JAMA | Review | TRANSLATIONAL SCIENCE

The Microbiome and Cancer
A Translational Science Review

Estefania Fernandez, MD, PhD; Jennifer A. Wargo, MD, MMSc; Beth A. Helmink, MD, PhD

IMPORTANCE Growing evidence suggests that microbes located within the gastrointestinal tract and other anatomical locations influence the development and progression of diseases such as cancer.

OBSERVATIONS Clinical and preclinical evidence suggests that microbes in the gastrointestinal tract and other anatomical locations, such as the respiratory tract, may affect carcinogenesis, development of metastases, cancer treatment response, and cancer treatment–related adverse effects. Within tumors of patients with cancer, microbes may affect response to treatment, and therapies that reduce or eliminate these microbes may improve outcomes in patients with cancer. Modulating gastrointestinal tract (gut) microbes through fecal microbiota transplant and other strategies such as dietary intervention (eg, high-fiber diet intervention) has improved outcomes in small studies of patients treated with cancer immunotherapy. In contrast, disruption of the gut microbiota by receipt of broad-spectrum antibiotics prior to treatment with cancer immunotherapy has been associated with poorer overall survival and higher rates of adverse effects in patients treated with immune checkpoint blockade for solid tumors and also with chimeric antigen receptor T-cell therapy for hematologic malignancies.

CONCLUSIONS AND RELEVANCE Microbes in the gut and other locations in the body may influence the development and progression of cancer and may affect the response to adverse effects from cancer therapy. Future therapies targeting microbes in the gut and other locations in the body could potentially improve outcomes in patients with cancer.

JAMA. doi:10.1001/jama.2025.2191
Published online May 12, 2025.

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Author Affiliations: Department of Gynecologic Oncology & Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston (Fernandez); Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston (Wargo, Helmink); Department of Genomic Medicine, The University of Texas MD Anderson Cancer Center, Houston (Wargo).

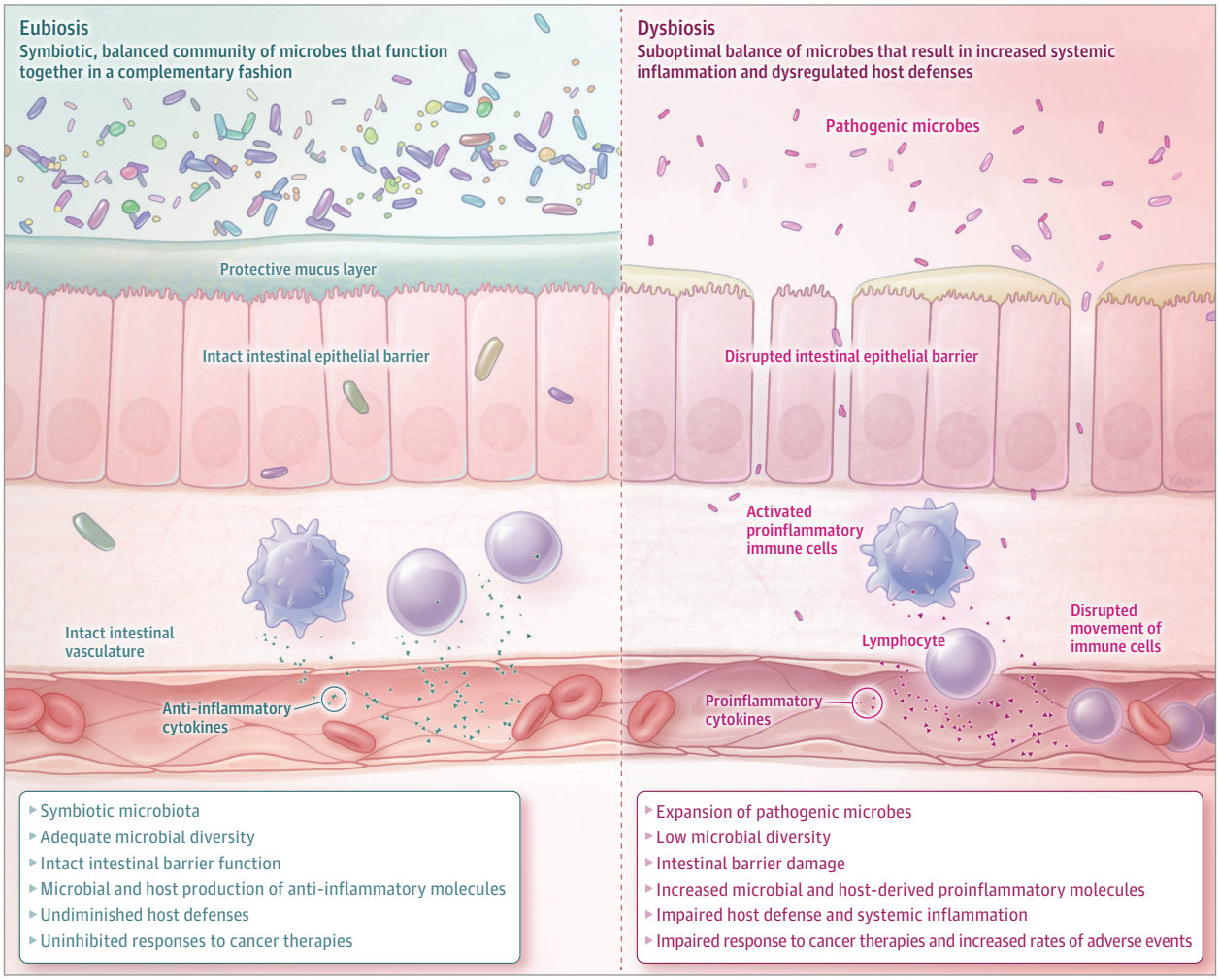
Corresponding Author: Jennifer A. Wargo, MD, Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030 (jwargo@mdanderson.org).

The microbiome is composed of bacteria, viruses, fungi, and archaea (a domain of unique prokaryotic single-celled organisms), along with their respective genomes and secreted byproducts, such as short-chain fatty acids and other metabolites, that inhabit and evolve within an individual. The surface of the human body (skin), as well as the gastrointestinal (gut) and respiratory tracts, have distinct microbiomes, as demonstrated by the Human Microbiome Project.[1] The taxonomic and functional aspects of the human microbiome can be affected by factors that include age, geography, medications, genetic factors, disease states, and dietary and lifestyle habits such as smoking and physical activity,[2-5] resulting in marked variability of the diversity and composition of microbial species within and between individuals. Microbes indirectly affect human health and disease by influencing immunity, metabolism, and mucosal barrier maintenance.[6,7] Variations in the microbiome, inside and outside of the gut, have been linked to response to cancer treatment, treatment-related adverse effects, and long-term outcomes in patients with cancer.[8-10] This review summarizes current evidence regarding the human microbiome and cancer, including how the microbiota in the gut and other anatomical locations affect cancer outcomes.

Microbes in the Gastrointestinal Tract Influence Systemic and Antitumor Immunity

Microbes coexist with humans and influence virtually every aspect of physiology in a dynamic interaction—including host immunity.[1] This is particularly evident within the gut, where a large number of microbes in the gastrointestinal lumen and at the mucosal surface interact with immune cells locally and within mesenteric lymph nodes. Through these interactions, microbes within the gut can affect systemic immunity as well as immune responses to vaccination and cancer immunotherapy. *Eubiosis* refers to a symbiotic, balanced community of microbes that function together in a complementary fashion. In the gut, eubiosis is associated with an intact epithelial barrier and a high diversity of microbes, as well as a high relative abundance of microbes that improve immune function, such as those that promote fiber fermentation, defined as the breakdown of nondigestible dietary fiber into short-chain fatty acids. Additionally, eubiosis is defined by a low relative amount of pathogenic microbes that can promote systemic inflammation and blunt immune responses.[7,11,12] In contrast, dysbiosis in the gut, defined as a suboptimal balance of microbes, is associated with

Figure. Microbes and Dietary Factors Within the Gut Affecting Eubiosis and Dysbiosis



The diversity and composition of the microbes within the gut may influence health and disease, including cancer. A state of eubiosis is characterized by a high diversity of microbes and the presence of favorable bacteria including fiber-fermenting bacteria. The mucosal barrier of the gut is characterized by an intact epithelial layer and protective mucus layer. Favorable microbes metabolize dietary factors like fiber, yielding anti-inflammatory metabolites that can circulate systemically. In eubiosis, microbial activities promote host defense while limiting systemic inflammation. Eubiosis is associated with enhanced responses to anticancer therapies and low rates of adverse effects. In dysbiosis, this equilibrium is disrupted via alterations in microbial composition and function. Proinflammatory immune cell subsets are activated locally, which can promote systemic inflammation and decreased host defenses. Dysbiosis is associated with a poor response to anticancer therapies and increased rates of adverse effects.

a disrupted epithelial barrier, lower diversity of microbes, low levels of favorable microbial ecologies, and a relatively high amount of microbial taxa that promote proinflammatory immune cell phenotypes, cytokines, and microbial metabolites/byproducts, resulting in increased systemic inflammation and dysregulated host defenses (**Figure**).[7,10-13]

Microbes interact with immune cells within the gut at multiple levels, including at the mucosal surface, gut-associated lymphoid tissue, and mesenteric lymph nodes. These microbes may provide stimulatory signals, such as damage-associated molecular patterns and pathogen-associated molecular patterns, among others, to antigen-presenting cells, which may then interact with lymphocytes and other immune cell types, altering both local and systemic immune function.[7,11,14] Also, gut microbes can affect the migration of immune cells from the gut into the systemic circulation by modulating the expression of adhesion molecules on endothelial cells within the intestinal vasculature.[15,16] Microbial metabolites and byproducts can also circulate systemically and affect immune function.[17-19] Lymphocytes that recognize antigens on commensal organisms could potentially recognize tumor-associated antigens or tumor neoantigens and promote antitumor immunity through cross-reactivity between antigens recognized on microbes that demonstrate cross-reactivity to those recognized on human tumors. Antigens from bacteriophages that infect *Enterococcus hirae* have been shown to promote response to treatment with chemotherapy and immune checkpoint blockade in preclinical models of cancer through cross-reaction to tumor antigens. This mechanism may also exist in patients with cancer.[20]

Examples of mechanisms by which gut microbes affect antitumor immunity have been demonstrated in several studies. In preclinical models, treatment with cyclophosphamide was associated with decreased gut epithelial integrity, allowing for movement of

Table. Role of Gastrointestinal and Tumor Microbiome on Cancer Outcomes, Potential Treatments, and Challenges

Potential effect of microbes on cancer	Relationship to cancer progression and treatment	Specific examples	Potential treatments	Potential challenges
Microbes may induce cancer development and promote tumor metastases	Some microbes have been associated with the onset and progression of cancer[8-10]	Microbes associated with cancer development, including *Helicobacter pylori* or HPV[22,23] Microbes associated with cancer progression, including *Fusobacterium nucleatum*[24]	Specific antimicrobial treatments, such as antibiotics and vaccines Targeted antibiotics	Potential poor intratumoral penetration and possible immune response and tolerance against therapeutic agents
Microbes in the gastrointestinal tract promote or inhibit response to cancer treatment	Several gut microbes have been associated with response or resistance to cancer treatment (including immunotherapy as well as cytotoxic chemotherapy)[25-54]	Response-associated gastrointestinal microbes, including *Akkermansia muciniphila*,[27] *Bifidobacterium*,[26] *Clostridiales*,[25] *Faecalibacterium*,[25] *Lachnospiraceae*[27] Non–response-associated gastrointestinal microbes, including Enterobacteriaceae and oral bacteria[28,29]	Strategies to enhance the abundance or function of response-associated taxa, such as fecal microbiota transplant; diet and lifestyle modification, such as dietary fiber intake and exercise; prebiotics/probiotics; microbial consortia and microbial-derived metabolites; engineered microbial communities Targeted antibiotic approaches to deplete resistance-associated microbes	Technical challenges, including product development and availability as well as issues with adherence to dietary strategies
Microbes in the tumor microenvironment promote or inhibit response to cancer treatment	The presence of some microbes within tumors is associated with response or resistance to cancer treatment (including immunotherapy as well as cytotoxic chemotherapy)[24,43,45,55-61]	High microbial diversity in tumors is associated with better long-term outcomes in patients with pancreatic cancer[59] Specific microbes in tumors associated with worse outcomes with tumor therapy, including *F nucleatum*,[55-57,60] *Gammaproteabacteria*,[43] Lactobacillus iners[45]	Strategies to modulate intratumoral microbes	Tissue penetration of therapeutic agents, lack of clarity regarding targets, and potential contamination limits accuracy of microbial targets
Microbes may promote or inhibit adverse events during cancer treatment	Gut microbes have been associated with the incidence and severity of treatment-related adverse events[33-38,42,48-54,62-64]	Toxicity-associated gastrointestinal microbes, including *Bacteroides intestinalis*,[62] Enterococcaceae[33-35,42] Dysbiosis in the gastrointestinal tract[37,38]	Strategies to eliminate microbes using targeted antibiotics and other approaches such as CRISPR Strategies to increase richness of microbes, including fecal microbiota transplant, restorative microbial therapies	Technical challenges including product development and availability

Abbreviations: CRISPR, clustered regularly interspaced short palindromic repeats; HPV, human papillomavirus.

microbes from the gut lumen into the mesenteric lymph nodes and spleen, which induced maturation of naive CD4+ T cells into T_H1 and pathogenic T_H17 subtypes with antitumor immune activity.[21] Another study reported that, in mice, immune checkpoint blockade facilitated translocation of endogenous gastrointestinal bacteria into mesenteric lymph nodes and subcutaneous melanoma tumors through activation of dendritic cells.[14]

Administering broad-spectrum antibiotics in a murine model was associated with dysbiosis, decreased expression of mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1) on the gut vascular endothelium, efflux of immunosuppressive regulatory T cells from the gut, and decreased efficacy of cancer immunotherapy.[15] Consistent with these data, reduced levels of soluble MAdCAM-1 in patients with cancer were associated with dysbiosis and poor responses to immunotherapy in several different cancer types, including in 299 patients with non–small cell lung cancer (NSCLC) and 212 patients with metastatic renal cell carcinoma (RCC).[15]

Microbes in Tumors of Patients With Cancer

In addition to gut microbes, microbes within the tumor affect cancer development and response to cancer treatment (**Table**). Microbial factors that contribute to cancer development include *Helicobacter pylori,* which can be treated with antibiotics, and high-risk strains of human papillomavirus (HPV) such as HPV 16 and HPV 18, which may be prevented with vaccination.[22,23] The mechanisms by which microbes colonize tumors, and the potential consequences of intratumoral microbes, are incompletely understood, although preliminary evidence suggests that the microbes affect antitumor immunity and tumor biology.[9,55-59]

In patients with oral squamous cell carcinoma and patients with colorectal cancer, histologic and spatial profiling studies have demonstrated areas within tumors that have a higher density of bacteria and other areas with a lower density of bacteria.[56] Regions with a higher density of bacteria were typically located in poorly vascularized regions of the tumor and were associated with impaired immune cell function in the tumor microenvironment and with increased expression of immune checkpoint molecules.[56] *Fusobacterium nucleatum* is a microbe particularly associated with colorectal cancer,[24,55-57] and this microorganism has been identified in 7 of 11 paired primary and metastatic colorectal cancer tumors in 1 human sample assessment.[24] In preclinical models using human cells, proteins produced by *F nucleatum* interacted with immunomodulatory molecules on T cells and natural killer cells, suppressing antitumor immunity.[60]

In some patients, the presence of a high diversity of microbes within a tumor was associated with improved antitumor immunity. A study of 111 patients with pancreatic cancer from 2 separate institutions demonstrated that patients who survived longer than 5 years after surgery had a higher diversity of microbes within the tumor microenvironment and a greater abundance of cytotoxic (killer) T lymphocytes.[59] In preclinical study, administering a fecal microbiota transplant (FMT) from a patient with pancreatic cancer who survived longer than 5 years after surgery was associated with reduced tumor growth and improved antitumor immunity in mice, compared with mice receiving transplants from patients with pancreatic cancer surviving short term.[59] There are several pathways through which microbes may improve antitumor immunity, including through recognition of microbial neoantigens by antigen-specific T cells,[61] among other mechanisms. High-quality studies are needed to validate the presence of and mechanisms by which intratumoral microbes affect tumor biology and response to cancer treatment.[9,58,65,66]

Microbes in the Gastrointestinal Tract and Tumor Affect Cancer Therapy Response

In preclinical and clinical studies, microbes in the gut and other anatomical locations can affect cancer therapy response, including treatment with immunotherapy such as immune checkpoint blockade,[25-30,62,63,67] stem cell transplantation,[31-35] and chimeric antigen receptor (CAR) T-cell therapy (Table).[36-38,64] In several studies, a higher diversity of microbes and specific microbial taxa such as *Akkermansia muciniphila, Clostridiales*, *Ruminococcaceae*, and *Faecalibacterium* species were associated with improved outcomes to treatment with immune checkpoint blockade in patients with melanoma,[25,26] NSCLC, and RCC.[27] In addition, antibiotics may reduce diversity of gut microbes and negatively affect cancer outcomes, such as overall survival and incidence of adverse events, as detailed below.

Several studies of patients with cancer who received broad-spectrum antibiotics prior to treatment with immune checkpoint blockade had lower tumor response rates to therapy, reduced overall survival, and higher rates of adverse effects.[39,67] For example, in an observational study of 196 patients with cancer (119 NSCLC, 38 melanoma, and 39 other tumor types) who were treated with immune checkpoint blockade, those who received broad-spectrum antibiotics 30 days prior to immune checkpoint blockade had shorter overall survival than those without prior antibiotic treatment (2 vs 26 months; hazard ratio [HR], 7.4 [95% CI, 4.2-12.9]) and higher risk of disease progression (81% vs 44%, respectively; $P < .001$).[40] In a systematic review and meta-analysis of 41 663 patients from 123 observational cohorts, the 11 785 patients receiving treatment with antibiotics around the time of treatment with immune checkpoint inhibitors for cancer had significantly shorter overall survival (HR, 1.61 [95% CI, 1.47-1.76]) and poorer progression-free survival (HR, 1.45 [95% CI, 1.32-1.60]), compared with 29 878 patients who did not receive antibiotics (absolute rates not reported).[41] The indications for receipt of antibiotics were not available in that analysis; therefore, there may be confounding factors contributing to worse outcomes with antibiotic use.

Gut microbes may influence response to therapy in patients with hematologic malignancies undergoing treatment with stem cell transplant or CAR T-cell therapy.[31-38] For example, among 80 patients with acute myelogenous leukemia treated with allogeneic hematopoietic stem cell transplant (HSCT), patients with a higher diversity of microbes within their gut had improved overall survival compared with those with a low diversity of gut microbes. Three-year overall survival rates were 67% in patients with high diversity of gut microbiota, 60% in those with intermediate diversity, and 36% in those with low diversity (log-rank $P = .02$).[31] Differences in the composition of the gut microbiota were also noted; patients with higher mortality rates had a higher relative abundance of specific microbial taxa in the gut (such as *Gammaproteobacteria*, including *Enterobacteriaceae*).[31] Subsequent studies reported improved overall survival in patients with a higher diversity of gut microbiota after treatment with HSCT for hematologic malignancies.[32,33] Similar findings were reported for treatment with CAR T-cell therapy for hematologic malignancies. Patients with a higher diversity of microbes in their gut had improved response and survival rates in the setting of treatment with CAR T-cell therapy.[37,38] In a clinical trial of 99 patients with multiple myeloma undergoing CAR T-cell therapy, patients with complete response had significantly different gut microbiome within-sample diversity after therapy ($P = .047$) (absolute rates not reported) compared with those with partial response despite no differences observed at baseline. Furthermore, those with complete response had enrichment of members of *Faecalibacterium*, *Bifidobacterium*, and *Ruminococcus* compared with partial responders ($P < .05$) (absolute rates not reported). Patients who received broad-spectrum antibiotics prior to initiation of CAR T-cell therapy had significantly shorter survival rates.[36,38]

Microbes within tumors of patients with cancer may also influence response to cancer treatment. For example, microbes (including members of the class *Gammaproteobacteria*) were identified in tumors from patients with pancreatic cancer, and, in preclinical models, these intratumoral microbes increased resistance to chemotherapy (gemcitabine) by metabolizing it into its inactive form.[43] However, microbes within the tumor may also be influenced by cancer treatment. Studies have demonstrated that the growth of *F nucleatum* isolated from human colorectal cancer samples was inhibited by 5-fluorouracil, a standard chemotherapeutic agent used for colon cancer.[44] Microbes may mediate resistance to chemoradiotherapy in patients with cervical cancer. In 1 study, the obligate L-lactate-producing lactic acid bacterium *Lactobacillus iners* was associated with shorter recurrence-free survival and overall survival in patients with cervical cancer.[45]

Microbes in the Gastrointestinal Tract Influence Adverse Effects of Cancer Treatment

Microbes may influence adverse events associated with cancer treatment, although these associations and biological pathways responsible for this association are not thoroughly delineated.[46,47] In both clinical and preclinical studies, lower diversity of the gut microbiome and distinct gut microbial signatures were associated with a higher incidence of immune checkpoint blockade–associated colitis.[62,63] Among 94 patients with

malignant melanoma treated with immune checkpoint blockade, a higher abundance of gram-negative microbes, such as *Streptococcus* spp, was associated with shorter progression-free survival (HR, 3.62; *P* = .007) (absolute rates not reported) and increased immune-related adverse events.[29] These gram-negative microbes were also associated with higher levels of inflammation, including increased expression of proinflammatory cytokines, such as IL-1B and CXCL8, in cells exfoliated from the gut.[29] For patients undergoing HSCT, across several different studies, treatment with broad-spectrum antimicrobials (often within 7 days prior to and up to 28 days after HSCT) and reduced gut microbiome diversity was associated with increased graft-vs-host disease and graft-vs-host disease–related mortality.[33-35,48-50] Additionally, in some patients undergoing treatment with HSCT, administration of antimicrobials led to the dominance of a single species of bacteria within the gut microbiome (defined as >30% of gut microbiota composed of 1 bacterial subtype). Antimicrobials targeting anaerobes were associated with a domination of *Enterococcus* in the gut microbiota and correlated with an increased risk of bacteremia with vancomycin-resistant *Enterococcus* (VRE) (8/9 patients; HR, 9.35 [95% CI, 2.43-45.44]; *P* = .001).[42] In CAR T-cell therapy, disrupting the microbiome by broad-spectrum antibiotic use up to 4 weeks prior to therapy was associated with an increased incidence of cytokine release syndrome, characterized by fevers, exhaustion, arthralgias, and, sometimes, neurotoxicity (such as impaired cognition and overall confusion), which were associated with an overall hyperinflammatory response with release of IL-2 and IL-6, among other cytokines.[36-38] The indication for antibiotic treatment was not available in this study; therefore, this may represent a cohort at high risk of infection. Chemotherapy[51,52] and radiation-induced[53,54] gastrointestinal adverse events were associated with decreased diversity and dysbiosis of the gut microbiome.

Box. Commonly Asked Questions About the Gut Microbiome and Cancer

What is the relationship between the microbiome and cancer?
Microbes present in the gastrointestinal tract and other anatomical locations affect human health and disease by influencing immunity, metabolism, and mucosal barrier maintenance. Variations in the microbiome secondary to medications (including though not limited to antimicrobials) and dietary exposure (including dietary fiber intake) have been linked to response to cancer treatment, treatment-related adverse effects, and long-term outcomes in patients with cancer.

Should the gut microbiome be assayed for all patients with cancer?
Currently, assessment of the microbiome in patients with cancer is only being performed in research settings. Assays evaluating the microbiome (in the gastrointestinal tract, tumor, and other anatomical sites) in patients with cancer are being developed; however, it remains unclear whether these diagnostic tests can help improve outcomes in patients with cancer.

How can patients with cancer improve their gut microbiome?
Although there are currently no established strategies to modulate the gut microbiome to improve outcomes in patients with cancer, certain behaviors may improve the function of a patient's inherent gut microbiome. Patients with cancer should be advised to avoid ultraprocessed foods, increase intake of fiber to 25 to 30 g/d, and participate in physical activity in accordance with established guidelines from the American Cancer Society.

Gastrointestinal Microbial Therapies to Improve Outcomes to Cancer Therapy

The Table provides details on the role of the gastrointestinal and tumor microbiome on cancer outcomes, potential treatments, and challenges related to these treatments. Questions commonly asked about the gut microbiome and cancer are provided in the **Box**.

Fecal Microbiota Transplant

Fecal microbiota transplant has been used experimentally to treat several specific disease conditions, such as *Clostridioides difficile* colitis, in the US.[68] Fecal microbiota transplant may be administered via several different routes, including during colonoscopy, as an enema, or orally. In 2022, the US Food and Drug Administration (FDA) approved a proprietary combination of donor stool–derived live fecal microbial product delivered rectally,[69,70] and a separate oral spore–based product similarly derived from donor stool,[71] to prevent recurrence of *C difficile* infection after antibiotic treatment for recurrent *C difficile* infection.

Although no FDA-approved FMT-based microbiome modulation strategies exist for other medical conditions, this approach is being studied along with immune checkpoint blockade treatment in patients with melanoma.[72-74] Treatment with FMT (with stool from patients with melanoma who achieved either a complete response or durable partial response) along with reinduction of immune checkpoint blockade therapy was associated with reversal of resistance to immune checkpoint blockade in 2 small clinical trials of patients with metastatic melanoma who had initially experienced disease progression with immune checkpoint blockade.[72,73] In a phase 1 clinical trial of 10 patients with metastatic melanoma, the response rate to FMT and reinduction with immune checkpoint blockade was 30% in patients previously unresponsive to immune checkpoint blockade.[72] Patients who responded to treatment after FMT had an increased relative abundance of *Ruminococcaceae* in the gut microbiota and improved mucosal immunity, compared with their gastrointestinal microbial composition prior to FMT.[72] Healthy-donor FMT is undergoing investigation in patients with metastatic melanoma receiving treatment with immune checkpoint blockade as initial therapy.[74] An ongoing clinical trial is investigating FMT in combination with standard-of-care therapy before surgery in patients with pancreatic adenocarcinoma. However, FMT and other microbiome-modulation strategies in patients with cancer remain in early stages of development. Current challenges to FMT treatment include the potential for transmission of multidrug-resistant organisms and other adverse effects, such as influencing other health outcomes (including risk of infection) that may be partially dependent on an individual's gastrointestinal microbiome profile.[75]

Prebiotics and Probiotics

The gastrointestinal microbiota may be modified with probiotic formulations (which may be composed of single microbial taxa or selected microbial communities) as well as prebiotic formulations (which include indigestible food ingredients—including fiber—that

can promote the growth of health-associated microbes in the gastrointestinal tract). Few studies have evaluated probiotics in the setting of cancer treatment.[76,77] However, 1 clinical trial that randomized 29 participants with metastatic RCC reported that a probiotic containing a single strain of *Clostridium butyricum*[76] combined with treatment with immune checkpoint blockade targeting CTLA-4 and PD-1 was associated with significantly improved progression-free survival compared with combined immune checkpoint blockade alone (12.7 months vs 2.5 months, respectively; HR, 0.15 [95% CI, 0.05-0.47]; *P* = .001).[76] However, other studies have reported a potential deleterious effect of probiotic formulations on restoration of baseline gut microbiota composition following antibiotic use,[78] and preclinical studies reported worse outcomes in the setting of treatment with immune checkpoint blockade for cancer following administration of commercially available probiotics (*Lactobacilli*-based or *Bifidobacteria*-based probiotics).[79]

Diet and Lifestyle Modification

Ongoing studies are evaluating gastrointestinal microbes (and response to cancer treatment) using dietary and lifestyle interventions. These interventions may modulate the microbiota by altering the diversity and composition of the overall microbiota within the gastrointestinal tract as well as through functional alterations of microbes within the gut and other anatomical locations.[2,80]

A retrospective analysis of 128 patients with metastatic melanoma treated with immune checkpoint blockade reported that the 37 patients with dietary fiber intake of at least 20 g per day had significantly longer progression-free survival (median progression-free survival not reached vs 13 months, respectively; log-rank *P* = .047) compared with 91 patients with dietary fiber intake less than 20 g per day.[79] Patients who ingested at least 20 g per day of dietary fiber had a higher relative abundance of fiber-fermenting bacterial taxa in the gut microbiome, such as *Ruminococceceae* (*P* = .04) and *Faecalibacterium prausnitzii* (*P* = .02).[79] In preclinical models, mice administered a low-fiber diet in the setting of treatment with immune checkpoint blockade for melanoma had more rapid tumor growth. Gene expression profiling of immune cells within the tumor microenvironment of these mice showed impaired T-cell signaling pathways important for antitumor immune responses in the mice administered low-fiber diets.[79] In a clinical trial of prebiotic food intervention, healthy participants were randomized to a high-fiber diet (n = 18) or a diet high in fermented foods (including yogurt and kombucha) (n = 18) in a 17-week study. Participants in the high-fiber diet group had increased levels of short-chain fatty acids and carbohydrate-degrading enzymes in their gut microbiota, while those in the high-in-fermented-foods group had increased microbiota diversity and decreased inflammatory markers (such as IL-6 and IL-10), despite the fact that composition of the gut microbiota was not significantly different between the 2 groups.[81] Physical activity may also affect gut composition and diversity.[80,82] Among 21 patients with Lynch syndrome, which is associated with increased risk of endometrial and colon cancer, those randomized to a 12-month exercise program that included cycling classes 3 times weekly had a significant increase in oxygen consumption measured by cardiopulmonary exercise testing, decreased inflammatory marker levels, and more functional immune cells in the colon, compared with a control group that received an exercise counseling session only.[83] The study did not report on cancer outcomes.

Tumor Microbiota Modulation as a Clinical Intervention

Targeted Antimicrobial Therapy

Current studies are evaluating whether intratumoral microbes can be altered to improve cancer treatment outcomes. *Fusobacterium nucleatum is* a pathogenic microbe that stimulates colorectal cancer development and promotes resistance to chemotherapy in patients with colorectal cancer. Reducing the abundance of *F nucleatum* with metronidazole reduced colorectal cancer tumor growth in preclinical models.[24] A retrospective analysis of 36 105 patients with colorectal cancer undergoing surgical resection demonstrated that 4413 patients who received antibiotics targeting anaerobic bacteria (such as nitroimidazole or lincomycin classes) in the 6 months prior to surgical resection had significantly lower colorectal cancer recurrence compared with those who did not receive treatment with these antimicrobials (n = 31 692 patients) (HR, 0.75 [95% CI, 0.57-0.98]; *P* = .04) (absolute rates not provided).[84] These analyses were post hoc and exploratory, and further studies are required to validate these findings, including mechanistic studies in preclinical models. These analyses also demonstrate the nuanced impact of using targeted vs broad-spectrum antimicrobials on cancer outcomes, which can variably modulate gastrointestinal and tumor microbial composition as well as local and systemic immune responses.

Bacteriophages are viruses that infect, replicate, and kill specific bacteria, making them a potential treatment to selectively eliminate specific bacteria. Currently, there are no FDA-approved bacteriophages for patients with cancer, but multiple clinical trials are underway.[85] Therapies to modify tumor-specific strains of *Lactobacillus* in patients with cervical cancer using antimicrobial peptides are under active clinical investigation, with the goal of increasing abundance of *Lactobacillus crispatus*, which is associated with improved response to treatment.[86]

Using Microbes to Treat Cancer

Bacteria and other microbial products, such as intravesicular instillation of a live-attenuated strain of *Mycobacterium bovis* (BCG) as a treatment for bladder cancer, have been studied for treatment of cancer. In a Cochrane analysis of 585 patients with non–muscle invasive bladder cancer, intravesical BCG was associated with lower rates of bladder cancer recurrence at 12 months compared with surgical resection alone (odds ratio, 0.30 [95% CI, 0.21-0.43]) (absolute rates not provided).[87] BCG activates both innate (defined as activation of pattern recognition receptors through nonspecific pathogen-associated molecular patterns) and adaptive (defined as activation of antigen-specific immune cell receptors) antitumor immunity. Cytokines released in response to BCG improve the immune response to cancer by recruiting and activating tumor-specific immune cells.[88]

Other treatments that use bacteria (including species of *Salmonella, Clostridium,* and *Escherichia)* that thrive in the hypoxic, nutrient-rich tumor microenvironment are being studied in preclinical and clinical settings. These microbes can be modified to reduce their ability to infect healthy cells, while simultaneously stimulating the immune system and promoting antitumor immune responses.[89,90] In a preclinical study, commensal skin bacteria were altered to express tumor antigens bound to proteins to recruit

tumor-specific T cells and promote antitumor immunity in a murine melanoma model.[91] Bacteria can be modified to deliver novel cancer therapies to tumors including peptides, nanobodies, enzymes, small molecules, and radioisotopes.[89,90] For example, in a murine model, an *Escherichia coli* strain delivered into cancer cells was modified to bind and internalize a systemically administered form of radiotherapy. This novel method of targeting radiotherapy improved survival time compared with placebo in murine xenograft models of colon and breast cancer (8 days vs 13 days [$P < .05$] for colon cancer; 11 days vs 18 days [$P < .01$] for breast cancer).[92] While these microbe-based cancer treatments appear promising, they have not been tested in patients, due to a lack of proven efficacy and concern about introduction of potentially infectious agents in patients with cancer who are immunocompromised.

The Gastrointestinal Microbiome as a Biomarker of Response to Immunotherapy

Biomarkers can be useful for indicating response to treatment with immune checkpoint blockade and include measures of total mutational burden, expression of PDL-1, and microsatellite instability.[93] Gastrointestinal microbiome is another potential biomarker of response to treatment with immune checkpoint blockade for cancer, because of the potential role that microbes in the gut have on immunity and response to immunotherapy. Next-generation sequencing methods, defined as high-throughput techniques that allow rapid sequencing of large amounts of genetic material, can potentially be used to profile the gastrointestinal microbiome of patients with cancer undergoing treatment with immune checkpoint blockade.[94] Investigators developed a topology score (TOPOSCORE) based on next-generation sequencing of the gut microbiota of 245 patients with NSCLC and applied machine-learning approaches to identify taxa that correlated with improved (or impaired) overall survival. Thirty-seven metagenomic species were identified that were associated with either response or resistance to treatment with immune checkpoint blockade. The TOPOSCORE was validated in an additional 254 patients with NSCLC and 216 patients with genitourinary cancer.[94] A polymerase chain reaction–based assay of 21 bacterial probes based on the TOPOSCORE was subsequently studied in prospective cohorts of patients with cancer (melanoma, colorectal cancer, and NSCLC) treated with immune checkpoint blockade. This assay could be performed in the clinic.[94] Assays under development could detect molecular signatures of dysbiosis in the peripheral blood of patients with cancer, including soluble MAdCAM-1.[15]

Limitations

This review has several limitations. First, some aspects of the microbiome and cancer treatment, such as specific mechanisms through which microbes contribute to cancer development and progression, were not discussed. Second, many of the presented concepts were based on data from murine models and human cohorts that were relatively small. Third, this review is not a systematic review and did not evaluate quality of included studies.

Conclusions

Microbes in the gut and other locations in the body may influence the development and progression of cancer and may affect the response to adverse effects from cancer therapy. Future therapies targeting microbes in the gut and other locations in the body may be developed and could potentially improve outcomes in patients with cancer.

ARTICLE INFORMATION

Accepted for Publication: February 11, 2025.

Published Online: May 12, 2025. doi:10.1001/jama.2025.2191

Conflict of Interest Disclosures: Dr Wargo reported serving as an advisory board member for OSE Immunotherapeutics, Weston Foundation, Institute Gustave Roussy, and The James Cancer Center and having a patent issued (US Patent No. 11,395,838). No other disclosures were reported.

Additional Contributions: We acknowledge Rebecca Soto, PhD, and Nadim J. Ajami, PhD, from the Platform for Innovative Microbiome and Translational Research (PRIME-TR), Manoj Chelvanambi, PhD, Laurence Diggs, MD, and Golnaz Morad, DDS, PhD, from the Department of Surgical Oncology, all at The University of Texas MD Anderson Cancer Center, for their invaluable contribution to the review and revision of the manuscript. No authors or contributors received compensation for their efforts.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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