restoration of microbial diversity and function	Recurrent *Clostridioides difficile* infection, IBD	[118]
Engineered Microbes	Genetically modified microorganisms for targeted therapy	Controlled delivery of therapeutic molecules, biosensing	Cancer, inflammatory diseases, and precision medicine	[121]

6. Preclinical Animal Studies and Mixed with Human Subjects (Preclinical and Clinical Evidence)

Preclinical studies using rodent models with varying microbiome status (germ-free, SPF, conventional), including rats (55.8%), mice (44.2%), C57BL/6 mice, Apc Min/+ mice, and gnotobiotic IL-10−/− mice, were used to evaluate microbiome-driven cancer strategies. predominant cancer types, using chemically induced models (DMH, AOM/DSS) and genetic models [122]. Probiotic therapies using Lactobacillus and Bifidobacterium strains markedly reduced lesions or tumors in the majority of preclinical mouse trials, whilst the multi-strain formulation VSL#3 reduced both tumor number and size in typical mice [123]. Pathogenic bacteria administered via oral gavage facilitated tumorigenesis: E. coli NC101 augmented tumor load in gnotobiotic IL-10−/− mice, whereas *F. nucleatum* increased tumor burden in APC Min/+ mice [124]. In immunotherapy models, *Bifidobacterium* spp. increased anti-PD-L1 effectiveness in non-responder mice by promoting CD8+ T cell infiltration. In vitro investigations were confined to two papers, which analyzed CRC cell lines cocultured with *F. nucleatum* and intestinal epithelial cell lines subjected to bacterial products, with fragilysin inducing spermine oxidase synthesis in epithelial cells [125]. The observed benefits varied significantly across animal models due to microbiome composition, genetic background, and housing conditions, encompassing pathways such as IL-10-mediated immunoregulatory effects, IgA production, metabolite synthesis (including butyrate), and augmentation of barrier function [125] (Table 4).

Table 4. Summary of representative preclinical, clinical, and literature-based studies describing microbiome-associated experimental strategies across different cancer types.

Study Type	Animal Models	Cell Lines	Cancer Type	Microbiome Strategy	Reference
In vivo only	Rats (55.8%), Mice (44.2%), Apc (Min/+) mice; age 21 days-20 weeks	Not applicable	(chemically induced with DMH)	Probiotics (*Lactobacillus*, *Bifidobacterium*)	[122]
Mixed (in vivo + human trials)	C57BL/6 mice (germ-free or conventional)	Not mentioned	Metastatic melanoma, colorectal, pancreatic adenocarcinoma	Probiotics (*Bifidobacterium*), FMT, and antibiotics	[123]
Mixed (in vivo + human)	Germ-free (GF) and specific pathogen-free (SPF) mice	Not mentioned	Non-small cell lung cancer, renal cell carcinoma, metastatic melanoma	FMT, probiotics	[59]
Review-based evidence summary	Not mentioned	Not mentioned	Colorectal cancer	Microbiota analysis, modulation	[49]
In vivo only	Germ-free mice	Not mentioned	Not specified	Not specified	[76]
Mixed (in vivo + in vitro)	C57BL/6 mice, Apc Min/+ mice (germ-free, conventional, SPF)	Coculture of CRC cell lines with *F. nucleatum*, *E. coli*, and incubation with cancer cell lines	(chemically induced AOM/DSS, genetic Apc Min/+)	Probiotics (VSL#3), microbiota colonization	[125]
Review-based evidence summary	Not mentioned	Not mentioned	Various tumor types	Fecal microbial transplant (FMT)	[126]
Mixed (in vivo + in vitro)	Gnotobiotic IL-10−/− mice, APC Min/+ mice, wild type mice (SPF conditions)	Intestinal epithelial cell lines	(chemically induced AOM/DSS, genetic IL-10−/−, APC Min/+)	Bacterial gavage (*E. coli*, *F. nucleatum*, ETBF)	[124]
In vivo only	Female Dark Agouti rats, mice	Not mentioned	(chemotherapy-induced mucositis)	Probiotics (*B. infantis*, *B. bifidum*, *L. acidophilus*, VSL#3)	[127]
Review-based evidence summary	Not mentioned	Not mentioned	Various cancers across species	Not mentioned	[128]

7. Limitations and Future Prospects

Globally, microbiomes are emerging as a novel frontier in cancer diagnostics, yet researchers face substantial obstacles to the clinical application of microbiome-based strategies. Persistent challenges include inconsistent sampling, heterogeneous sequencing methodologies, the absence of standardized protocols, a lack of reliable biomarkers, and an incomplete understanding of microbial associations, all of which obscure treatment options and hinder reliable cancer diagnosis. Despite these challenges, the field of mi-

crobiome research holds considerable promise for transforming targeted cancer therapy. *Bacteroides fragilis* and *Fusobacterium nucleatum* were identified as specific microbial hallmarks associated with cancer progression. These outcomes highlight the course of action for novel diagnostic and therapeutic strategies. However, the process is riddled with challenges, as the complex nature of microbe-host associations varies across numerous cancers. In immunotherapy, particularly given the likelihood of microbiome research to enhance treatment success, professionals face the intricate nature of microbial variation and the pressing need for standardized screening protocols. Histopathological examination is still highlighted as the gold standard for the diagnosis of cancer. Presently, microbiome-based biomarkers are used as an adjunctive tool for risk grouping, prognosis, and prediction of response to therapy, rather than as a definitive replacement for diagnostics.

8. Conclusions

In the field of cancer diagnostics and therapeutics, microbiomes have emerged as a promising frontier, offering advances in understanding, monitoring, and treating cancer. The association of pancreatic, colorectal, and gastric cancer types with specific microbial hallmarks has identified potent diagnostic biomarkers that aid cancer detection, enhance immunotherapy efficacy, and prevent carcinogenesis, thereby supporting targeted therapeutic interventions. Intramural colonization and metabolite production are major metabolic pathways through which microorganisms can affect cancer biology. Nonetheless, many gaps in this field require broader, large-scale, clinically validated studies to establish the main causal associations. Taken together, early diagnosis, treatment stratification, and novel therapeutic strategies through the microbiome play a vital role in redefining cancer biology.

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