Interaction of the Gut Microbiome With Cancer Treatment

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Abstract

The gut microbiome is known to influence health and well-being beyond the gastrointestinal system, including metabolism, mood, and cognitive function. Research on the influence of the gut microbiome on cancer and cancer treatment has expanded in recent decades. This review discusses the effects of the gut microbiome on the pathogenesis of certain cancers, as well as the current guidelines and recommendations for health-care professionals for modifying the gut microbiome in cancer patients currently receiving chemotherapy or immunotherapy. The focus of this review is on five major areas of gut microbiome research (colorectal cancer, melanoma, renal cell carcinoma and non–small cell lung cancer, lymphoma, and acute leukemia) in which therapies, and particularly checkpoint inhibitors, have considerably improved survival outcomes. The relationship between microbial species and therapies to cure malignancies is largely unclear. This review will delineate the relationships being studied and conclusions to draw from the research in these areas thus far.

The gut microbiome contains millions of microorganisms that live in a symbiotic manner with their hosts, which are humans. Without these microorganisms, the gut does not operate at its intended capacity. The gut microbiome is an emerging area of medical interest not limited to the gut, because the microbiome plays an important role in metabolism, mood, and cognitive function (Aarnoutse et al., 2019). The relationship of the gut microbiome to health and well-being has widened our view and led to initiatives to better understand the gut microbiome. Within the past decade, research has expanded to understanding the gut microbiome's composition in the context of its impact on cancer treatment. This review will discuss the gut microbiome's effect on cancer pathogenesis, cancers in which the gut microbiome is currently studied, modifications of the gut microbiome in preparation for and while receiving cancer treatment, and current guidelines and recommendations for modifying the gut microbiome in cancer patients receiving surgery for tumor removals, chemotherapy, or immunotherapies such as a checkpoint inhibitors.

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GUT MICROBIOME AND CANCER PATHOGENESIS

The human gut microbiome holds tens of trillions of microorganisms that contribute to the functioning of metabolism and immunity of each person (Ursell et al., 2012). It is vastly diverse, and this diversity is key to optimizing gut function and regulating mood. Although certain groups of microbes in the gut microbiome in colorectal cancer are linked to an increased risk of developing inflammatory, autoimmune, and malignant diseases, these effects are not limited to the gastrointestinal system (Suraya et al., 2000). For example, dysbiosis, which is an imbalance of the gut microbial community, is related to the development of breast cancers, lung cancers, and adult T-cell leukemias (Suraya et al., 2000).

In a review of the gut microbiome, Suraya and colleagues (2000) noted that the ability of the microbiome to create dysregulation and lead to the development of malignant neoplasms is three-fold. First, this dysregulation can involve immunologic tissues. The stimulation of chronic inflammation mediators can lead to mutagenesis, oncogene activations, and angiogenesis. Second, parenchymal cell interaction with microbes can initiate proinflammatory and procarcinogenic pathways while impeding cellular apoptosis. Lastly, microbes can affect the development of neoplasms by producing hormonal mediates and metabolites that migrate to affect distant sites (Suraya et al., 2000).

GUT MICROBIOME RESEARCH IN CANCERS

Current research on the gut microbiome is focused on certain cancer types and their etiologies or the successful use of immunotherapy as the primary treatment. This review will focus on colorectal cancer, melanoma, renal cell carcinoma (RCC) and non–small cell lung cancer (NSCLC), and leukemia or lymphoma treated with allogeneic hematopoietic cell transplantation (HCT).

Colorectal Cancer

There is a consensus that intestinal dysbiosis, as a result of lifestyle and nutrition habits, is a major factor in the development of colorectal cancer (Montalban-Arques, 2019). However, prebiotics and probiotics help limit intestinal inflammation and provide a regulated composition of bacterial species in the gut when dysbiosis occurs (Rossi et al., 2018). Whereas prebiotics are food for gut microorganisms, probiotics are beneficial microorganisms intended to live in the gut. As a result, there is ongoing investigation to better understand whether prebiotics, probiotics, or both significantly improve intestinal microbial homeostasis and mitigate pathologic processes (Rossi et al., 2018).

Recent gut microbiome studies in mice have identified certain gut microbes associated with the promotion or inhibition of colorectal cancer. *Clostridium butyricum* is one such species found to inhibit intestinal tumor development, and levels of *Fusobacterium nucleatum* and *Bacteroides fragilis* correlate with the development of colorectal cancer (Montalban-Arques & Scharl, 2019; Chen et al., 2020).

Because surgery is an essential component of curative treatment of colorectal cancer, several studies have focused on understanding postsurgery probiotic benefits in relation to reducing postoperative infectious complications and improving quality of life. In a randomized, controlled prospective study comparing oral probiotics with antibiotics given before colorectal cancer surgery, Sadahiro and colleagues (2014) reported a higher incidence of surgical-site infections in the group receiving probiotics than in the group receiving three doses of oral antibiotics the day before surgery (Sadahiro et al., 2014; Mota et al., 2018). These findings were compared with those of Rayes and colleagues (2007), in which patients received a combination of probiotics and prebiotics (synbiotics) or enteral nutrition alone after a pylorus-preserving pancreatoduodenectomy. In that study, the incidence of postoperative bacterial infections was significantly lower in the group receiving synbiotics postoperatively (Rayes et al., 2007). Similarly, in a randomized, controlled prospective study in which patients received probiotics for 30 days starting from the third day after colorectal surgery, Bajramagic and colleagues (2019) reported a statistically significant reduction in surgical site infections and intra-abdominal abscesses (Bajramagic et al., 2019). Taken together, the findings of these studies emphasize the importance of timing with administration of probiotics or synbiotics. Probiotics or synbiotics

given postoperatively appear to improve postsurgical outcomes, whereas probiotics given preoperatively do not.

One more study worth noting is a randomized, double-blind clinical trial in which Xie and colleagues (2019) reported that patients who received prebiotics 7 days before colorectal cancer surgery had increased serum immunologic indicators and considerable amounts of four commensal bacteria (Xie et al., 2019). In considering this finding, Stavrou and Kotzampassi (2017) speculated that outcomes are affected not only by the timing of probiotic administration but also the length of time that synbiotics or probiotics are given. These findings are summarized in Table 1.

Melanoma

In melanoma, immunotherapy, and more specifically, checkpoint inhibitors, are used as first-line therapy. The programmed cell death protein 1 (PD-1) blockade therapy obstructs the PD1 signaling pathway that is currently on overdrive from the tumor cells and has been shown to be effective against melanoma, RCC, and NSCLC. A few studies have increased understanding of gut microbial composition in patients with metastatic melanoma who responded favorably to PD-1 blockade therapy. Gopalakrishnan and colleagues (2018) reported relatively higher microbial diversity and relative abundance of species within the Ruminococcaceae family in the gut microbiome of PD-1 blockade therapy recipients (Gopalakrishnan et al., 2018). PD-1 blockade therapy responders with a high abundance of the *Faecalibacterium* genus, which is in the Ruminococcaceae family of the Clostridiales order, had significantly prolonged progression-free survival compared with responders with a low abundance of *Faecalibacterium* (Gopalakrishnan et al., 2018). Similarly, Matson and colleagues (2018) reported a statistically significant association between response to PD-1 blockade therapy and the presence of the commensal bacteria *Bifidobacterium longum*, *Collinsella aerofaciens*, and *Enterococcus faecium* (Matson et al., 2018). In summary, these studies demonstrate that the presence and abundance of commensal bacteria correlate with increased immunotherapeutic responses in patients receiving PD-1 blockade therapy.

In considering CTLA-4 blockade therapy, one may be able to predict outcomes by the presence of certain species in the microbiome. Dubin and colleagues (2016) reported that an increased fecal abundance of species in the Bacteroidetes phylum and Bacteroidaceae, Rikenellaceae, and Barnesiellaceae families correlated with less immune-mediated colitis in patients who received ipilimumab (Yervoy; Dubin et al., 2016). Frankel and colleagues (2017) found that the presence of *Bacteroides caccae* enriched the immune-checkpoint therapeutic response in all patients studied and compared, which included patients receiving ipilimumab only, nivolumab (Opdivo) only, pembrolizumab (Keytruda) only, or ipilimumab plus nivolumab. In patients treated with ipilimumab plus nivolumab, the presence of *Faecalibacterium prausnitzii*, *Bacteroides thetaiotaomicron*, and *Holdemania filiformis* was correlated with higher response rates. Specifically, *Faecalibacterium* and *Bacteroides* species led to an expansion of T-regulatory cells and production of anti-inflammatory cytokines (Frankel et al., 2017). These mechanisms improve the host's immune response, and therefore the presence of these species helps promote the effects of

Table 1. Perioperative Probiotic And Symbiotic Treatment Regimens Used in Colorectal Cancer

Study	Modification	Timing	Findings
Sadahiro et al. (2014)	Probiotics vs. antibiotics given 1 day before surgery	Before surgery	Higher incidence of surgical-site infections in group receiving probiotics than in group receiving antibiotics
Bajramagic et al. (2019)	Probiotics for 30 days starting on day 3 after surgery	After surgery	Improved quality of life and reduced postoperative complications
Xie et al. (2019)	Prebiotics 7 days before surgery	Before surgery	Increased serum immunologic markers; increased amounts of four major commensal bacteria
Stavrou & Kotzampassi (2017)	Prebiotics, probiotics, or antibiotics	Before or after surgery	Timing and length of time receiving treatment affects outcomes

immunotherapy (Frankel et al., 2017). In conclusion, the presence of species in the Bacteroidetes phylum such as Bacteroidaceae is correlated with less immune-mediate colitis.

For the use of antibiotics with immunotherapy and the effect of antibiotics on therapy outcomes, the findings of Routy and colleagues (2018) are worth noting. In that study, mice with *RET*-positive melanoma, or the overexpression of the *RET* gene in mice, receiving ampicillin, colistin, and streptomycin had a significantly compromised immune response after PD-1 blockade therapy alone or in combination with CTLA-4 blockade therapy (Routy et al., 2018). Antibiotics can have beneficial effects in terms of prophylaxis against bacterial infections, but these findings point to the less-discussed negative effect of antibiotics, in which they can compromise the immune system response created by PD-1 and/or cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) blockade therapy. Further discussion of duration and timing of antibiotics, and moreover applying these concepts in humans, is unclear and debated.

Taken together, these findings, as summarized in Table 2, indicate that certain groups of microbes increase responses to immunotherapy and that receiving antibiotics after immunotherapy has some potential consequences.

RCC and NSCLC

In both RCC and NSCLC, immunotherapy is routinely used. As with melanoma, the relative abundance of species in the microbiome has been shown to affect immunotherapy outcomes, and thus understanding the effect of antibiotics on relative outcomes is important. In a study of patients with RCC and NSCLC receiving antibiotics for active pneumonia or urinary tract infection, Routy and colleagues (2018) reported that antibiotics given before immune checkpoint inhibitor therapy correlated with increased PD-1 blockade resistance. More precisely, decreased progression-free survival and overall survival were observed in the antibiotic-receiving groups (Routy et al., 2018). In a subsequent study by Derosa and colleagues (2018), the use of antibiotics, in both RCC and NSCLC, also correlated with less favorable clinical outcomes (Derosa et al., 2018). Patients with RCC who received antibiotics had an increased risk of primary progressive disease, shorter progression-free survival, and shorter overall survival. Patients with NSCLC who were given antibiotics showed decreased primary progressive disease but experienced even shorter progression-free survival and overall survival than patients with RCC who received antibiotics (Derosa et al., 2018).

In both RCC and NSCLC, low levels of *Akkermansia muciniphila* in the gut microbiome correlate with decreased response to PD-1 blockade therapy (Routy et al., 2018). Further investigation is needed to understand why this correlation exists, as well as whether the presence of *A. muciniphila* correlates with increased therapeutic effectiveness.

In summary, the use of antibiotics is correlated with unfavorable outcomes in patients with RCC or NSCLC receiving immunotherapy. However, finding ways to enhance the presence of *A. muciniphila* while not eliminating any particular bacterial strain may be a potential approach to avoid these poor outcomes.

Acute Leukemia and Lymphoma Treated With Allogeneic HCT

Allogeneic HCT is a curative treatment for acute leukemias and lymphomas. In patients receiving allogeneic HCT, gut dysbiosis can be associated with adverse outcomes, including increased infectious complications and generally poor post-HCT outcomes (Rashidi et al., 2019a; Rashidi et al., 2019b). Gut dysbiosis occurs more commonly in patients who have tested positive for vancomycin-resistant enterococcal strains via rectal swab 2 weeks before or up to 2 weeks after allogeneic HCT (Rashidi et al., 2019b). Induction chemotherapies for leukemia have been found to increase the propensity for vancomycin-resistant enterococcal strains in some patients who later receive allogeneic HCT.

Induction chemotherapy for acute leukemia is generally given along with several antibiotics over the course of a month. Subsequently, a fraction of patients later require reinduction chemotherapy, salvage chemotherapy, or a conditioning regimen for allogeneic HCT (Rashidi et al., 2019a). Patients who received a second or potentially third chemotherapy regimen have a significantly diminished diversity and abundance of intestinal microbes compared with their prechemotherapy baseline, resulting in ecosystem instability that more easily

Table 2. Microorganism Presence and Outcomes of Immunotherapy in Patients With Metastatic Melanoma

Study	Subjects	Microorganisms present	Antibiotics given	Immunotherapy	Findings
Gopalakrishnan et al. (2018)	Humans	Low levels of *Akkermansia muciniphila*; relatively high alpha diversity and abundance of Ruminococcaceae species	None	PD-1 inhibitors	Low levels of *A. muciniphila* correlated with poor response to PD-1 therapy; relatively high abundance of *Ruminococcaceae* species correlated with higher immunotherapy response rate
Matson et al. (2018)	Humans	*Bifidobacterium longum*, *Collinsella aerofaciens*, and *Enterococcus faecium*	None	PD-1 inhibitors	Statistically significant association between responders and presence of these commensal bacteria
Dubin et al. (2016)	Humans	Increased fecal abundance of Bacteroidetes, Bacteroidaceae, Rikenellaceae, and Barnesiellaceae species	None	CTLA-4 inhibitors	Correlated with less immune-mediated colitis
Frankel et al. (2017)	Humans	*Bacteroides caccae*; ipilimumab and nivolumab: *Faecalibacterium prausnitzii*, *Bacteroides thetaiotaomicron*, and *Holdemania filiformis*; pembrolizumab: *Dorea formicigenerans*	None	PD-1 inhibitors, CTLA-4 inhibitors, or combination of both	Correlated with enriched immune system response; ipilimumab and nivolumab: presence correlated with higher immunotherapy response rates; pembrolizumab: presence correlated with higher immunotherapy response rate
Routy et al. (2018)	Mice	None specified	Ampicillin, colistin, and streptomycin	PD-1 inhibitor ± CTLA-4 inhibitor	Use of these antibiotics significantly compromised immune response

leads to *Enterococcus* outgrowth and colonization (Rashidi et al., 2019a). In addition to the expansion of *Enterococcus,* this population had a significantly decreased presence of all other major genera, including *Clostridium*, *Alistipes*, *Veillonella*, *Faecalibacterium*, *Blautia*, *Akkermansia*, *Lactobacillus*, *Parabacteroides*, and *Bacteroides* (Rashidi et al., 2019). Interestingly, Rashidi and colleagues (2019a) investigated the vancomycin-resistant enterococcal strains of *Enterococcus gallinarum* and *Enterococcus casseliflavus* and found a significant association between the presence of *E. casseliflavus* and reduced all-cause mortality after HCT (Rashidi et al., 2019a). One may deduce that exposure to antibiotics during these induction and salvage chemotherapies is related to the differences in *Enterococcus* species abundance, but antibiotic exposure did not significantly differ between allogeneic HCT recipients with gut colonization by *E. casseliflavus* and those with gut colonization by *E. gallinarum*. Rashidi and colleagues (2019a) also found that in patients receiving induction chemotherapies, the use of anti-anaerobic antibiotics was associated with the expansion of *Enterococcus*, which was consistent with a cited murine study by Caballero and colleagues showing that anaerobic commensal bacteria, specifically *Parabacteroides distasonis*, prevent and clear already present vancomycin-resistant enterococcal infections in the murine gut (Rashidi et al., 2019a).

In conclusion, patients who receive allogeneic HCT and test positive for a vancomycin-resistant enterococcal strain prior to HCT have an increased risk of post-HCT mortality. This can be due to salvage and reinduction chemotherapies that significantly alter the presence and diversity of gut microbes other than *Enterococcus*. As Rashidi and colleagues (2019a) showed, *Enterococcus* species, except for *E. casseliflavus*, are detrimental (Rashidi et al., 2019). Thus, further studies are

needed focusing on eliminating *Enterococcus* with anti-anaerobic antibiotics to reduce mortality in allogeneic HCT recipients.

MODIFYING THE GUT MICROBIOME FOR CANCER TREATMENT

Diet is a factor that affects the gut microbiome composition, which can influence the development and progression of cancer (Wallace et al., 2010). The intestinal microbiome plays important roles in carbohydrate metabolism, vitamin production, and processing of bile acids and sterols (Wallace et al., 2010). Certain diets low in animal protein and high in fiber may be associated with lower risks of developing colorectal cancer, but diets that enhance the antitumor response to chemotherapy or immunotherapy are largely unknown (Alexander et al., 2017).

Dysbiosis of the microbiome can occur as a result of chemotherapy or immunotherapy. Zitvogel and colleagues (2015) noted that dysbiosis can be either beneficial or detrimental (Zitvogel et al., 2015). Detrimental dysbiosis is a composition of gut microbes associated with decreased therapeutic effectiveness or increased toxicities, whereas beneficial dysbiosis is a composition of gut microbes associated with improved therapeutic clinical activity (Zitvogel et al., 2015). This desired state of beneficial dysbiosis has been achieved using the following methods, from least to most precise: fecal microbial transplantation (FMTs), prebiotics, antibiotics, probiotics, and bacterial engineering.

The least precise method of modifying the gut microbiome is FMT, in which an encapsulated fecal microbiome from a healthy individual is transplanted into a patient who would benefit from the composition of the healthy individual's microbiome. Studies have shown that FMT is beneficial in treating *Clostridium difficile* infections, but research to determine the effectiveness of FMT in cancer treatment is still underway (Buchta Rosean et al., 2019). Several clinical trials of FMT in patients with cancer are ongoing. A few of the most recent clinical trials use FMT to decrease the tumor burden in patients undergoing treatment for advanced melanoma, reduce gut toxicities in patients with acute myeloid leukemia, and reduce infection rates and graft-vs.-host-disease in patients who have received allogeneic HCT (Buchta Rosean et al., 2019). Overall, this is a growing area of interest in oncology, with the potential to benefit cancer patients.

Prebiotics are components of food that cannot be ingested by humans but can be digested by microorganisms in the gut. Therefore, they can lead to the proliferation of certain microbes in the gut (Davani-Davari et al., 2019). Prebiotics are also being used in clinical trials to make microorganisms with antitumor therapeutic properties proliferate (Davani-Davari et al., 2019).

In considering the approach of eliminating certain bacterial strains, antibiotics can target strains that are detrimental to treatment outcomes. Antibiotics are being used in this capacity in many clinical trials to further investigate the feasibility and effectiveness of eliminating bacterial species without increasing the risk of infections.

Probiotics are living bacterial strains that transiently colonize the gut mucosa and have shown success in preventing carcinogenesis in animal tumor models (Zitvogel et al., 2015). However, there are limited studies investigating the effectiveness of probiotics in improving clinical outcomes in patients currently receiving cancer treatment. Recommending probiotics to cancer patients is also controversial because of the inherent risk of fungemia and bacteremia in immunocompromised individuals receiving probiotics (Davani-Davari et al., 2019; Didari et al., 2014).

Bacterial engineering is also being considered as a potential anticancer therapeutic approach. This relatively new approach involves engineering bacteria to attack cancerous cells. Various studies have shown that bacteria can be reconfigured with vectors to encode RNA, cytokines, toxins, and antibodies (Buchta Rosean et al., 2019). However, one of the major factors developers must consider is the number of bacteria to introduce, because too many can overwhelm an already compromised immune system (Buchta Rosean et al., 2019).

CLINICAL IMPLICATIONS FOR ADVANCED PRACTICE PROVIDERS

Current research is gradually providing an understanding of the important relationship between the gut microbiome and cancer prevention and treatment. Research in the past decade has made strides

in understanding not only which microbial strains are present in patients who are responding well to chemotherapies and immunotherapies but also ways to promote these beneficial microbial species in humans. Nevertheless, more research is needed to clarify the practical implications and develop guidelines for patients undergoing chemotherapy or immunotherapy. Currently, there are no guidelines for oncology health-care practitioners regarding modulating the gut microbiome to improve the effectiveness of cancer treatment. Although research findings are currently only correlative, the groundwork for understanding the significance of these findings and translating them to clinical practice is underway.

As discussed in this review, murine model studies have already demonstrated that gut-modifying methods are possible and that they enhance the effects of therapy. In addition, research in gastrointestinal medicine outside of oncology has shown that new methods, such as FMT, can be safely and effectively administered to immunocompetent patients (Davani-Davari et al., 2019). However, there is ever-growing concern for safety in immunocompromised patients, who have an inherently elevated risk of infection.

Probiotics and FMT, compared with prebiotics and antibiotics, have shown more potential for use in oncology (Vivarelli et al., 2019). In particular, probiotics containing *Lactobacillus rhamnosus* GG have shown anti-inflammatory effects in the gut microenvironment (Vivarelli et al., 2019). Multiple clinical trials are investigating the use of probiotics to synergistically aid by adding it to the standard treatment of neoplastic processes. Although most of these trials focus on gastrointestinal malignancies, many are also evaluating the effects of probiotics on chemotherapy, immunotherapy, and radiation. Fewer clinical trials of FMT are underway. Fecal microbial transplantation has been studied and applied in patients with graft-vs.-host disease after allogeneic HCT, and currently there are clinical trials of FMT for melanoma and acute myeloid leukemias (Vivarelli et al., 2019). Most FMT clinical trials are phase I and II, and none are currently in phase IV, whereas current and previous probiotic trials range from phase I to phase IV (ClinicalTrials.gov., 2021).

Although probiotics appear to be the most promising approach considering their prevalence in oncology clinical trials and the current phase of the trials, these probiotics will need to be highly adapted and specialized from the well-known over-the-counter probiotics for use in oncology. In a small study of melanoma patients at The University of Texas MD Anderson Cancer Center, patients receiving over-the-counter probiotics while receiving chemotherapy were shown to have a less diverse microbiome, and immunotherapy was less effective in these patients than in those who were not receiving probiotics (Raeke, 2021). In that study, Nadim Ajami, PhD, executive director of the MD Anderson Program for Innovative Microbiome and Translational Research, which provides support and resources to further understanding of the human microbiome and its interaction with cancer, noted that probiotics are "considered safe products, but unlike the new oral microbiome therapies currently being studied, over-the-counter probiotics are one-size-fits-all and not designed to treat any specific disease or condition. They might give you temporary benefits, but we're not sure it's the most efficient strategy to modulate the microbiome. Commercial probiotics may work for some people, some of the time, but they don't work for everyone, all of the time" (Raeke, 2021). The goal of clinical practice is to improve outcomes predictably, safely, and consistently for patients. Practically speaking, a more advanced stage in our knowledge and research of probiotics is needed to provide recommendations that will consistently work for all patients.

Recommendations for modifying the gut microbiome may be more complex than perhaps originally expected. Advanced practice providers in oncology must remember that although they might be able to provide options for improving the efficacy of therapy by modifying the gut microbiome, complications such as endocarditis, fungemia, and bacteremia are still prevalent in immunocompromised patients (Didari et al., 2014; Borriello et al., 2003). Modification of the gut microbiome has the potential to bring benefit or harm, and given the complexities of the gut microbiome, more research in immunocompromised patients is needed. Larger studies focusing on certain therapies and cancers, with targeted bacterial strains and repeatable methods, will generate the information needed to guide the formulation of safe and effective recommendations for patients.

CONCLUSION

As research continues to explore new areas of cancer treatment, modification of the gut microbiome has emerged at the forefront as a way to improve treatment outcomes and reduce side effects. Although there are currently no guidelines for using FMTs, prebiotics, antibiotics, probiotics, or bacterial engineering in cancer treatment, further investigation and research continues to improve understanding of the ways in which bacterial strains affect clinical outcomes. Studies are primarily in animal models, although a limited number of human studies are currently ongoing. Although there are no current guidelines in place, advanced practice providers can follow research developments in the use of the gut microbiome to improve the effectiveness of cancer treatment, as well as partake in the discovery and unfolding of these new therapeutic approaches in oncology. ●

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The author has no conflict of interest to disclose.

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