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A Personalized Medicine Perspective on the Microbiome's Role in Colorectal Cancer Progression

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Abstract:

Colorectal cancer (CRC) is a very prevalent kind of cancer that is regularly diagnosed on a global scale. The lifestyle is recognized as a significant risk factor for CRC, particularly in cases of sporadic colorectal cancer. The gut microbiota undergoes significant alterations in its natural composition over the first ten years of life. Ensuring homeostasis in the gut is crucial because the structural and metabolic activities of the commensal microbiota prevent the colonization of pathogens in the intestines. Dysbiosis, which refers to an abnormality in the function or structure of the intestinal microbiota, has been linked to several disorders, including CRC. Without a doubt, some probiotics, when correctly prescribed and given, may effectively restore balance to the gut microbiota. This might potentially have a beneficial impact on immunological regulation in the gastrointestinal tract and reduce inflammation of the intestinal lining. New research strongly supports the concept that regular use of certain probiotics might be a practical method to successfully shield patients from the potentially harmful effects of radiation treatment or chemotherapy. Conversely, emerging therapeutic methods known as personalized medicine have provided a fresh perspective in the field of medical science. The correlation between microbiome and personalized medicine has emerged as a particularly intriguing area of further study, with significant implications for the treatment of diseases like cancer. This study aims to investigate the potential relationship between dysbiosis in the intestinal microbiota and colorectal cancer, as well as the possible involvement of probiotics in the improvement of colon cancer. Also, the relationship between personal medicine and intestinal microbiome in the development of various diseases related to the intestine has been mentioned.

Keywords: Colorectal cancer, Gut microbiota, Probiotics, Precision medicine

Introduction

The gut microbiome encompasses the combined genetic material and genome of all bacteria that inhabit the gastrointestinal tract (GIT) (1). The human gastrointestinal tract (GIT) harbours a population of more than 100 trillion microorganisms, with the bulk of them being concentrated in the colon. Metagenomic investigations reveal the presence of

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around 1,952 bacterial species in the human gut that have not been successfully grown in a laboratory setting. Furthermore, a significant number of these species have not yet been categorised or classified (2). This enhances significant variety within the microbial environment. The interaction between host and microorganism may either be mutually beneficial or disease-causing. The microbial ecology is significantly impacted by several external variables, including nutrition, medicine, and lifestyle (3). The symbiotic relationships between humans and microbes have many implications for physiological functioning and general well-being. The advantageous substances serve several purposes, including supplying essential nutrients, controlling immunity, regulating enterocyte action, impacting metabolism, and inhibiting the colonization of harmful microbes (4). The composition of the intestinal microbiome is strongly influenced by a person's diet and its chemical constituents since the bacteria metabolise and flourish in response to the ingested food. Dietary fibres, carbohydrates that can be accessed by the microbiota (MAC), and certain proteins obtained from plants are metabolised to produce short-chain fatty acids (SCFAs) (5). Short-chain fatty acids (SCFAs) possess anti-inflammatory characteristics, protect the structural integrity of the mucosal lining, and preserve bacterial diversity. Fluctuations in the levels of vital components and harmful poisons are associated with several diseases, including cancer (5). The primary processes implicated in cancer development due to the microbiome include changes in microbial diversity, compromised immune response, and the production of chemicals that are carcinogenic or genotoxic (5). This study aims to provide novel insights into the role of the gut microbiota in the advancement of colorectal cancer (CRC). Furthermore, we researched the potential of nutritious dietary changes to repair and maintain a properly functioning layer of cells in the colon, hence reducing the risk of colorectal cancer.

Colorectal cancer

Lung cancer is the predominant cancer reported in both men and females, comprising 11.6% of all reported cases. Among women, breast cancer has the highest incidence rate at 11.6%, while prostate cancer is the second most common disease among males, affecting 7.1% of the male population (6). Colorectal cancer has the third highest occurrence rate at 6.1%, but it is the second most common reason for death, responsible for 9.2% of all cancer-related fatalities. By 2035, it is estimated that deaths caused by rectal cancer will increase by 60%, while fatalities resulting from colon cancer will climb by 71.5%. Therefore, sickness is often regarded as a reliable measure of the socioeconomic advancement of the country (7). Lifestyle choices, levels of body fat, and dietary trends all contribute to the rise in morbidity. There is significant proof indicating that participating in physical activity has a protective impact (8). Greater consumption of red and processed meat, as well as alcoholic beverages, elevates the likelihood of having the condition. In addition to ameliorating socioeconomic circumstances, advancements in civilization and economic growth give rise to a transformation in dietary habits known as the "Westernisation of the lifestyle." This results in an increased intake of animal lipids, processed foods, refined cereals, and desserts, while dietary fibres, fruits, and vegetables are scarcer, and physical activity is reduced (9). The prevalence of overweight or obesity frequently arises as a consequence of such a way of life. By 2035, it is projected that fatalities from rectal and colon cancer will rise by 60% and 71.5% respectively. The variation in these values among countries is contingent upon the level of economic advancement. Hence, the ailment is commonly seen as an indicator of the nation's socioeconomic progress (10).

Factors that increase the CRC

Multiple variables have been linked to the onset of colorectal cancer. Studies have shown that individuals are more prone to colorectal cancer (CRC) if they or their relatives have cancer over the course of history, prior polyps in the colon, inflammatory bowel conditions, diabetes, or have had cholecystectomy (11). Environmental factors have a crucial role in the occurrence of CRC. The research findings indicate that various factors increase the likelihood of developing colorectal cancer (CRC), such as being overweight or obese, a lack of exercise, drinking and smoking, and an unhealthy diet characterised by low levels of fibre, fruits, vegetables, calcium, and nutritional content, and high consumption of red and processed meat (12). Moreover, the susceptibility to colorectal cancer is impacted by variables like gut microbiota, age, gender, ethnicity, and economic position.

Genealogical and Individual Background

An individual's predisposition to colorectal cancer is significantly increased by a family history of the illness. This phenomenon is impacted by both hereditary susceptibility that is inherited over generations and lifestyle factors. Key determinants for forecasting the likelihood of future colorectal cancer encompass (i) the discrepancy in age between individuals at risk and their immediate family members; (ii) the age at which relatives in the first degree were diagnosed with colorectal cancer; (iii) the count of family members diagnosed with colorectal cancer; (iv) the existence of additional

cancer types (such as endometrial, ovarian, urinary tract, and pancreatic) within the family; and (v) the familial cancer tumour history of a person (13). Previous studies have shown that those with a single first-degree relative (parents, siblings, or children) affected by CRC had, on average, a two-fold higher likelihood of acquiring CRC compared to individuals without a family history. The chance of developing CRC is substantially elevated if a family member is diagnosed with the disease before to the age of Sixty (14). Furthermore, an increased number of relatives who are afflicted by the condition, including not only first-degree but also second and third-degree relatives, further amplifies the chance of developing the disease (14).

Inflammatory bowel disease (IBD) is classified as the 3rd major reason for the occurrence of colon cancer, behind HNPCC and FAP. IBD is a collection of persistent and untreatable conditions that impact the immunity of the gut, resulting in ongoing inflammation. Crohn's condition and ulcerative colitis are the main forms of IBD. The aetiology of IBD remains uncertain (15). The onset of IBD is thought to be a result of the interaction of genetic, immune-mediated, and external factors. persons with IBD have a significantly increased chance of acquiring CRC due to the promotion of tumour development and progression by chronic inflammation. This risk is estimated to be 2-6 times greater compared to healthy persons. The likelihood of developing CRC is higher as the length of IBD rises, along with the degree and severity of the condition (16).

Colon polyps, referred to as precancerous neoplastic lesions, are abnormal tissue growths that protrude from the mucous membrane of the colon. From a histological perspective, these polyps may be classified into two main groups: non-neoplastic (such as hamartomatous, hyperplastic, and inflammatory polyps) and malignant. Adenomatous polyps are very noteworthy since they have the intrinsic ability to transform into malignant tumours (17). Adenomatous polyps are thought to be the source of around 95% of colorectal cancer cases. Although the majority of cancer cases originate from adenomas, it is anticipated that only around 5% of polyps develop into colorectal cancer (18). The time frame for the development of an adenomatous polyp into invasive adenocarcinoma varies between five and fifteen years of age. The probability of polyps developing into cancer increases with bigger polyp size, higher level of dysplasia, and advanced age of individuals. Polyps exceeding a diameter of 1–2 cm, displaying a significant degree of dysplasia, and occurring in older individuals are unfavourable prognostic factors. Considering that over 40% of adults aged 50 or older possess one or more adenomatous polyps, it is essential to identify and eradicate these polyps before their progression into cancer (19).

The impact of food choices and lifestyle on CRC

Currently, it is predicted that 30%-40% of various types of cancers are attributed to dietary, nutritional, and other lifestyle variables, hence rendering cancer to some extent avoidable. Compelling epidemiological evidence indicates that dietary variables, namely those leading to excessive weight and obesity, have a significant impact on the incidence, severity, and death rates of several malignancies, including CRC (20). In response to this, the Department of Health and Human Services at the National Institutes of Health and The Agency for Healthcare Research and Quality has endeavoured to introduce lifestyle changes to the general public, to emphasise the significance of eating habits and healthy habits in preventing diseases, such as cancer. The correlation between nutrition and cancer may be disguised by confounding factors that impact health, including smoking, drinking, a lack of activity, and susceptibility to external toxins (21). All of these characteristics are widely acknowledged as risk factors for the onset of cancer. While it may be difficult to pinpoint precise nutritional risk variables in epidemiological studies, animal studies have clearly shown the influence of diet on cancer development (22).

The correlation between the incidence of CRC and an overabundance of lipids and proteins (especially from animal sources), processed meat, and high levels of alcohol intake (above 30 g per day) demonstrates the direct influence of dietary components on cancer development (23). Higher consumption of heterocyclic amines increases an individual's susceptibility to getting CRC. The main heterocyclic amines generated are 2-amino-1-methyl-6-phenyl-imidazo[4,5-b]pyridine (PhIP), 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), and benzo[a]pyrene (Bap), which belongs to the class of polycyclic aromatic hydrocarbons. These chemical carcinogens were the first ones to be recognised as detrimental to human cells (24). On the other hand, a vegetarian diet seems to provide a defence against cardiovascular diseases, type 2 diabetes, and cancer. The presence of antioxidants in fruits and vegetables is responsible for successfully eliminating damaging free radicals and preventing DNA damage (25). A vegetarian diet encompasses a diverse range of nutrients that are linked to a decreased risk of cancer. These substances may safeguard cells by influencing the processes of bio-transformation and detoxification (phases I and II), as well as the cell signalling and endogenous antioxidant system (26). Extensive research has been conducted on certain micronutrients, namely

zinc and selenium, which appear to play significant roles in preventing cancer. On the other hand, complex compounds like carotenoids, flavonoids, curcumin, silymarin, resveratrol, folate, and total oligomeric flavonoids have demonstrated both direct anti-tumour activity and immunomodulatory effects in laboratory studies (27).

The relationship between the gut microbiome and CRC

The gut microbiota may have an impact on the development of CRC via many mechanisms. Disruptions in the gut microbiota can lead to the presence of harmful substances in the gastrointestinal tract (GIT), such as secondary bile salts, trimethylamine-N-oxide (TMAO), hydrogen sulphide (derived from amino acids containing sulphur), heme, nitrosamines, heterocyclic amines, and polyaromatic hydrocarbons (28). These substances are often found in red or processed meat and diets lacking in fibre, and they can cause inflammation and damage to genetic material. Dietary components, together with lifestyle variables such as alcohol use, smoking, and being overweight or obese, enhance the likelihood of developing abnormal growths in the cells that make up the lining of the colon. The colon houses the primary bacterial population in the human body (29). A "reference man" weighing 70 kg is predicted to have around 3.8×10^{13} germs. The human symbiotic bacteria play an additional role in enhancing the immune system to fight against harmful strains, in addition to the inherent defences of the gut. The immune system, in response, produces many inflammatory mediators, mostly including anti-microbial peptides, inflammasomes, and cytokines such as interleukin (IL)-22, IL-17, and IL-10. Crucially, continuous stimulation of the immune system has its detrimental consequences (30). Inflammation over time may initiate oxidative stress by producing reactive oxygen species (ROS), which have both toxic and damaging effects on the cells of the intestinal mucosa. In response to inflammation, the innate immune system produces inflammasomes, which may lead to colitis and increase the risk of developing CRC (31). Furthermore, the continuous release of growth factors caused by inflammation, the inhibition of apoptosis, and the enhanced formation of new blood vessels are additional factors that contribute to the development of tumours. Carcinogenic metabolites, also known as oncotoxins, are produced due to alterations in microbial metabolism resulting from changing eating habits, including the consumption of processed and refined foods. These oncotoxins are associated with the promotion of CRC (32). Yang et al. conducted a comprehensive study using metagenomic and metabolomic analysis. They discovered that a decrease in microbial diversity and a rise in the generation of harmful polyamines, including cadaverine and putrescine, are linked to a higher risk of CRC (33). Consuming diets that are rich in red and processed meats and lacking in dietary fibres elevates the risk factors for CRC. The gut microbiota metabolises indigestible food fibres in the lower GIT into short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate. These SCFAs have an anti-inflammatory impact on the mucous membrane of the colon. The dysbiotic microbiome contributes to CRC via several pathways, such as enhanced microbial adhesion to colon cells, suppression of tumour suppressor genes, triggering of oncogenes, production of genotoxic impacts on colonic enterocytes, and stimulation of angiogenesis. External variables can influence the gut microbiome, which may have either a stimulating or regulating effect on the development of tumours in the intestinal microenvironment (34, 35).

There is a strong correlation between a decrease in microbial diversity and an increased probability of acquiring CRC. Wu et al. discovered a significant occurrence of Helicobacter spp. in right-sided CRCs that were moderately to weakly distinguished. In contrast, the Firmicutes phylum exhibited a higher prevalence in developed CRCs with lymph node metastasis, as compared to CRCs without lymph node metastasis (36). Colonic adenomatous polyposis (CAP), an earlier-stage lesion to CRC, is distinguished by an excessive presence of Bacteroides and Citrobacter species, whereas *Weissella* and *Lactobacillus* are conspicuously scarce. The main metabolites identified in the fecal samples of individuals with community-acquired pneumonia (CAP) were acetic acid and butyric acid (37). In contrast, healthy individuals had elevated amounts of the protective compound t10, c12-conjugated linoleic acid, which is distinct from dietary linoleic acid. Conjugated linoleic acid, namely c9, t11-CLA, may be produced by some natural gut bacteria such as probiotic Bifidobacteria species. Additionally, strains of ruminal bacteria, such as *Megasphaera elsdenii*, create t10, c12-conjugated linoleic acid (38). Although butyrate has shown pro-apoptotic and anti-proliferative effects in CRC, it has paradoxically been seen to stimulate the growth of polyps in mice with impaired mismatch repair, namely Apcmin/+Msh2−/− (adenomatous polyposis colimin/+ and mutS homolog 2−/−) animals. Eliminating the secretion system inhibits the production of proteins that are involved in bacterial adhesion to HT29 cells in a laboratory setting, and reduces the colonisation of *Streptococcus gallolyticus* subspecies gallolyticus in mouse colon cancer models. This indicates that some bacterial proteins generated by certain species can promote tumour growth (39).

The significance of probiotics in both the avoidance and treatment of colon cancer

In the past few years, probiotics, which are natural sources with anti-carcinogenic characteristics that can prevent colon cancer, have garnered considerable interest. Several investigations have shown that regular use of probiotics may improve the makeup and properties of the gut microbiota, resulting in a reduction in chronic inflammation and the production of carcinogenic chemicals during an imbalance in intestinal bacteria (40). Liu et al. conducted research where persons with CRC who were having a colectomy were given a high dose of *L. plantarum*, *L. acidophilus*, and *B. longum* for 16 days. The study found that this frequent intake enhanced the variety and microbial richness in these individuals. The gut microbiota makeup of the sick closely mirrored that of the healthy persons in our investigation (41). Certain intestinal enzymes, including β-glucosidase, β-glucuronidase, nitrate reductase, azoredutase, and 7-α-dehydroxylase, can convert aromatic hydrocarbons and amines into active carcinogens by synthesising aglycones, phenols, cresols, ammonia, and N-nitroso compounds. These enzymes can exhibit cytotoxic and genotoxic effects, thereby playing a role in the progression of colon cancer (42). Hatakka et al. performed research on a live creature which showed that consuming certain strains of probiotic bacteria may reduce the function of these enzymes and provide defence against colon cancer. Particular strains of probiotics may influence the immune response by activating phagocytes and assisting in the maintenance of immunological vigilance, which can eliminate cancer cells at their first stages of development (43). It should be emphasised that the immunomodulatory qualities vary according to the strain. The ability to survive and remain in the gastrointestinal tract, as well as the dosage, may also have a significant impact on the immune system. Hence, not all probiotics can regulate the immune system and avert the onset of CC. Galdeano et al. emphasised that a dose of around 10^9 colony-forming unit-CFU per day and an intestinal persistence time of 48 to 72 hours are the best parameters for inducing immunostimulation in the animal (44).

A potential use for treating colorectal cancer involves manipulating the human microbiome, which entails using certain probiotics. As far as I am aware, there are few early studies, particularly those that are randomised and controlled, that investigate whether altering the microbiota in patients undergoing therapy for colorectal cancer might impact outcomes, such as the objective response rate or progression-free survival (45). However, several studies have shown that regularly consuming probiotics may effectively decrease intestinal permeability by altering the arrangement of cell junction proteins and reducing the absorption of potentially cancer-causing substances that have a detrimental effect on the colon cells. The administration of a combination of probiotics (*L. plantarum*, *L. acidophilus*, and *B. longum*) to persons resulted in enhanced results and an augmentation in the levels and distribution of cell junction proteins (claudin, occludin, and JAM-1) inside the colonic epithelium (46). The proapoptotic activity triggered by the intake of probiotics, particularly via the augmentation of TNF-α production, has been extensively studied about human cancer. According to Wan et al., the probiotic *L. delbrueckii* was shown to boost the production of caspase-3, leading to the induction of death in tumour cells. The alteration of the microbiota composition during immunotherapy is a novel and intriguing topic that has the potential to pave the way for new treatment approaches in colon cancer (47). The first study findings indicate a significant interaction between the gut microbiota and the immune system, suggesting the potential to manipulate the microbiota to improve the effectiveness of cancer therapy. Undoubtedly, more comprehensive investigations will be required to assess the correlation between the microbiota and the effectiveness of colon cancer immunotherapy (48). Emerging research indicates that microbiota, particularly the microbiota of the gut, may impact the reaction to cancer therapy and the probability of encountering adverse side effects. The increasing evidence highlighting the microbiota's ability to impact chemotherapy, radiation, and immunotherapy, particularly in terms of microbial composition, is becoming more noteworthy.

Probiotics' mode of action

Inhibiting the proliferation of tumour cells

Probiotics may inhibit the growth of cancerous cells by triggering programmed cell death pathways, including both internal and external mechanisms. The pro-apoptotic impact has been validated by several in vitro investigations, often by manipulating the expression of apoptosis-related proteins, including death ligand receptors, procaspase, caspase-3, 8, and 9, as well as Bax/bak and Bcl-2/Bcl-X (49). Probiotics regulate the various phases of the cell cycle to restrict the growth and division of cancer cells, which may be identified by alterations in cyclin expression. Studies have shown that two types of probiotic bacteria, *Propionibacterium acidipropionici* and *Propionibacterium freudenreichii*, generate short-chain fatty acids (SCFAs) like propionate and acetate (50). These SCFAs can trigger cell apoptosis in the HT-29 human colon cancer cell line and colorectal adenocarcinoma. Cell apoptosis is triggered by the activation of the caspase 3 enzyme, which leads to the condensation of chromatin, the formation of apoptotic nuclei, and the generation of reactive oxygen species.

One research has found the apoptotic impact of heat-inactivated probiotic yeast strain *Saccharomyces cerevisiae* PTCC 5052 on human colorectal cancer cells (51). This research demonstrated that the apoptotic process was disrupted due to the upregulation of BAX, caspase-3, and caspase-9, as well as the downregulation of Bcl-XL, procaspase-3, procaspase-9, p-Akt1, and Rel-A (52).

Immune system regulation

The interaction and correlation between the intestinal microbiome and immunity in the intestines are crucial for creating favourable circumstances for equilibrium. The gut microbiome provides instructions to immune cells, allowing them to operate optimally by effectively eliminating harmful bacteria while also tolerating beneficial bacteria (53). When different compounds produced by microorganisms function as ligands or microorganism-associated molecular patterns (MAMPs), Toll-like receptors (TLRs) on epithelial cells often respond to them, triggering a cascade of events. They initiate certain safety protocols. Dysbiosis, an imbalance in the ecology of microorganisms in the intestines, triggers the activation of MAPK (mitogen-activated protein kinases) and NF-κB pathways (54). This activation leads to the synthesis of pro-inflammatory cytokines, such as nitric oxide and IL-8, eventually contributing to the pathogenesis of IBD and colon cancer. Probiotic therapy replenishes the population of microorganisms in the gut and activates regulatory T cells (Treg) to release cytokines that counteract inflammation, such as TGF-β2 and IL-10 (55). Both laboratory research conducted in test tubes (in vitro) and studies conducted in living organisms (in vivo) demonstrate that the chemokine IL-8 is excessively produced in CRC cells. IL-8 has features that promote the growth of blood vessels (pro-angiogenic) and the development of tumours. It also enhances the spread of cancer cells to other parts of the body (metastasis) and their resistance to chemotherapy (chemoresistance). These findings imply that IL-8 may be present. It is an appropriate candidate for the therapy of colorectal cancer. Lopez et al. conducted an experiment demonstrating that both *live Lactobacillus rhamnosus* GG (LGG) and UV-inactivated LGG decreased flagellin-induced IL-8 production in Caco-2 cells by 66% and 59% respectively [56]. In CT26 cells, the administration of a probiotic mixture consisting of B. *longum*, L. acidophilus, and *L. plantarum*, together with prebiotics such resistant dextrin, isomalto-oligosaccharides, fructose, and stachyose oligosaccharides, had an inhibitory impact on cell proliferation and decreased cell migration and metastasis. The anticancer activities of these synbiotics are attributed to the T cell-mediated immunological response, namely the augmentation of CD8+ T cells (56).

The significance of the microbiome in individualized treatment and personalized medicine

Multiple lines of confirmation indicate that the dysregulation of the relationship between microbiota and the host is associated with many disorders, including inflammatory bowel disease (IBD), diabetes, cirrhosis, and CRC (57). Recent research has examined the interplay between microorganisms and medications used in cancer therapy. The results suggest that the participation of bacteria in the immune system is essential for the efficacy of these medications (58). However, there is limited data accessible regarding the impact of different combinations of human microbiome and its impact on the results of treatment in cancer patients. Several investigations indicate that patients with certain combinations of gut microbiota can either exhibit a positive response or not react at all to immunotherapy (59). This issue must be considered while evaluating pharmaceutical interactions. Furthermore, the significance of the gut microbiome's function as a biomarker for illness phenotype, prognosis, and treatment effectiveness is well-documented, particularly in connection to the changes in microbial population structure seen in different diseases (60). Studies have shown that there is a connection between the gut microbiome and surgery in individuals with Crohn's disease, specifically a rise in mucosa-associated *F. prausnitzii* in cases of recurrent disease (61). Although extensive research on the microbiome in IBD, there is a lack of consensus on the findings. This discrepancy may be attributed to variations in geographical locations as well as the influence of antibiotics, food, and other significant variables that impact the composition of the gut microbiome (62) Hence, more study on mucosal bacteria is required in the context of inflammatory illnesses like IBD. Furthermore, microbiome profiles are linked to several additional gastrointestinal illnesses. As an example, *F. nucleatum* is employed as a diagnostic indicator via the usage of FadA adhesin in colorectal cancer. Similarly, infection with *Clostridium difficile* (*C. difficile*) is linked to decreased diversity of bacteria and diminished synthesis of secondary bile acids (62). Furthermore, two recent investigations have shown specific microbiome patterns in individuals with *C. difficile* infection that may accurately forecast the occurrence of the illness (64, 65). Research yielded significant findings, indicating that patients saw a 90% improvement in their clinical condition after the administration of fecal microbiota transplantation (FMT) using stool samples obtained from healthy subjects (58).

Treatment reactions are correlated with a multitude of microorganisms. Illustratively, patients who

exhibited a favorable response to anti-PD1 therapy exhibited a significantly elevated prevalence of *Faecalibacterium*, whereas those who weren't responsive to treatment exhibited a high prevalence of *Bacteroidale*. According to research, microbial populations may provide bacterial immune synergy necessary for anti-PD1 treatment to be effective (63). Individuals with metastatic melanoma who experienced a more favorable response to therapy demonstrated a significant frequency of *Bifidobacterium longum*. The detection of these species in the intestines of rats with tumors indicated enhanced efficacy of anti-PD-L1 therapy. In contrast, those who did not exhibit a response to therapy were found to have two specific types of bacteria, namely *Ruminococcus obeum* and *Roseburia intestinalis*. Routly noted that the use of antibiotics during cancer treatment may be associated with the response to anti-PD1 medication. Furthermore, it has been shown that the disruption of the microbial network and the elimination of certain bacteria might hinder the effectiveness of the immune system. The patients' microbiota, in response to the medication, exhibited immunoregulatory bacteria, including Akkermansia, Faecalibacterium, and Bifidobacterium, which outperformed anti-PD1 therapy. In a separate investigation, it was noted that mice that received fecal microbiota transplantation (FMT) from people who had a positive response to therapy had a more pronounced recovery response to anti-PD1 medication compared to mice who received FMT from patients who did not react to the therapy. The study revealed that the enhanced reaction was linked to the abundance of *Faecalibacterium* in the rat feces [64, 65, 66].

These results together indicate that the personalized medicine approach, which incorporates the gut microbiome, has therapeutic promise. In conclusion, these findings indicate that endeavors are underway to develop artificial microbial communities for the management of diverse ailments such as IBD and Clostridioides difficile infection (CDI) (66). The gut microbiota may influence a person's health by interacting with several kinds of immune and non-immune cells, such as RNA, DNA, and membrane chemicals. This interaction occurs via the formation of a complex network of metabolites. It is noteworthy that patients who react to treatment may exhibit improved coordination with the therapy due to the movement of intestinal bacteria to secondary lymphoid organs, resulting in a targeted immune response against the malignancy (66).

Conclusion

One of the crucial elements of personalized medicine is the creation of diagnostic assays that use biomarkers for initial detection. CRC, or colorectal cancer, has been the subject of numerous investigations in which researchers have assessed the possibility of using fecal microbiota as a screening tool for early diagnosis. These investigations have included diverse clinical groups, such as healthy individuals, as well as those with adenoma and carcinoma. The first inquiries have confirmed the importance of the microbiome in human diseases, suggesting that the makeup of the microbiome might be used as a diagnostic and medicinal indicator shortly. Although these trials are still in their first phases, more study is necessary to carry out in vitro and in vivo studies with more definitive testing for each disease, to produce a suitable microbiome signature.

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Authors' Contribution

Akram Sadat Ahmadi and Yeganeh Yousefi were involved in the conceptualization, design, and support of the study. All authors read and confirmed the final manuscript.

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Competing interests

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