Diet-microbiome interactions in cancer treatment: Opportunities and challenges for precision nutrition in cancer

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Abstract

Dietary patterns contribute to cancer risk. Separately, microbial factors influence the development of several cancers. However, the interaction of diet and the microbiome and their joint contribution to cancer treatment response needs more research. The microbiome significantly impacts drug metabolism, immune activation, and response to immunotherapy. One of the critical factors affecting the microbiome structure and function is diet. Data demonstrate that the diet and microbiome composition affects the immune response. Moreover, malnutrition is a significant confounder to cancer therapy response. There is little understanding of the interaction of malnutrition with the microbiome in the context of cancer. This review aims to address the current knowledge of dietary intake patterns and malnutrition among cancer patients and the impact on treatment outcomes. Second, this review will provide evidence linking the microbiome to cancer treatment response and provide evidence of the potentially strong effect that diet could have on this interaction. This review will formulate critical questions that will need further research to understand the diet-microbiome relationship in cancer treatment response and directions for future research to guide us to precision nutrition therapy to improve cancer outcomes.

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Recent evidence demonstrates that dietary intake directly impacts cancer treatment response to immunotherapy in patients with melanoma through a dietary fiber-gut microbiome mechanism.1 However, the mechanisms by which the diet-microbiome relationship effects other cancers or treatment modalities remains unknown. In general, a prudent dietary pattern in cancer patients is associated with lower overall mortality in multiple cancer types.2-5 This prudent diet includes higher consumption of vegetables, whole fruit, whole grains, nuts and legumes, omega-3 fatty acids, polyunsaturated fat, and lower consumption of sugar-sweetened beverages, red/processed meat, sodium, trans fat, and moderate alcohol consumption. Specifically, in colorectal cancer (CRC) higher intakes of fiber, calcium, omega-3 fatty acids, and milk are also associated with a lower risk of death, while whole-grain intake is associated with lower CRC-specific mortality.6-8 In contrast, a diet high in processed meat is associated with decreased disease-free survival in CRC.7 Critically, a variety of dietary patterns are also known
to affect the composition and function of the microbiome (e.g., bacteria, viruses, fungi, archaea, and their genomic content). The impact of the diet on the microbiome is well-established, and comprehensive reviews on this relationship have been recently published.4,5,8,9 Evidence for the importance of the relationship between diet and the microbiome in colon inflammation, a risk factor for CRC, was demonstrated by seminal work from O’Keefe et al.10 They showed that a two-week dietary exchange, in which rural Africans consumed the typical low-fiber Western diet of African-Americans (AA) and African-Americans consumed the high-fiber plant-based diet of Africans, resulted in improvements in microbial structure and function, in particular increases in butyrate-producing bacteria and decreased secondary bile acids.10 Furthermore, they saw reductions in inflammatory (bile acids) and proliferative markers (Ki-67) among the AA consuming the rural African diet in only two weeks. Together, these data suggest that long-term dietary patterns and acute dietary changes made before/during treatment may have favorable effects on the gut microbiome structure and function, which we propose could improve treatment response. Before dietary patterns can be harnessed as adjuvants to improve cancer treatment response several areas need to be addressed. This review will focus on the following topics to explore diet and the microbiome in cancer treatment: A) the effect of diet and malnutrition on treatment response during cancer therapy, B) the effect of diet on the microbiome structure and function during cancer treatment, and C) the modifying effect of the microbiome on nutrient and drug metabolism during treatment, and overall treatment response (Fig. 1). We believe a precision nutrition approach to cancer treatment is achievable with a greater understanding of these critical relationships.

The current knowledge regarding medical nutrition therapy in cancer patients during treatment

Although data show prudent dietary patterns improve cancer treatment response, challenges from tumor burden and the effects of cancer treatment limit the ability to follow these dietary regimens. Patient-related factors complicating healthy dietary patterns or nutrition intervention include lack of appetite, altered taste, difficulty swallowing, nausea, vomiting, painful mouth, digestive issues, amongst others.11 Studies show a strong association between inadequate nutritional status and severity of treatment-related symptoms.12 The symptom burden, both physical and physiological, only increases upon initiation of chemotherapy.13 Specifically, symptom burden among cancer patients is most severe one week after chemotherapy administration, leading to malnutrition.14 As a result of the process of carcinogenesis and anti-cancer therapy, a vicious cycle of cancer-induced nutritional deficiencies and malnutrition-driven cancer complications ensues, further reducing beneficial patient treatment response. Addressing the issue of malnutrition among cancer patients is one of the most critical needs in cancer patient care.15

The incidence of malnutrition among hospitalized cancer patients is as high as 50%, which in itself is a strong predictor of overall survival.16 Untreated malnutrition during therapy can significantly reduce chemotherapy or radiotherapy tolerance, increase toxicity, prolong hospital stay, complicate post-therapy patient care, and increase financial burden.16–19 Malnutrition can also result from metabolic alterations due to tumor burden and treatment, precisely, an imbalance between patient nutritional

Fig. 1. Concept map of the diet-microbiome relationship in cancer treatment. (1) Prior to diagnosis, dietary patterns can affect both microbiome structure/function and malnutrition status at diagnosis, as well as treatment outcomes. (2) At diagnosis, microbiome structure/function affects anti-cancer therapy effectiveness, and possibly effects dietary intake and malnutrition status. Subsequently, dietary intake and malnutrition status can affect nutrient and drug metabolism, which itself can mediate* the relationship between dietary intake, malnutrition and treatment response. (3) During treatment, anti-cancer therapy affects dietary intake, malnutrition, and microbiome structure/function. The microbiome also impacts treatment response, which is likely mediated* by nutrient and drug metabolism. Other diseases states show a relationship between microbiome structure/function and malnutrition status, but this had not been demonstrated specifically for cancer. Note: While this model does not include the contribution of the immune system, it is understood to play a key role. (solid arrows = direct evidence; transparent arrows = indirect evidence).
needs, tumor demands, and nutrient availability. In CRC, there is an association between low serum levels of glutamine, histidine, and alanine and poor cancer survival.\(^{20}\) Specifically, protein-energy malnutrition or chronic protein restriction increases the risk of amino acid deficiency, influencing cancer response.\(^{21}\) Since we know that the microbiome can itself confer metabolic alterations in the host (mediator), as demonstrated by fecal microbiome transplant studies in mice, the relationship between malnutrition and altered metabolism suggest a mediating effect of the microbiome on metabolic alterations.\(^{22–25}\) The microbiome can also act as an effect modifier, in which the structure/function of the microbiome prior to dietary intervention or drug treatment (e.g. immunotherapy) modifies the effect of the intervention on host response.\(^{26}\) Evidence in animal models of protein restriction, supplemented with fiber (cellulose or inulin), demonstrates that the microbiome is critical in producing metabolic products that induce changes in metabolism; mainly through activation of fibroblast growth factor 21 (FGF21).\(^{27}\) Specifically, supplementation with cellulose, but not inulin, was sufficient to mitigate the increased expression of FGF21 resulting from protein restriction, and to prevent weight loss in part through increased abundance of cellulose-responsive bacteria. Towards this idea of using diet and the microbiome to prevent or treat malnutrition, links have been identified between malnutrition in children and microbiome dysfunction. In general, protein energy malnutrition or undernutrition (PEU) in children (e.g. Kwashiorkor) is the result of prolonged food and nutrient deprivation related to starvation in the absence of disease.\(^{28}\) In the context of cancer, malnutrition can result from several factors including tumor metabolism or burden and cancer treatment effects; while cancer cachexia is a complex syndrome that is represented mainly by skeletal muscle loss along with metabolic derangement.\(^{28}\) Recently, significant strides have been made in reversing acute moderate malnutrition in children using microbiome-targeted therapeutic foods.\(^{29,30}\) Given that PEU in children has components of fat and muscle wasting seen in cancer cachexia, this link between PEU and cancer cachexia provides proof-of-principle that a similar dietary approach may work by targeting the microbiome in cancer cachexia to prevent or treat metabolic dysfunction and wasting. However, much more research is needed in this area to address malnutrition in cancer, focusing on possible microbial mediating factors.

Studies indicate that the microbiome can be a factor affecting some of the negative anti-cancer treatment effects. Several animal model studies demonstrate that the gut microbiome is a contributing factor to inflammatory and neuropathic pain resulting from cancer therapy, and that modulation of the microbiome through fecal microbiome transplant (FMT), antibiotics, or probiotics can counter these effects.\(^{31–37}\) A small number of studies using dietary prebiotics (e.g., pectin and inulin) and/or probiotics demonstrate improvements in side-effects from cancer treatment.\(^{38–42}\) However, a more recent study indicates that for immunotherapy response probiotics may be counterproductive to efficacy.\(^{43}\) In general, probiotic interventions demonstrate moderate impacts on weight gain, BMI, and diarrhea but are still preliminary and not conclusive.\(^{44–47}\) However, intervening during cancer treatment with dietary or supplementary adjuvants will be challenging given the physical and mental stress of cancer therapy. Although, several clinical trials are ongoing to address this lack of information regarding dietary intervention during cancer treatment.\(^{48}\) Overall, tackling the issue of malnutrition and designing personalized nutrition therapy will require an in-depth understanding of the contribution of the gut microbiome to malnutrition, as well as genetics, nutrient and drug metabolism at diagnosis and during anti-cancer treatment.

One of the significant barriers to providing personalized nutrition therapy for cancer patients is the lack of standardized dietary capture tools, among several other factors (Table 1).\(^{15}\) These tools would drastically improve the identification of at-risk patients early after diagnosis to manage and treat malnutrition and optimize treatment response. While there are several different malnutrition assessment tools available, including, Malnutrition Screening Tool (MST), NUTRISCORE, and Patient-Generated Subjective Global Assessment (PG-SGA), unfortunately, there is no current consensus on which screening tool to use for cancer patients specifically.\(^{39,50}\) Furthermore, the dietary assessment tools such as Food Frequency Questionnaires (FFQs), Healthy Eating Index (HEI), Food Diaries, 24-hour recall, and short dietary screeners are designed for healthy populations and do not include questions specifically designed for cancer patients. Cancer patients represent a unique population with special nutritional needs, which may require specific evaluation tools on dietary intake assessment. Very little is known, however, about the dietary patterns or food intake fluctuations of cancer patients undergoing therapy, though numerous dietary interventions have been conducted.\(^{41}\) Based on anecdotal clinical observations, cancer patients can experience dramatic shifts in diet intake, which are dependent upon multiple factors, including the cycle of treatment and treatment type. Unfortunately, current dietary tools designed for healthy individuals do not adequately capture dietary collection from cancer patients. The most often used tools in dietary studies with cancer patients include 24 hour recalls and/or food FFQs (unpublished data). The advantage of the 24 hour recall is its ability to capture detailed short-term dietary intake, like dietary supplements or medical nutrition formulas often used by cancer patients (e.g. Two Cal HN), however, they rely on specific memory and trained interviewers, both of which are often limited in the cancer setting. Furthermore, multiple 24 hour recalls would be critical to capture fluctuations in diet intake around treatment cycles and surgery. Similarly, the FFQs, which are limited to a finite set of foods, captures long-term diet (past month or year) based on the probability of consuming the food and amount on a given day. This estimate of usual intake assumes the person's diet does not fluctuate dramatically over the month or year, an assumption which may be violated during cancer treatment.\(^{41}\) These limitations are extensively reviewed in Shim et al.\(^{32}\) and indicate the need to develop more appropriate cancer-specific dietary capture tools.
Enhanced pathogen invasions and bacterial toxin secretion can trigger pattern recognition receptors (PRRs) that activate toll-like receptors (TLRs) on epithelial and immune cells resulting in the production of chemokines and cytokines that recruit neutrophils, macrophages, and other immune cells, which enhance the pro-inflammatory signaling (Fig. 1D). Disruption of the microbiota by chronic inflammation, a risk factor for multiple cancer types, can also result in induction of pro-inflammatory pathways and select for pathogenic microbes, induce biofilm formation, or encourage the expression of virulence factors in commensal microbes. The precise mechanisms of microbial homeostasis are unclear and likely heterogeneous between cancer types and between individuals.

Apart from exogenous and endogenous effects on the microbiome during carcinogenesis, microbes and microbial communities themselves can contribute to both initiation and promotion of several cancer types. Currently, ten microbes are classified as carcinogens by the International Agency for Research on Cancer. Beyond these known carcinogens, four microbes (Salmonella enterica, Fusobacterium nucleatum, Enterotoxigenic Bacteroides fragilis (ETBF), Escherichia coli pks+) are possible cancer promoters based on current literature. In general, they can produce toxins that damage DNA (e.g., pks+ E. coli and ETBF), initiate biofilm formation and inflammation, and contribute to immune evasion. Specifically, F. nucleatum can bind T cell immunoreceptor with Ig and ITIM domains (TIGIT) receptors on NK- and T-cells, reducing the anti-tumor response. Of importance to this review, is the ability of the microbiome to metabolize components of the Western diet (high in red meat, saturated fats, added sugars, and low in fiber) into metabolic products that can contribute to inflammation and cancer development. Hydrogen sulfide-producing bacteria...
that metabolize sulfur compounds in red and processed meats and microbes that convert primary to secondary bile acids can induce DNA damage and reduce gut barrier function.\(^{69}\) In contrast, a diet higher in whole grains, fruits, and vegetables contributes to increased microbial diversity, beneficial short-chain fatty acid production, and higher numbers of activated T-regulatory cells.\(^{70}\) This latter beneficial effect of the microbiome could contribute to enhancing the immune response to anti-cancer therapy, notably immunotherapy.

Beyond the effects of carcinogenesis, the microbiome can alter the effects of cancer treatment and is affected by cancer treatment. Cancer-directed therapies, chemotherapy, and radiation directly affect the microbiome, surrounding tissues, and immune response. These treatments can lead to damaged villi in the gut, loss of diversity, decreases in commensals, and subsequently chemotherapy-induced diarrhea, mucositis, and tissue atrophy (Fig. 2).\(^{71}\) Specifically, chemotherapy-induced diarrhea occurs in as many as 50% of CRC patients and is associated with changes in the microbiome.\(^{72}\) Similarly, radiation therapy has effects on the microbiome in reproductive tract cancers. In peri or postmenopausal females, radiation may permanently alter the vaginal mucosa making Lactobacillus spp. replenishment difficult despite vaginal estrogen replacement.\(^{72,73}\) This loss of diversity results in a neutral pH, making the vagina more conducive to the growth of pathogenic bacteria.\(^{74}\) Furthermore, pelvic radiotherapy can increase the abundance of E. nucleatum, a key species known to promote CRC and metastasis.\(^{74}\) Among women undergoing chemotherapy for cervical cancer treatment, the gut microbiome diversity at treatment initiation was also predictive of survival.\(^{75}\) Specifically, long-term survivors had enrichment of Escherichia shigella, Enterobacteriaceae, and Enterobacteriales and increases in CD4+ T cells, suggesting that these factors may be involved in positive treatment response to chemoradiation.\(^{76-78}\) This evidence indicates that restoring microbial diversity and possibly gut barrier function would improve treatment response before or during cancer therapy.

Evidence supports that the microbiome also impacts the effectiveness of treatment through several different modes of action, including drug metabolism, immune modulation, and host diet/nutrient interaction.\(^{79-81}\) Microbial taxa, like mammalian cells, possess enzymes capable of metabolizing drugs into various forms. In the case of the chemotherapeutic gemcitabine, the intestinal Gammaproteobacteria can induce gemcitabine resistance,\(^{82}\) while the species R. planticola, E. coli, and K. pneumonia can detoxify the chemotherapeutic doxorubicin, which also confers protection to the greater microbial community.\(^{83}\) Likewise, microbial tax carries the enzyme β-glucuronidase can reactivation the anti-cancer drug irinotecan in the GI tract leading to severe diarrhea,\(^{84}\) a significant complication in several types of anti-cancer therapies. Furthermore, studies demonstrate a causative effect of the chemotherapy-exposed microbiota on the development of side effects. Specifically, FMT from paclitaxel-treated mice induces inflammation, which is reversed through passive microbial transfer (soprophagy) when co-housed with unexposed mice.\(^{85}\) Thus, the microbiota is a crucial player in therapeutic activity and toxicity for multiple anti-cancer therapies through pharmacodynamics and immunological pathways.

Likewise, the microbiome is critically essential to chemo- and immunotherapy effectiveness. Early work established that antibiotic treatment inhibits the efficacy of the chemotherapeutic oxaliplatin and immunotherapy through mechanisms that converge on the microbiome-immune axis.\(^{86}\) Specifically, antibiotics decrease the LPS-producing bacteria, which are necessary to activate TLR4 on tumor-infiltrating myeloid cells to enhance tumor-killing ROS production upon oxaliplatin treatment.\(^{87}\) Additional seminal work went on to identify specific microbial taxa that could either enhance (Bacteroides ovatus and Bacteroides xylanisolvens) or inhibit anti-cancer treatments.\(^{88}\) Specifically, treatment with different consortia of probiotic bacteria (e.g., Roseburia intestinalis, Eubacterium hallii, Faecalibacterium prausnitzii, and Anaerostipes caccae) appears to promote a beneficial response to immunotherapy and, in some cases, work as well as chemo- and immunotherapy.\(^{89-91}\) A recent key finding among individuals with melanoma treated with immunotherapy (i.e., anti-PD-1) showed that those who responded favorably also had the greatest fecal microbial diversity before treatment.\(^{92}\) However, a more recent follow-up study could not replicate this finding.\(^{93}\) Nonetheless, they later went on to show that those patients with melanoma who were responders to immunotherapy also had a higher intake of dietary fiber, which tends to increase overall microbial diversity and enhance gut barrier function.\(^{94}\) To further interrogate this dietary fiber effect, they used an animal model of melanoma and found that supplementation of dietary pectin along with immunotherapy improved treatment response.\(^{95}\) This beneficial effect of dietary pectin occurred through enhancing the microbial production of c-di-AMP, triggering the secretion of type I interferon by intertumoral monocyes creating an anti-tumorigenic environment. Following these studies, a more comprehensive study used both a previous cohort of patients with melanoma and a new cohort of melanoma patients treated with immunotherapy (e.g., anti-PD-1).\(^{96}\) Both cohorts could recapitulate the increased abundance of Ruminococcaceae in responders vs. non-responders of immunotherapy. They also compared the survival time among those using or not using probiotics during treatment and found a lower but non-significant difference in survival among those using probiotics. However, in preclinical models of melanoma receiving FMT from responder patients, further treatment with either a Bifidobacterium or lactobacillus-based probiotic combined with anti-PD1 therapy significantly increased tumor size and decreased gut microbiome diversity. This effect of probiotics on response to immunotherapy had a similar deleterious effect by reducing IFN-γ producing CD8+ and CD4+ T-cells, indicating a harmful effect of these probiotics on response to immunotherapy. When they examined dietary fiber intake in patients using baseline intake at diagnosis, they found a significant increase in survival per 5gd/day increase in dietary fiber (HR=0.71, P=0.04). Furthermore, when examining survival in those with both sufficient fiber intake (>20g/d) and no probiotic intake, the survival was significantly higher in those reporting adequate dietary fiber intake (HR=0.44, P=0.03) than those reporting insufficient fiber or probiotic use. In their preclinical melanoma models treated with anti-PD1, mice fed high fiber diets without probiotics had higher survival rates than the other treatments and a higher abundance of IFN-γ producing T-cells. These studies indicate that diet is likely a key contributing factor to the microbiome and its ability to modulate the immune system to affect a significant anti-cancer response. Furthermore, these data also suggest that diet may impact chemo- and radiotherapy response by modulating the microbiome, but much more work is needed in this area to understand the diet-microbiome effect.

**Dietary patterns and impact on cancer treatment outcomes**

To counter the effect of microbial alterations during anti-cancer therapy and the subsequent impact on treatment response, we propose using the diet to alter the microbial structure and function before or during treatment to improve cancer outcomes. As evidence, a significant body of work related to diet and the gut microbiome in healthy individuals demonstrates the beneficial impact of short-term dietary interventions on the composition and function of microbes in the gut mucosa and systemically in the following review.\(^{97}\) However, it should be noted that the beneficial outcomes of dietary interventions can be small (e.g. 5%–16%) and heterogeneous due to the large variation in the gut microbiome between individuals.\(^{98,99}\) There are only a small number of studies, however, that have attempted to use diet to modify the gut microbiome during cancer therapy. In particular, dietary prebiotics (e.g., fructo- and galactooligosaccharides) in animal models and human studies of cancer demonstrate the ability to modify the therapeutic response favorably through altering the microbial structure and immune function.\(^{3,39-47}\) Additionally, the ketogenic diet (high fat, low carbohydrate diet) has shown favorable preliminary results in animal models of glioblastoma,\(^{100}\) and early
Molecular pathological epidemiology: an approach to precision nutrition therapy

While precision nutrition therapy does not yet have an official definition, it can generally be defined as a nutrition intervention that improves treatment outcomes using an individual's unique characteristics, including genetics, gender, race/ethnicity, health history, lifestyle, and microbiome. An approach to precision nutrition that incorporates these factors is molecular pathological epidemiology (MPE). It is well understood that germline genetic variations impact tumorigenesis, the immune system, but more recently also the microbiome. A study investigating the impact of genetics on the microbiome, using 113 mouse strains, demonstrated a 26-65% heritability of the most prevalent gut microbiota. They further demonstrate a gene-environment interaction with the gut microbiome. In addition to finding a significant effect of genetic background differences on response to a high-fat/high-sucrose diet, they also demonstrated through cross-fostering a significant effect of the microbiome in altering metabolism. These data along with other studies indicate the gut microbiota can modify the effect of gene-environment interactions, especially dietary interactions. In the context of cancer, MPE studies also demonstrate diet-immune interactions, where higher intake of omega-3 fatty acids in individuals with high FOX3P+ T regulatory cells (vs low FOX3P+ T regulatory cells) had lower risk of CRC. Similarly, MPE studies of the microbiome show that prudent dietary patterns significantly impact development of Fusobacterium nucleatum-positive, but not F. nucleatum-negative, CRC. F. nucleatum also demonstrates interactions with genetic features of tumors (e.g., microsatellite instability-high), which is associated with lower immune infiltration. Together these data indicate that precision nutrition therapy for cancer patients will require an understanding of both the genetic and environmental factors contributing to the pathology of their tumor in order to enhance the effectiveness of standard therapy.

Conclusions and future directions

Just as precision or personalized medicine has transformed cancer treatment from a one-size-fits-all to biomarker-guided drug therapy, we propose a similar approach to precision nutrition therapy in cancer treatment. By incorporating genetics, nutrition and the microbiome as factors in cancer therapy, we can dramatically improve treatment outcomes for cancer patients. To operationalize this concept will require several parallel approaches. First, we will need a more precise understanding of the critical genetic, dietary and microbial biomarkers predictive of treatment efficacy, toxicity, and drug resistance. To identify these factors, we will need large, well-designed studies to answer the following questions: a) which microbial factors mediate or modify the effects of diet on treatment response? and b) what biomarkers predict a favorable microbial response to nutrition intervention during cancer treatment? Expanding the research in this area will be an essential step toward precision nutrition in cancer.

Second, addressing malnutrition as part of the cancer treatment plan must become standard practice. While we work to collect more evidence towards precision nutrition therapy, several barriers must be overcome that are holding back improvements in nutrition therapy during cancer treatment. These include insufficient funding and reimbursement for nutrition support staff (e.g., oncology dietitians), lack of integration of nutrition services into the health care plan, lack of or inconsistent malnutrition screening, use of non-validated malnutrition screening tools, and in general, a lack of tools for dietary collection that meet the needs of cancer patients and their providers. Cancer patients with weight loss, a significant sign of malnutrition, have the worst treatment outcome for chemotherapy. Creating a robust tool for providers and patients to capture dietary data is a preventative approach to facilitate a personalized dietary plan for cancer patients. Capturing critical dietary and microbiome data in longitudinal cohorts will enhance our understanding of the diet-microbiome interactions along the treatment continuum and begin to inform our efforts toward precision nutrition therapy during cancer treatment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

K. Leigh Greathouse: Conceptualization, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing. Madhur Wyatt: Conceptualization, Project administration, Writing – original draft, Writing – review & editing. Abigail J. Johnson: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. Eugene P. Toy: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. Joetta M. Khan: Conceptualization, Writing – original draft, Writing – review & editing. Kelly Dunn: Conceptualization, Writing – original draft, Writing – review & editing. Deborah J. Clegg: Conceptualization, Writing – original draft, Writing – review & editing. Sireesha Reddy: Conceptualization, Writing – original draft, Writing – review & editing.

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